Health Behaviour of Older Adults with Neurological Disorders: Predictors of Nonadherence and Influence on Quality of Life

Thesis

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Abstract

Aim: With advancing age, the prevalence of chronic disorders rises. Medical treatment is the cornerstone in managing these illnesses, still research suggests that up to half of older patients do not take their medication as agreed upon with healthcare providers. This nonadherence to medication is associated with worse health outcomes and lower quality of life. Although factors contributing to nonadherence have been determined, interventions to improve medication intake remain inefficient. This is because studies are often disease-specific or not tailored to older adults. However, the specific challenges faced by older adults, such as multimorbidity and cognitive decline, necessitate a differentiated approach to understanding their needs.

Methods: Cross-sectional data on sociodemographic information, self-reported nonadherence, depressive symptoms, cognition, personality, mobility, health-related quality of life, and medical information were collected in N = 910 older adults with neurological disorders. Using regression analyses, publication I describes factors contributing to nonadherence. Publication II identifies which depressive symptoms in particular drive nonadherence using regression and network analyses. Publication III then examines the association between nonadherence and quality of life in analyses of variance, with a focus on the effect of depressive symptoms.

Results: Only 21.1% of the patients were fully adherent. Nonadherence was classified into three sub-types: *forgetting* to take medication (46.2%), *missing knowledge* about medication (29%), and intentional *modification* of medication (24.8%). Although these sub-types were differentially influenced by clinical factors, depressive symptoms and a higher number of medications were identified as key factors. The depressive symptoms *loss of interest* and *difficulty with concentration* were identified as links between nonadherence and other affective or somatic symptoms. Health-related quality of life is not linked with self-reported nonadherence when controlling for covariates; instead, both are influenced by underlying factors, especially depressive symptoms.

Conclusions: Health-related quality of life appears unsuited as an endpoint for clinical interventions targeting nonadherence. Although disease-specific factors and polypharmacy play a role, depressive symptoms appear to be key drivers of nonadherence in this patient population of older adults with neurological disorders, and should be targeted in interventions to effectively improve medication adherence.

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Referat

Zielsetzung: Mit zunehmendem Alter steigt die Prävalenz chronischer Erkrankungen, die primär medikamentös behandelt werden. Die Forschung zeigt jedoch, dass etwa die Hälfte der älteren PatientInnen die Medikation nicht wie verschrieben einnimmt. Diese Nonadhärenz führt zu schlechterer Gesundheit und Lebensqualität. Obwohl Faktoren für Nonadhärenz identifiziert wurden, sind Interventionen zur Verbesserung von Medikamentenadhärenz oft nur unzureichend wirksam. Dies liegt daran, dass viele Studien krankheitsspezifisch ausgerichtet und nicht auf ältere Menschen zugeschnitten sind. Altersspezifische Herausforderungen wie Multimorbidität und kognitiver Abbau machen ältere Erwachsene jedoch zu einer Personengruppe, deren Situation differenziert betrachtet werden muss.

Methodik: Querschnittsdaten zu Gesundheit, Soziodemografie, selbstberichteter Nonadhärenz, depressiver Symptomatik, Kognition, Mobilität und Lebensqualität wurden von N = 910 älteren PatientInnen mit neurologischen Erkrankungen gesammelt. Publikation I beschreibt mittels Regressionsanalysen die Faktoren, die mit Nonadhärenz assoziiert sind. Publikation II untersucht mit Regressions- und Netzwerkanalysen, welche depressiven Symptome mit Nonadhärenz verknüpft sind. In Publikation III wird mittels Varianzanalysen der Zusammenhang mit gesundheitsbezogener Lebensqualität beleuchtet.

Ergebnisse: Nur 21.1% der PatientInnen waren voll adhärent. Nonadhärenz kann in die drei Subtypen *Vergessen* der Medikation (46.2%), *Unwissen* über Medikation (29%), und absichtliche *Veränderung* der Medikation (24.8%) eingeteilt werden. Diese Subtypen werden unterschiedlich von den Kovariaten beeinflusst, wobei Polymedikation und depressive Symptomatik übergreifende Einflussfaktoren sind. Die depressiven Symptome *Interessensverlust* und *Konzentrationsprobleme* verknüpfen Nonadhärenz mit anderen somatischen und affektiven Symptomen. Gesundheitsbezogene Lebensqualität hingegen ist nach Einschluss von Kovariaten nicht mehr mit Nonadhärenz verknüpft.

Schlussfolgerungen: Gesundheitsbezogenene Lebensqualität scheint ungeeignet als Endpunkt für klinische Studien zur Verbesserung von Nonadhärenz. Stattdessen werden beide durch gemeinsame Faktoren, insbesondere depressive Symptomatik, beeinflusst. Obwohl krankheitsspezifische Faktoren und Polymedikation eine Rolle spielen, sind depressive Symptome die Kernfaktoren für Nonadhärenz bei älteren PatientInnen mit neurologischen Erkrankungen und daher verstärkt in Interventionen berücksichtigt werden, um Nonadhärenz zu verbessern.

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Content

List of Abbreviations

AUC	Area Under Curve
BDI	Beck Depression Inventory II
HRQoL	Health-Related Quality of Life
ICF	International Classification of Functioning
MANCOVA	Multivariate Analysis of Covariance
NeuroGerAdh	Neuro-Geriatric Adherence, abbreviated study name
PD	Parkinson's Disease
QoL	Quality of Life
ROC	Receiver Operating Characteristics
SAMS	Stendal Adherence to Medication Score
SF36/SF12	Short Form 36/12 measure of Health-Related Quality of Life
WHO	World Health Organization

1 Introduction and Aim

1.1 Sociodemographic Development and Challenges of Older Age

The demographic shift towards an aging society presents a multitude of challenges for a health-care system that is not yet adapted to the needs of older adults (1,2). The World Health Organization (WHO) estimates that by 2050, 2 billion people worldwide will be aged 60 or older (3). In contrast to the increasing number of older adults, only a handful of over 900 guidelines for clinical practice in the German Association of Scientific Medical Societies address older patients (4). This is startling, as the risk of illness increases along with age, and people aged 85 and above have the highest daily medication prescription dose of the country (1).

1.1.1 Health-Related Challenges

The increase in illness and functional impairments is one of the defining characteristic of older age (1,5). While ageing is not a linear process (5,6), biological changes lead to a vulnerability of older adults, often cumulating in multimorbidity. Defined as the presence of two or more simultaneous illnesses (1), up to 95% of people aged 65 or older suffer from multimorbidity (7). Especially neurological illnesses are amongst the leading causes of disability across the globe (8,9), with an increased prevalence in older age (10,11).

Notably, the standard treatment for neurological disorders is pharmacotherapy (9). Thus, multimorbidity often goes hand in hand with polypharmacy, defined as the intake of ≥ 5 distinct medications daily (12). In Germany, a third of people with chronic illness receive more than four medications per day (13, 14), often leading to adverse drug reactions, prolonged hospital stays, and worse overall health (1,4,12). Multimorbidity and polypharmacy pose a challenge in the care of older patients, because managing these complex medication regimes is difficult for patients and providers alike (2,4,15,16). They also challenge scientific research, as it is difficult to disentangle the multitude of symptoms. In advancing age, symptoms may be part of multiple illnesses; consequently, managing a single diagnosis cannot address the overlapping symptomology or improve functionality (17).

In addition, healthy aging comes with restrictions in memory and information processing, decision making and executive functioning (18,19). This cognitive decline can already impact health and well-being at a subclinical level (20). Neurological disorders in particular are characterized by cognitive decline (19,21). For example, cognitive impairment is common in Parkinson's Disease (PD), the prevalence of PD dementia may be as high as 70% (22,23). Likewise, stroke can lead to lesions in the brain that may significantly impact its functioning (24,25). Cognitive functioning is a cornerstone to comprehend both illness and treatment, and to

implement the treatment plan in an effective manner. Thus, all stages of cognitive impairment are linked not only to health but overall Quality of Life (QoL) (26). Still, the particularities of older age reach beyond physical changes, as psychosocial aspects of aging have been demonstrated to significantly impact well-being and QoL (5,6,27).

1.1.2 Psychosocial Challenges

As defined in the International Classification of Functioning (ICF), health is multidimensional, containing physical and mental health but also QoL and social connectedness (1, 28). Although older age per se is not a risk factor for psychosocial challenges like depressive symptoms or loneliness (29), age-related difficulties may impact a person's mental well-being (6,27).

Changes in physical health and the social environment pose a challenge for mental health, increasing the risk of depressive symptoms of older adults (3,30,31). Depressive symptoms may emerge due to maladaptive coping, or underlying disease mechanisms in the body (31,32). Neurological disorders in particular exhibit a bidirectional relationship and high comorbidity with depressive symptomology (32,33). Depressive symptoms in turn impact not only mental health but also disease progression and QoL (31,34-36). Depressive symptoms are multifaceted, commonly including worthlessness, fatigue and sleep disturbances, loss of interest, hopelessness, social withdrawal, and problems with concentration (35,37). To incorporate this complexity in scientific research, the influence of individual symptoms must be considered instead of focusing on overall sum scores (38-40). Especially in older adults, depressive symptoms paired with the heightened risk of physical illness represent a significant risk factor for nonadherence. This is, in part, because depressive symptomology is linked to health behaviour such as the intake of medication, culminating in a lack of energy or motivation to perform behaviours, lack of hope for improvement, low expectations regarding treatment benefits, and reduced self-efficacy (41). Especially the latter has often been cited as a barrier to health behaviour, as patients may no longer believe that they can impact their health (42,43).

In summary, neurological disorders pose a predicament for older patients with their high prevalence, degenerative progress, polypharmacy, and comorbidity with cognitive decline and depressive symptoms. Thus, older adults face health-related and psychosocial changes, impacting health behaviour and QoL (44-46).

1.1.3 Quality of Life

Both physical and psychosocial factors contribute to QoL, a concept that describes a person's subjective perception of multiple life dimensions. The WHO defines QoL as "an individual's perception of their position in life in the context of the culture and value systems in which they

live and in relation to their goals, expectations, standards and concerns" (47). The Center for Disease Control and Prevention states that QoL encompasses both physical and mental well-being as well as social connectedness, the relative significance of which may vary individually, highlighting the complexity of QoL (48).

As a specification of QoL, health-related QoL (HRQoL) incorporates mainly the physical and mental health domains of QoL (48). HRQoL is considered an important outcome of healthcare interventions, as it provides information not only on the health status but also on a person's satisfaction with it (49,50). Especially in advancing age, where a full recovery from illness is not always possible, HRQoL takes precedence (50- 52). Self-reported outcomes such as HRQoL allow individuals to decide which aspects they include in their ratings, meaning that the rating incorporates a bandwidth of individual circumstances and expectations that objective measures cannot uncover (50,53,54). Thus, despite being subject to recall bias or social desirability, self-report provides valuable information (55,56). As Upton and Upton (2015, p.85) state, "HRQoL refers to the cognitive appraisal which a patient makes about the impact their health has on their daily life" (57). Consequently, QoL is also linked with personality and coping, defining how a person reacts to health events and adjusts their expectations (58, 59). Despite this individual character, HRQoL is closely related with actual physical and mental health, and is oftentimes diminished in persons with multimorbidity (56,60,61). For example, patients with stroke or epilepsy show reduced QoL due to impairments in daily activities, mobility, cognition and mental health (62,63).

1.2 Medication Nonadherence

Another highly complex and individual health variable is that of medication intake. Despite being the cornerstone in managing illnesses, up to half of older patients do not take their medication as agreed upon with healthcare providers (15,64,65). Even in PD, a disorder with immediate benefits of medication intake, research shows nonadherence rates of up to 67% (66,67). Similar nonadherence rates have been estimated for patients with epilepsy (68) and stroke (69). To address this issue, the WHO declared an urgent need for action to combat nonadherence (65). Adherence is defined as the degree to which patients follow recommendations by their healthcare providers (70). Consequently, *non*adherence to medication describes the degree to which they do not (15,64,71). Nonadherence may result in patients not receiving the full treatment benefit or experience adverse outcomes, resulting in worse health (72). In older patients, nonadherence to medication may result in a higher risk of hospitalization, worse health outcomes, and increased mortality (7374). Older patients with lower adherence further report lower HRQoL (66,67,75,76).

Due to this impact on health and well-being, many studies aimed understand this crucial health behaviour; however, the majority of those are either disease-specific (77-79) or not targeted at the particularities of older patients (80,81). Many intervention studies remain below the authors' expectations, indicating that the complex behaviour of medication intake is not fully understood (49,72,82,83). This is in part because nonadherence is dependent on a multitude of factors (15,64), out of which the WHO has defined five overall dimensions (65):

- Socioeconomic factors; such as socioeconomic status, insurance, and healthcare costs (46,84,85);
- Healthcare system factors; including the availability of healthcare, communication and satisfaction with providers, and patient involvement (46,61,84,85);
- Disease-specific factors; such as side effects or modes of administration, comorbidities, and physical or cognitive impairment (46);
- Therapy-related factors; including side effects, drug interactions, complex dosing regimens, and polypharmacy (84,16);
- Patient factors; including age, gender, education, depressive symptoms, cognition, mood, and physical health (46,61).

The often-employed classification of nonadherence into intentional and unintentional further suggests motivational aspects (15,71). While a part of nonadherent behaviour can be accounted for by unintentional forgetting, patients may intentionally modify their medication due to defiance, worries, or lack of beliefs in their efficacy (86-89). Although most patients show intentional and unintentional nonadherence simultaneously (86,89-91), both may be rooted in differing factors and should be differentially identified for tailored support (89,90).

In addition to this complexity, another reason why study results may diverge are different measurements. Nonadherence can be measured objectively and subjectively, with both having advantages and disadvantages (92,95). Objective measures such as pill counting, prescription data, or drug concentrations in the blood may be difficult to implement outside of funded clinical studies (72,92). While objective measures are considered to be free of report bias, patients must be informed that their medication intake will be monitored, potentially reflecting improved adhere for the duration of the study only. Additionally, some objective measures cannot assess whether the medication was ingested, nor can they detect different types of nonadherence. Like with HRQoL, using self-reported measures to assess nonadherence provides a richer understanding of a person's underlying reasons and individual circumstances (92). Monnette et al. (2018) conclude that self-report measures show moderate to high correlation with objective measures (93). Thus, when using validated scales, self-report measures are recommended due to their economic application while still obtaining useful information (72,94).

Therefore, a vast array of self-report measures have been developed to measure nonadherence. In their review, Lam and Fresco (2015) report the most commonly used questionnaires, all of which have advantages and disadvantages (92). However, none of the available instruments encompass all the important domains or cover all types of nonadherent behaviour (92,94-96). Out of the available measurement instruments, the Stendal Adherence to Medication Score (SAMS) has been developed as an extension of the Morisky Medication Adherence Scale (MMAS) with more nuanced Likert scale items (97). It was constructed by an expert panel and incorporates items analogous to previously validated questionnaires, such as items about medication knowledge in accordance with Rottlaender et al. (2007), as well as the Morisky scales (97-99). Additional items were added by the expert panel of patients and healthcare providers (100). The final SAMS version has since been used in a multitude of studies (91,101-109). In addition to providing an overall score, the SAMS provides a classification into three nonadherence types: *forgetting* to take medication, *missing knowledge* about medication, and intentional *modification* of medication (91,96,100,106). While *Missing Knowledge* refers to the knowledge about purpose, time, and mode of intake of each medication, the *Forgetting* scale inquires about the unintentional omission of mediation. In contrast, *Modification* describes the intentional modification of dosage or timepoint up to omission of intake (91,100,106). While the SAMS manual provides guidance on distribution-based cut-offs for adherence thresholds, the authors recommend these to be calculated for every patient population if considered useful for the respective scientific aim; otherwise, the SAMS score and its sub-types can be utilized as continuous scores (100).

Generally, the use of cut-offs to classify patients into adherent vs nonadherent is highly debated. Since nonadherence concerns multiple medications with different timepoints, frequencies, and modes of administration, following an all-or-nothing principle is of little use

(72). Cut-offs mainly serve a scientific purpose to determine prevalence rates, but they are oftentimes arbitrary and have limited clinical relevance (72,83,92,110,111).

As a result, there is no golden standard when measuring adherence (72,93). Oftentimes a clinical endpoint is used to determine the adherence threshold at which the endpoint changes (72,111). For some disorders, these endpoints are readily available, such as blood glucose level in diabetes or frequency of seizures in epilepsy (79,110). However, in the face of multimorbidity, choosing a singular disease-specific endpoint is not feasible (74,112). Instead, an overarching end-point such as HRQoL may be more useful (49,76,113-115).

In summary, advancing age may lead to unique challenges such as functional and cognitive decline or multimorbidity (112), resulting in complex medication regimes that culminate in high rates of nonadherence (46,72). Due to its impact of high healthcare costs and utilization as well as lower HRQoL, worse health outcomes and functional decline, this complex health behaviour must be better understood to facilitate effective interventions in the growing population of older adults with neurological disorders.

1.3 Aim of the Dissertation

With advancing age, patients face unique circumstances such as multimorbidity, polypharmacy, cognitive decline, and psychosocial changes, all of which pose a challenge to medication adherence (1,5,46). Especially in older adults with neurological disorders, the correct intake of medication is crucial as disease management depends on pharmacotherapy. Therefore, their particular situation must be differentially assessed from those of younger patients.

To understand the situation of older adults with regard to medication nonadherence, comprehensive data were collected from patients at the neurological department of Jena University Hospital, Germany (109,116). In addition to sociodemographic information, this data includes medical information such as diagnoses, healthcare usage and satisfaction, cognition, mobility, and depressive symptoms, as well as personality, nonadherence, and HRQoL. From the wide variety of potential research questions that this dataset invites, this dissertation presents three main topics:

First, despite research aiming to identify predictors of nonadherence, interventions to improve adherence behaviour remain below expectations (49). This may be because the majority of this research is disease-specific or not tailored to advancing age, and thus cannot unveil the nonadherence patterns of older adults with multimorbidity. Therefore, publication I identified the variables associated with medication nonadherence in older adults with neurological disorders. A secondary aim was to confirm the link between nonadherence and depressive symptoms (109).

Next, based on the results of publication I, publication II assessed which depressive symptoms in particular are linked to medication nonadherence (117), as these have been identified as key factors in previous research (46). Of note, unlike previous studies focusing on overall sum scores, publication II provides a unique insight into which of the many depressive symptoms in particular influence nonadherence by taking individual symptoms into account (39).

Lastly, as nonadherence is linked with poorer health outcomes and adverse health events (72), it has been shown to influence HRQoL. In previous research, HRQoL has therefore been used as a clinical endpoint to assess the effectiveness of nonadherence interventions (49). However, as the relationship between nonadherence and HRQoL remains unclear, it cannot yet be determined whether interventions remain ineffective due to an inefficient composition, or because HRQoL is not suited as an endpoint to measure their effectiveness. Therefore, publication III assessed the relation between nonadherence and HRQoL in this patient group of older adults with neurological disorders (105).

2 Discussion

In the *NeuGerAdh* (Neuro-Geriatric Adherence) study funded by the Bundesministerium für Bildung und Forschung (grant 01GY1804, DRKS registration DRKS00016774), data was collected from older patients with neurological diagnoses at Jena University Hospital between 2019 and 2020 (116,118). The study was approved by the local ethics committee of Jena University Hospital (approval-number 5290-10/17). From the plethora of resulting research questions, the aim of the presented publications was to answer three: First, which factors are associated with nonadherence in older adults with neurological disorders? Second, which depressive symptoms in particular impact nonadherence? Finally, we sought to determine whether there is a relationship between nonadherence and HRQoL, as this has implications for both clinical practice and scientific research.

Overall, we collected data on N = 910 patients with epilepsy as well as movement, cerebrovascular, neuromuscular, and miscellaneous neurological disorders. All patients received a comprehensive assessment including many of the above-mentioned influencing factors of nonadherence: cognition, mobility, depressive symptoms according to Beck's Depression Inventory II (BDI) (119), healthcare service use and satisfaction, personality, HRQoL as indicated by the SF-36 (120), and nonadherence measured using the SAMS (100). The study cohort is described in detail in the respective data paper (118) as well as in the included publications.

2.1 Factors associated with Nonadherence

The first publication (109) presents the factors associated with nonadherence in older adults with neurological disorders. Using Principal Component Analysis, three nonadherence sub-types, *forgetting* to take medication, *missing knowledge* about medication, and *intentional modification* of medication, were extracted (91,100,106). 192 patients reported to be fully adherent while the remaining patients exhibited varying degrees of nonadherence based on the SAMS sum score. When classifying patients into the three nonadherence groups based on their highest score within the sub-types, 46.2% of patients scored highest in the *forgetting* scale, followed by 29% with *missing knowledge* and 24.8% for *modification*, although the majority of the included patients showed nonadherence in all three sub-types (88,90).

Using linear regression, we determined the factors associated with higher levels of overall nonadherence as well as its sub-types. Higher levels of nonadherence were associated with male gender, higher BDI score, lower satisfaction with healthcare, and worse mobility. PD in comparison to the other diagnoses was also identified as a contributor to nonadherence. Furthermore, education, personality (especially neuroticism), and cognition remained in the

model after elastic net regularization despite not reaching statistical significance, indicating that they aid in explaining variance and thus contribute to nonadherence.

These results are in line with previous research highlighting the impact of depressive symptoms, cognitive deficits, worse physical health and, to a lesser degree, personality, on nonadherence (46,61,84,121). Despite the need to consider overarching factors instead of focusing solely on single diagnoses, certain illnesses may bring with them medication specifications that may influence the WHO criteria *disease-specific* and *therapy-related* factors. Especially in PD, medication regimes become highly complex, including frequent changes and varying dosages throughout a single day (122-124), thus leading to higher rates of nonadherence.

With regard to gender differences, the research evidence is inconclusive. While some studies identified gender differences, others did not (46,125). Since both life expectancy and the probability of obtaining certain conditions differ between men and women, a complex interplay between these factors and nonadherence may emerge (1,46,126,127). Likewise, certain personality types may be more common in women than men, further influencing health behaviour and nonadherence in particular (128).

Looking at the SAMS sub-types, a varying picture emerges. While *modification* is mainly reduced by a higher number of medications per day and the personality trait openness, *missing knowledge* is increased by a higher number of medications. This contradiction already highlights the need to differentiate between different reasons for nonadherence, as the same risk factors may increase or decrease it for different persons. It is reasonable that polypharmacy leads to difficulties with understanding the varying medications and time-points, and most of the previous literature confirms the detrimental effect of polypharmacy on adherence (16,46,82,124). However, *modification* refers to intentional changes in dosage or time-point, thus as polypharmacy increases, it seems plausible that patients no longer dare modify their medication due to fear of adverse effects. *Missing knowledge* is additionally associated with male gender and worse cognition. In contrast, *forgetting* is not associated with cognition, indicating that its often-cited effect on nonadherence is not due to simple forgetting but is instead rooted in a lack of understanding of the medication regime (123,124,129). Indeed, many studies on improving health behaviour highlight the need of habit building to fight forgetting, indicating that cognition itself plays a minor role (49,83). Of note, in the present study, patients with severe cognitive impairment were excluded. Thus, it is probable that above a certain level of cognitive impairment, forgetting to take medication is indeed linked with a poor cognitive status (130,131).

Instead of cognition, factors contributing to *forgetting* in our data were male gender, education, living with a partner, use of non-medical treatment, and low satisfaction with healthcare. These results may indicate that forgetting to take medication can be related to leading a comparably busy lifestyle with frequent routine changes, such as going to therapy or spending

time with the partner. Likewise, education and low satisfaction with healthcare may impact the importance allocated to the respective prescriptions, leading to more frequent omissions.

2.2 Depressive Symptoms and Nonadherence

Of note, in publication I, depressive symptoms emerged as a significant contributor to nonadherence for the SAMS sum score and all its sub-types. This is mirrored in a vast body of previous research (46,84). Depressive symptomology is associated with diminished motivation and self-efficacy, a lack of interest, and hopelessness, all of which may contribute to medication nonadherence (43,132-136). As Stewart et al. (2023) conclude, nonadherence depends on both motivation and ability to take medication (72). While factors such as cognition, physical impairments, and polypharmacy may reduce the ability to take medication correctly, depressive symptomology may tamper with the motivational aspect. Acharya and Agius (2018) propose that depressive symptomology and nonadherence form a vicious circle, as depressive symptoms occur more frequently in persons with multimorbidity, then leading to nonadherence which in turn results in even worse health (132). Especially anhedonia and apathy, the authors conclude, may become so severe that patients no longer care about the improvement of their health. Notably, the patients included in our study on average displayed subthreshold depressive symptomology; still, even in our subclinical patient group, depressive symptoms delivered the strongest effect on nonadherence (34). This invites an in-depth assessment of the association between depressive symptomology and nonadherence as performed in publication II.

Most studies utilize a questionnaire with an overall sum score to assess depressive symptomology, and find that higher sum scores are associated with higher levels of nonadherence. However, sum scores cannot provide information on the particular symptoms that cause this effect (39,40). This is detrimental, as depressive symptomology is highly complex and contains both somatic and mental symptoms which may differ in their impact. Therefore, in publication II (117), we used network (137) and regression analyses using individual depressive symptoms as assessed by the BDI (119) to understand which symptoms in particular are linked with nonadherence. Our results shed light on the previously hypothesized link between depressive symptoms and nonadherence by revealing that *loss of interest* and *difficulty with concentration* serve as hubs connecting other affective and somatic symptoms with nonadherence. Likewise, *fatigue*, *problems with decision making*, *suicidal thoughts*, and *worthlessness* were identified as relevant symptoms. These suggest that both an overall lack of interest in one's health, perhaps related to worthlessness and a weakened will to live, as well as an inability to look after oneself due to fatigue and cognitive deficits contribute to nonadherence. These results are of high importance, as they uncover different pathways through which depressive symptoms are associated with nonadherence.

Many previous studies link nonadherence with a lack of motivation and self-efficacy (133,135,136). These suggestions are congruent with our results and the identification of *loss of interest*, *worthlessness* and *suicidal thoughts* as connecting symptoms, corresponding to a reduced motivation to look after one's own health. In addition, our results suggest a second pathway not solely rooted in a lack of motivation, but a potential lack of ability to perform health behaviours (72) due to fatigue and a cognitive overload. In line with our results, Straka et al. (2019) reported associations between nonadherence and fatigue, cognition, memory, and mood in PD patients (124). To further substantiate these results, larger sample sizes and longitudinal data are needed to understand the exact interplay and direction of effects between depressive symptoms and nonadherence. Still, our analysis highlights the need to differentially assess the influence of the vast variety of depressive symptoms on health behaviour to understand their mechanisms of impact. This knowledge is imperative to effectively target them in clinical interventions and improve patients' overall QoL.

2.3 Nonadherence and Health-Related Quality of Life

In older adults with neurological diseases, physical health is dependent on effective pharmacotherapy. Therefore, nonadherence not only affects health but also HRQoL, as its impact exceeds health by secondarily hindering social participation, independence, and daily functioning (138). Therefore, publication III (105) aimed to answer the question whether and how nonadherence is linked to HRQoL. Additionally, in lieu of a disease-specific endpoint which are not readily available in patients with multimorbidity, HRQoL is often used as an endpoint in clinical studies to assess the improvement of nonadherence. However, as results on the association between nonadherence and HRQoL vary, with publication III we furthermore aimed to shed light on whether HRQoL is a suitable endpoint for studies targeting medication nonadherence.

In their review, Cross et al. (2020) describe 14 studies on nonadherence using HRQoL as an outcome with mixed results (49). Some studies report a link between HRQoL and nonadherence (113), especially cross-sectionally (75-78). However, intervention studies show little to no effect of nonadherence interventions on HRQoL (114,115). One reason why intervention studies continue to underperform is the complex nature of nonadherence, which requires several life domains to be addressed individually (49,83). Additionally, like the content of the intervention, the endpoint to assess its effect must also be appropriate. Therefore, it is important to understand if HRQoL is a suitable endpoint to detect changes in nonadherence. Notably, some studies examining the association between nonadherence and HRQoL yielded disparate findings, indicating that the link is only evident for the psychological/emotional subscale of HRQoL (76) or disappears entirely when controlling for covariates such as depressive

symptoms or mobility (75). Thus, the association between nonadherence and HRQoL requires a deeper analysis.

In our study, we found HRQoL to be an inappropriate variable for measuring cut-off points for nonadherence (105). Using Receiver operating characteristics (ROC) and Area Under Curve (AUC), we aimed to classify patients into adherent vs nonadherent based on the point at which the impact of their SAMS score on HRQoL was maximized. However, the cut-off scores exhibited considerable variability, rendering the identification of a cut-off based on the association between HRQoL and SAMS untenable. Correlations between nonadherence (SAMS) and the HRQoL were statistically significant ($p < .001$) but weak, showing overall stronger correlations with mental than physical health (76). After adjusting for covariates, in a Multivariate Analysis of Covariance (MANCOVA), the association between the SAMS and HRQoL was nullified, suggesting that there is no direct association between them. Rather, it seems that other variables carry their association. In line with other research (36,46,117,132), depressive symptoms carried the largest effect size in our MANCOVA. In a subsequent analysis, we examined the link between HRQoL and nonadherence in greater detail (139). Using regression and network analyses, we again found a weak association between the SAMS and the mental - but not the physical - component scale of the SF-36. This association was again nullified when covariates were included, particularly depressive symptoms. Of note, while these associations are only cross-sectional and do not allow for causal attributions, they suggest that HRQoL and nonadherence are not directly associated but instead simultaneously influenced by common underlying factors, such as depressive symptoms. The link both between depressive symptoms and nonadherence as well as between depressive symptoms and lower HRQoL is well-documented, making them a plausible connection between the latter two (36,46,84,140).

In addition, another reason why the relationship between nonadherence and HRQoL is not straightforward is because both are individual constructs that fluctuate within and between the included patients. Likewise, both are influenced by a multitude of other variables (15,50,54,55). Consequently, the relationship between nonadherence and HRQoL is not necessarily consistent across all patients. Divergence of associations and opposing directions of effects may negate any significant effect when averaging across patients. Likewise, nonadherence is only one of many health behaviours and circumstances that contribute to HRQoL (56,138). Researchers should therefore be cautious when using HRQoL as an end-point for clinical interventions and instead opt for a person-centered approach to detect the underlying individual patterns.

2.4 Limitations

While the presented publications provide new insights into the important health behaviour of medication nonadherence and its associated factors, they are not free of limitations.

One limitation is the use of cross-sectional data, which restricts the informative value of the analyses. Longitudinal analyses are needed to infer causality. Of note, the research team did collect HRQoL data after 12 months to assess whether baseline adherence level predicts future QoL, but found no significant associations (141). This can be rooted both in the indirect association between HRQoL and nonadherence described in publication III, and in the general fluctuation of HRQoL across time (142). Due to its personal nature and multidimensionality, HRQoL may oscillate idiosyncratically over a period of time. Therefore, the frequency of follow-up assessments must be carefully chosen. Future studies should therefore assess both HRQoL and nonadherence more frequently to be able to map out changes in nonadherence and HRQoL in detail (55,143).

Likewise, while a multitude of variables that can be considered important for medication nonadherence (46) were included in the collected dataset, we were unable to consider all variables due to the otherwise extensive length of the questionnaires. The data collection had to be constricted to ensure its applicability within the patient population of chronicall ill older adults. For a more encompassing understanding of the relation between nonadherence, depressive symptoms and HRQoL, their association should be re-assessed under consideration of other covariates.

Additionally, the single-center data collection may restrict its generalizability. Likewise, the SAMS is only one way of many measures of nonadherence, other measures may yield differing results. We purposely selected a self-report measure to assess nonadherence to detect different types of nonadherence. Both objective and subjective measures provide useful information depending on the underlying research question (72,92-95).

Of note, while we employed a disease-unspecific approach to address multimorbidity in advancing age, it is still important to consider nonadherence on an individual level (72). In clinical practice, it is crucial to provide tailored support to individual patients. However, this requires multiple assessments for each person, making the study participation time-consuming and exhausting for older patients. Thus, while a personalized approach is preferable, it is not always feasible to implement. Therefore, the identification of disease-unspecific factors in older patients with neurological disorders may already aid as a first step in understanding nonadherence and guiding interventions in an effective manner.

2.5 Conclusion and future directions

As a summary, older adults with neurological illnesses face several unique challenges concerning physical health, mental health, and social environment. Thus, their health, health behaviour, and HRQoL must be understood in detail. As many older patients suffer from multimorbidity, disease-specific approaches are not useful to facilitate a clinically important impact on patients' well-being. As the treatment of most illnesses is rooted in pharmacotherapy, addressing medication nonadherence is particularly relevant in this patient group, yet nonadherence rates remain high. To further the understanding of circumstances contributing to self-reported nonadherence in older patients with neurological disorders, we identified various influential factors depending on the sub-type of nonadherence, indicating that a differentiated view of nonadherence is required. Cognition, mobility, satisfaction with healthcare, and depressive symptomology were the main factors associated with nonadherence. Both in clinical practice as well as intervention studies, these influential factors should be targeted to provide effective support to patients in their medication intake.

Especially depressive symptoms also appear to drive the indirect association between nonadherence and HRQoL. This indicates that in future intervention studies aimed at nonadherence of older adults, not only should the identified factors be addressed in a tailored manner, but special attention should be paid to the choice of intervention endpoint. To assess the effectiveness of an intervention, its endpoint should be directly associated with nonadherent behaviour. While nonadherence directly influences health, its association with HRQoL is not straightforward and appears to be delivered by common underlying variables such as depressive symptomology. Likewise, temporal aspects in terms of individual fluctuations of both HRQoL and nonadherence should be taken into consideration. In a project starting at University Hospital Halle in August 2024, we thus plan to inspect the temporal stability of important self-report measures such as self-rated health, subjective age, and QoL in older adults.

Our research further extends the previously postulated link between depressive symptoms and nonadherence by proposing that especially loss of interest and concentration difficulties tie affective and somatic depressive symptoms to nonadherence. This approach shows that facilitating a more symptom-specific instead of the often-employed disease-specific approach is essential to provide the best care for older adults, as they are faced with a multi-faceted disease burden. In a related follow-up project, we therefore aim to understand not only medication nonadherence in particular but overall self-management for overarching geriatric syndromes instead of singular illnesses (17). The present results as well as their extension by using symptom-driven, disease-unspecific approaches to nonadherence may aid in both understanding and improving the crucial health behaviour of nonadherence in a patient population whose health depends on the correct intake of their medication.

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4 Theses

1) Using a self-report instrument to detect underlying reasons for nonadherence, three sub-types of nonadherence were identified in older adults with neurological disorders. These can be described as *Forgetting* to take medication, *Missing Knowledge* about medication, and intentional *Modification* of medication.

2) As older adults face unique age-related and psychosocial challenges, their needs must be differentially understood. Confirming previous studies, depressive symptomology has been identified as a key influencing factor across overall and all sub-types of nonadherence.

3) The three sub-types of nonadherence are differentially influenced by clinical factors, while all are related to depressive symptoms. Overall nonadherence is significantly associated with gender, underlying diagnosis, satisfaction with healthcare, and mobility, whereas *Modification* of medication is significantly linked with polypharmacy and personality. Likewise, *Missing Knowledge* about medication is related to polypharmacy as well as age, gender, education, and low cognition. Lastly, *Forgetting* to take medication is associated with diagnosis, gender, polypharmacy, education and satisfaction with healthcare.

4) Sum scores of depressive symptoms cannot reflect their multitude of included symptoms. Using a symptom-focused approach to assess the influence of individual depressive symptoms, Loss of Interest and Problems with Concentration serve as hubs between nonadherence and other affective and somatic depressive symptoms.

5) Health-Related Quality of Life (HRQoL) is often used as an endpoint in clinical studies addressing nonadherence. However, our data confirm that HRQoL is not directly linked with nonadherence after controlling for health-related and psychosocial variables.

6) Depressive symptomology is a common underlying factor influencing both nonadherence and Health-Related Quality of Life (HRQoL). Health and Cognition further contribute to their connection. These associations must be considered when planning clinical trials.

Publications

Publication I

Schönenberg, A., Mühlhammer, H. M., Lehmann, T., & Prell, T. (2022). Adherence to Medication in Neurogeriatric Patients: Insights from the NeuroGerAd Study. *Journal of Clinical Medicine*, 11(18), 5353. https://doi.org/10.3390/jcm11185353

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Conceptualization, T.P.; formal analysis, T.P., T.L. and **A.S.**; investigation, **A.S.** and H.M.M.; resources, T.P.; data curation, T.P., T.L. and **A.S.**; writing—original draft preparation, **A.S.**; writing—review and editing, T.P. and H.M.M.; funding, T.P.
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A.S. data collection and curation, analysis, writing: original draft. K.G.H. data analysis, writing: review and editing. T.P. study conception and design, writing: review and editing.
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Author contributions

Design of the study: TP. Collection of data: **AS** and HMM. Analysis: TP, TL. Writing of the paper: TP and HMM. Writing—editing and revision: **AS**. All authors read and approved the final manuscript.
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Appendix

Publication I

Supplementary Materials for Publication I

Publication II

Supplementary Materials for Publication II

Publication III

Supplementary Materials for Publication III

Declaration

Acknowledgement

Journal of
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MDPI

Article

Adherence to Medication in Neurogeriatric Patients: Insights from the NeuroGerAd Study

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Abstract: Nonadherence to medication is associated with increased morbidity, mortality, and healthcare costs, especially in older adults with higher chances of multimorbidity. However, comprehensive data on factors influencing adherence in this patient group are rare. Thus, data for 910 patients were acquired, including demographic data, nonadherence (Stendal Adherence to Medication), depression (Beck Depression Inventory), cognition (Montreal Cognitive Assessment), personality (Big Five Inventory), satisfaction with healthcare (Health Care Climate Questionnaire), quality of life (36-item Short Form Survey), mobility, diagnoses, and medication. Elastic net regularization was used to analyze the predictors of adherence. Principal component and general estimation equations were calculated to analyze the underlying patterns of adherence. Only 21.1% of patients were fully adherent. Nonadherence was associated with male gender, higher number of medications, diagnosis, depression, poor patient–physician relationship, personality, impaired cognition, and impaired mobility. Nonadherence was classified into three sub-factors: forgetting (46.2%), missing knowledge about medication (29%), and intentional modification of medication (24.8%). While depression exerted the strongest influence on modification, a high number of medications was associated with missing knowledge. The different patterns of nonadherence (i.e., modification, missing knowledge, and forgetting) are influenced differently by clinical factors, indicating that specific approaches are needed for interventions targeting adherence.

Keywords: depression; older adults; medication adherence; quality of life; multimorbidity

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1. Introduction

The treatment of chronic disorders commonly includes the long-term use of pharmacotherapy, and older adults especially are often expected to adhere to complex drug regimes [1]. Adherence is described as the extent to which a person's behavior corresponds to the recommendations from their healthcare providers [2]. However, many older adults either cannot, or do not want to, take medications as prescribed [3]. This nonadherence to medication contributes to adverse drug events, increased length of stay and readmissions to hospitals, higher healthcare costs, lower quality of life (QoL), and poorer health outcomes [2,4–6]. In general, nonadherence may be intentional, i.e., when a patient purposefully decides not to follow the recommended treatment, or unintentional, meaning that a patient cannot follow the recommendations, for example due to cognitive or physical impairments [7]. Several factors are known to contribute to nonadherence, such as depression and cognition [8]. While multiple studies have been conducted on the predictors of nonadherence in specific illnesses (e.g., hypertension, COPD, asthma, HIV, etc.), little is known about the mechanisms of nonadherence in elderly patients with neurological disorders [9], despite the fact that over 20% of adults aged 60 and older have a mental or neurological disorder [10]. As nonadherence poses problems for both patients and healthcare systems, it is essential to investigate further the occurrence of medication nonadherence and associated factors in this growing cohort.

We collected comprehensive data on adherence and its modifying factors from geriatric patients with neurological disorders. Additionally, we sought to understand whether adherence is influenced not only by known predictors (e.g., depression), but also by the underlying neurological disease itself [11]. Furthermore, we aimed to determine whether different patterns of nonadherence (i.e., intentional and unintentional) are influenced differently by clinical parameters.

2. Materials and Methods

2.1. Settings and Participants

This study was registered in the German Clinical Trials Register (registration number: DRKS00016774; registered on 2 February 2019), and the study protocol was published in advance [11]. The study was approved by the local ethics committee (approval number: 5290-10/17) of Jena University Hospital. All patients provided written informed consent. From February 2019 to March 2020, elderly patients with neurological disorders received a comprehensive geriatric assessment during their stay in the Department of Neurology. This study reports the results of the cross-sectional assessments.

We included patients (age > 60 with multimorbidity or age > 70) with a common neurological disorder (e.g., cerebrovascular disorders, movement disorders, epilepsy, and neuromuscular or peripheral neurological disorders). Patients with dementia, acute psychotic symptoms, or delirium were excluded. We screened all patients in the Department of Neurology for eligibility. Among the 2021 patients aged 60 years or older admitted during data collection, 113 were missed for timing reasons. Of the remaining 1908 patients, 997 were excluded because they did not meet the inclusion criteria, declined to participate, or were prevented from participating due to other medical reasons (e.g., unconsciousness or inability to speak). In total, 995 patients were eligible, of which 910 patients participated in the study. Thus, data for 910 patients were analyzed. A description of the screening procedure is provided in Supplementary Materials Figure S1.

Individual deviations from the study protocol needed to be made due to the onset of COVID-19 in the last three months of data collection. This resulted in a drastic reduction in the ward occupancy rate and the desired sample size of 250 subjects per neurological disorder was not reached. This limits the significance of the findings, especially for patients with epilepsy; thus, no conclusive statements can be made here. Additionally, we included patients younger than 60 years with multimorbidity (n = 139, aged between 55 and 59 years).

2.2. Assessments

The paper reports cross-sectional results on overarching factors influencing nonadherence in our population of older patients. Therefore, the primary outcome variable was nonadherence according to the Stendal Adherence to Medication Score (SAMS) [12]. Briefly, the SAMS is a self-report questionnaire consisting of 18 items, scores for which are totaled to produce a cumulative adherence score, with 0 indicating complete adherence and 72 complete nonadherence. The items are rated on a 5-point Likert scale. Scores for different sub-factors can be calculated, namely, for *forgetting* to take medication, intentional *modification* of medication, and *missing knowledge* about medication. *Modification* refers to the adjustment of medication (dosage, time points) without consulting a doctor, while *missing knowledge* represents patients who were unaware of the purpose of their medication and/or dosages. The factor *forgetfulness* includes patients who unintentionally forget to take their medication [12–14].

Patients' cognitive ability was tested using the Montreal Cognitive Assessment (MoCA) [15]. The MoCA result, along with the clinical impression during the face-to-face screening procedure, allowed us to decide whether the patient was able to provide valid self-assessments and could be included or not.

The following variables were recorded from the patients' medical records: age, gender, main neurological diagnosis, and medication regimen at admission and discharge.

The following variables were recorded via self-report: marital status (single, divorced, widowed, or married); living condition (alone or not alone); level of education (high: German abitur or university; medium: German Realschule or general certificate of secondary education; or low: German Hauptschule or no school); employment status; number of medications per day; medical diagnoses; Beck Depression Inventory (BDI) score [16]; Big Five Inventory (BFI) scores [17]; Health Care Climate Questionnaire (HCCQ) scores [18]; Stendal Adherence to Medication Score (SAMS) [12] and results of the 36-item Short Form Survey (SF-36) to measure QoL [19].

The following variables were recorded in face-to-face assessments by trained study staff: changes in medications in the last six months (yes/no); Timed Up and Go test (TuG) [20], if medically possible; MoCA; use of walking aids; use of visual aids; use of other aids; regular physiotherapy (yes/no); occupational therapy (yes/no); speech therapy (yes/no); and frequency of neurologist/GP consultations. See Supplementary Materials Table S1 for details of the questionnaires.

2.3. Statistical Analysis

Descriptive statistics were used to describe the study population. Mean and standard deviation (SD) are reported for continuous variables, and categorical variables are presented as absolute and relative frequencies. Missing data were treated according to the pairwise deletion process [21].

As a first step, linear regression with elastic net regularization was performed to determine the predictors of the total SAMS score [22]. Elastic net regularization performs variable selection by shrinking the parameters toward zero and attenuating overfitting, a well-known problem when applying regression models [23], and leads to interpretable, parsimonious models. Tenfold cross validation was performed to choose the model with the lowest mean cross-validated error. Within the elastic net algorithm, variables remain in the model if the prediction error averaged over the cross-validation samples is reduced. In contrast to ordinary least squares regression, or least absolute shrinkage and selection operator regularization, the elastic net algorithm performs well with highly correlated variables, either including all variables with similar regression coefficients or excluding all variables from the best model. Regression coefficients of the model with 95% confidence intervals (CIs) were reported. Elastic net regularization was performed using the package glmnet [24] in R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

A principal component analysis (PCA) with varimax rotation was performed to assess the underlying structure of the adherence (SAMS) data and to confirm the three factors found in previous literature [12,13,25].

Subsequently, to understand the predictors of adherence in more detail, generalized estimating equations (GEEs) [26] were developed to assess the influence of the factors (gender, education, living situation, diagnosis group, and BFI) and covariates (age, medication intensity, TUG, and MoCA) on the different SAMS sub-factors *modification*, *missing knowledge*, and *forgetting*. Since three-factor scores for each patient were evaluated in one model, the correlation of these measurements required to be considered; therefore, GEE models for correlated data were fitted following the steps described below [27]:

(i) Fit a standard regression model assuming that observations are independent
(ii) Take the residuals from the regression and use them to estimate the parameters that quantify the correlation between observations in the same individual.
(iii) Refit the regression model using a modified algorithm incorporating a matrix that reflects the magnitude of the correlation estimated in step ii.
(iv) Keep alternating between steps ii and iii until the estimates stabilize.

An exchangeable covariance structure was used assuming that every observation (i.e., factor score) of a patient was equally correlated with the other factor scores of that patient. Robust standard errors were calculated to ensure consistent inferences from a GEE model even if the prespecified covariance structure was inappropriate.

All statistical tests were applied two-sided at a significance level of 0.05.

(iv). Keep alternating between steps ii and iii until the estimates stabilize.

An exchangeable covariance structure was used assuming that every observation (i.e., factor score) of a patient was equally correlated with the other factor scores of that patient. Robust standard errors were calculated to ensure consistent inferences from a GEE model even if the prespecified covariance structure was inappropriate.

All statistical tests were applied two-sided at a significance level of 0.05.

3. Results

Nine hundred and ten adults participated in the study, consisting of 389 female and 521 male patients aged 70 ± 8.6 years. The main neurological diagnoses derived from the patients' medical records were movement disorders (n = 303; 33.3%), cerebrovascular disorders (n = 233; 25.6%), neuromuscular and peripheral neurological disorders (n = 168; 18.5%), epilepsy (n = 48; 5.3%) and miscellaneous diagnoses (n = 158; 17.4%). The characteristics of the cohort are summarized in Table 1 and the mean levels for the eight SF-36 subscales are presented in Figure 1, showing that QoL was substantially impaired in our patients compared to the general German population as assessed by the German Health Interview and Examination Survey for Adults [28].

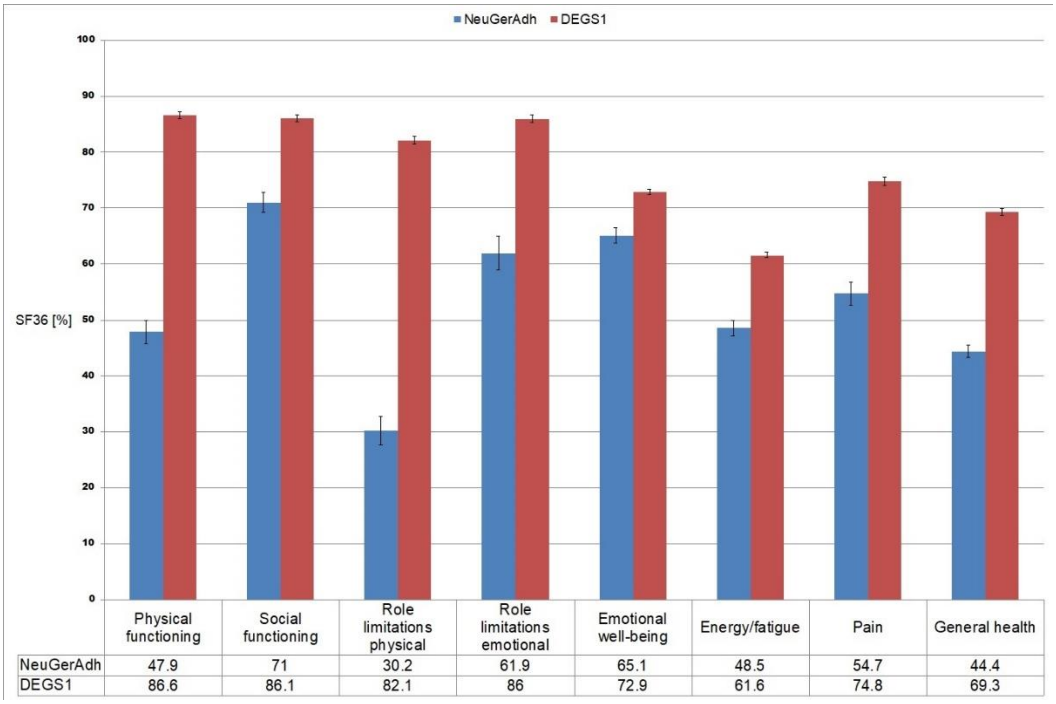

Figure 1. Mean and 95% Confidence intervals from SF-36 domains in comparison with the general German population. Note: NeuGerAdh = Data from the current study; DEGS1 = German Health Interview and Examination Survey for Adults.

Table 1. Clinical and demographical characteristics.

Variable	Value	n	%
Sex	Female	389	42.7
	Male	521	57.3
Marital status	Single, divorced, widowed	277	30.8
	Married	621	69.2
Living situation	Alone	376	41.4
	Not alone	533	58.6
Education	High	325	36.3
	Middle	304	34.2
	Low	265	29.6

The distribution of the SAMS results is given in Figure 2.

Initially, PCA was used to reduce the 18 SAMS items into three factors representing different reasons for nonadherence (see Supplement Table S3 for the item classification). According to our previous research [13], we attributed these three factors to *modifications*, *missing knowledge*, and *forgetfulness*. For every patient with a SAMS > 1 point (n = 608), the regression coefficients for each PCA factor were calculated; the highest value indicated into which group the patient was categorized. 281 (46.2%) belonged to the *forgetting* group, 176 (29.0%) to the *missing knowledge* group, and 151 (24.8%) to the *modification* group.

As an initial step to understand overall adherence, elastic net regularization was applied to determine the predictors for the total SAMS score. Increased adherence was associated with female gender ($p < 0.001$), whereas nonadherence was associated with higher levels of depression ($p < 0.001$), lower HCCQ scores ($p = 0.03$), and impaired mobility ($p = 0.01$) (Table 2).

Table 1. Clinical and demographical characteristics.

Variable	Value	*n*	%
Sex	Female	389	42.7
	Male	521	57.3
Marital status	Single/widowed/divorced	277	30.8
	Married	621	69.2
Living situation	Alone	204	24.1
	Not alone	641	75.9
Education	High	325	36.3
	Middle	306	34.2
	Low	265	29.6
Occupation status	No work	756	84.0
	Working	144	16.0
Diagnosis group	Movement disorder	303	33.3
	Cerebrovascular disorder	233	25.6
	Epilepsy	48	5.3
	Neuromuscular	168	18.5
	Others	158	17.4
Depression according to BDI [16]	No depression	468	51.4
	Minimal depression	187	20.5
	Mild depression	139	15.3
	Moderate depression	61	6.7
	Severe depression	27	3.0
Cognition [29]	Normal (MoCA $\geq$ 23)	536	61.1
	deficits (MoCA < 23)	300	35.9
Mobility (TuG) [20]	1–20 s	558	61.3
	20–30 s	22	2.4
	>30 s	5	0.5
Use of walking aids	Yes	297	32.6
	No	547	60.1
Use of visual aids	Yes	596	65.5
	No	247	27.1
Use of other aids physiotherapy	Yes	221	24.3
	Yes	356	39.1
	No	488	53.6
Occupational therapy	Yes	125	13.7
	No	719	79.0
Speech therapy	Yes	57	6.3
	No	787	92.7
Medication change in the last 6 months [30]	Yes	387	45.9
	No	457	54.1
Medication preparation	Independent	706	77.6
	Needing help	141	16.6
Adherence	Total Adherence (SAMS = 0)	192	21.1
		M	**SD**
Age		70.1	8.6
BDI sum score		9.8	7.6
HCCQ		5.6	1.1
MoCA		22.5	4.4
SAMS		6.3	7.6
TuG duration in seconds		10.5	4.3
Quarterly frequency of consultation with neurologist (or GP if neurologist is not available)		2.1	2.7
Number of medications per day (Range: 20–0)		5.6	3.6

Note: BDI = Beck Depression Inventory, HCCQ = Healthcare Climate Questionnaire, MoCA = Montreal Cognitive Assessment, GP = General Practitioner, SAMS = Stendal Adherence to Medication Score, TuG = Timed Up and Go Test.

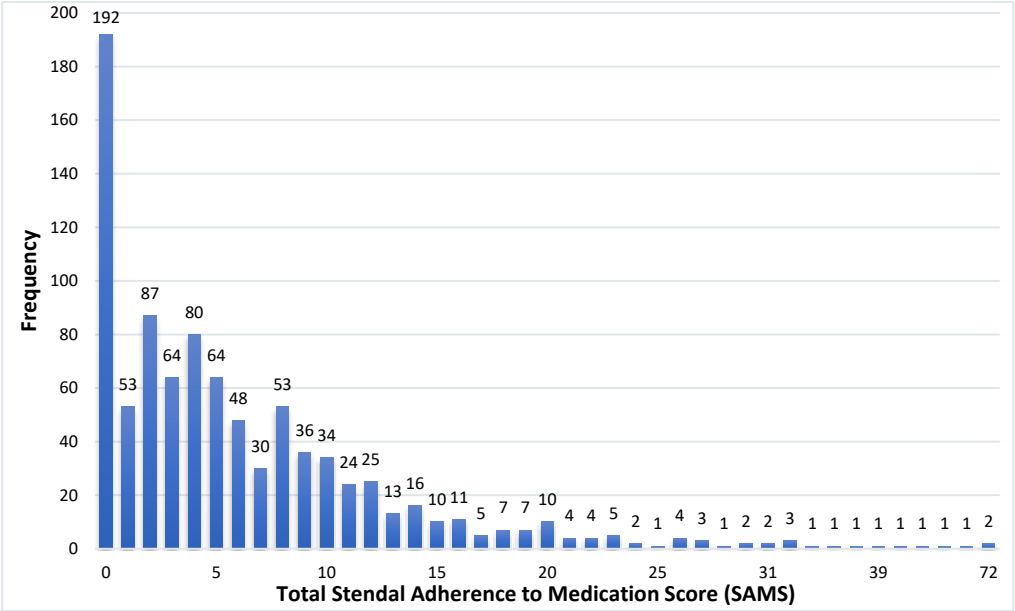

Figure 2. Histogram of the Stendal Adherence to Medication Score (SAMS).

Table 2. Summary of elastic net regularization for SAMS and SAMS factors.

Input Variables	SAMS Total		Modification		Missing Knowledge		Forgetting	
	Coeffic.	*p*	Coeffic.	*p*	Coeffic.	*p*	Coeffic.	*p*
Age			−0.01	0.24	0.01	0.02		
Gender: female	−1.85	<0.001			−0.16	0.03	−0.18	0.04
Education:								
Middle		0.56			−0.05	0.58		
Low	−0.35				0.17	0.07	−0.21	0.03
Living: not alone	0.56	0.40					0.24	0.02
Number of medications/day			−0.04	<0.001	0.05	<0.001	0.01	0.21
Diagnosis group:								
Cerebrovascular *								
Epilepsy *	−1.09	0.42	−0.27	0.19	0.19	0.28		
Neuromuscular *	−1.23	0.09	0.12	0.26	−0.10	0.29	−0.25	0.01
Other *	−1.28	0.09						
BDI	0.31	<0.001	0.04	<0.001	0.01	0.01	0.01	0.03
HCCQ	−0.57	0.03	−0.04	0.30			−0.07	0.09
BFI								
Conscientiousness +								
Neuroticism +	−1.27	0.17						
Openness +			−0.34	0.02				
Agreeableness +	0.83	0.44						
MoCA	−0.07	0.50	0.02	0.33	−0.07	<0.001		
TuG	0.13	0.05	0.01	0.19	0.01	0.14		
Use of non-medical treatment	0.18	0.76					0.18	0.04
Change of medication in last 6 months					0.07	0.38		

* in reference to Parkinson's disease, + in reference to extraversion. Note: cells are left blank if the respective variable was no longer included in the final model after variable selection via elastic net regularization. SAMS: Stendal Adherence to Medication Score, BDI II: Beck Depression Inventory II, HCCQ: Health Care Climate Questionnaire, BFI: Big Five Inventory, MoCA: Montreal Cognitive Assessment, TuG: Timed Up and Go test.

To understand the predictors of adherence in more detail, additional models were calculated to determine the predictors of the SAMS sub-factors (Table 2). Our analyses revealed that *modification* of medication was significantly increased by depression ($p < 0.001$),

but reduced by a higher number of daily medications ($p < 0.001$) and neurotic personality traits ($p = 0.02$). *Forgetting* to take medication was enhanced by living with a partner ($p = 0.02$), depressive symptoms ($p = 0.03$) and additional use of non-medical treatment ($p = 0.04$). In contrast, female gender ($p = 0.04$), low education ($p = 0.03$) and a neuromuscular disorder as main diagnosis ($p = 0.01$) decreased the probability of *forgetting* to take medication. Finally, *missing knowledge* was associated with higher age ($p = 0.01$), male gender ($p = 0.03$), worse cognitive performance ($p < 0.001$), higher levels of depressive symptoms ($p = 0.01$) and an increasing number of daily medications ($p < 0.001$).

Lastly, as depression is a known predictor of nonadherence and was related to all SAMS factors in our analysis, we aimed to answer exactly how the different SAMS factors are influenced by depression using a GEE model (Table 3). We found significant main effects for gender ($p = 0.001$) and depression ($p = 0.039$) and additionally observed significant interactions for modification with the number of medications ($p = 0.001$) and depression ($p = 0.017$), as well as for missing knowledge with number of medications ($p = 0.013$) and MoCA ($p < 0.001$). In the univariate regression models for each SAMS factor, we again found that the number of medications per day ($p < 0.001$) and depression ($p < 0.001$) exerted the strongest influence on *modification*, whereas the number of medications ($p < 0.001$), MoCA ($p < 0.001$) and depression ($p = 0.042$) had the strongest impact on *missing knowledge*. *Forgetting* was enhanced by depression ($p = 0.057$) and decreased by living alone ($p = 0.03$) (Supplemental Table S4).

Table 3. Parameter estimators derived from generalized estimating equation model.

		ß	SE	95% CI Lower	95% CI Upper	*p*
constant		−0.599	0.460	−1.500	0.301	0.192
Gender	female	−0.139	0.044	−0.224	−0.053	0.001
	male	0 [a]				
BFI	extraversion	−0.065	0.080	−0.221	0.091	0.414
	conscientiousness	−0.001	0.073	−0.144	0.142	0.992
	neuroticism	−0.111	0.094	−0.294	0.072	0.235
	openness	−0.011	0.096	−0.199	0.177	0.906
	agreeableness	0 [a]				
SAMS factor	Modification	−0.048	0.639	−1.300	1.203	0.940
	Missing Knowledge	2.126	0.592	0.966	3.286	0.000
	Forgetting	0 [a]				
Education	high	−0.001	0.064	−0.126	0.124	0.986
	middle	−0.048	0.063	−0.173	0.076	0.446
	low	0 [a]				
Diagnosis	movement disorder	0.064	0.070	−0.074	0.201	0.363
	cerebrovascular disorder	−0.021	0.059	−0.138	0.095	0.721
	epilepsy	0.005	0.096	−0.183	0.192	0.961
	neuromuscular	−0.053	0.060	−0.169	0.064	0.378
	others	0 [a]				
Living situation	alone	−0.050	0.051	−0.150	0.050	0.332
	not alone	0 [a]				

Table 3. *Cont.*

		ß	SE	95% CI Lower	95% CI Upper	*p*
Use of nonmedical treatment	no	−0.035	0.047	−0.127	0.058	0.462
	yes	0 [a]				
Medication change in last 6 months	no	−0.011	.050	−0.109	0.087	0.822
	yes	0 [a]				
Age		0.002	0.003	−0.005	0.008	0.615
Number of medications/day		0.013	0.012	−0.011	0.036	0.300
BDI		0.016	0.008	0.001	0.031	0.039
HCCQ		−0.041	0.023	−0.087	0.004	0.077
MoCA		0.020	0.015	−0.009	0.049	0.180
TuG		0.010	0.009	−0.007	0.026	0.265
Interactions						
Modification * Number of medications/day		−0.060	0.018	−0.095	−0.025	0.001
Missing Knowledge * Number of medications/day		0.040	0.016	0.008	0.071	0.013
Forgetting * Number of medications/day		0 [a]				
Modification * BDI		0.026	0.011	0.005	0.048	0.017
Missing Knowledge * BDI		−0.004	0.010	−0.023	0.015	0.692
Forgetting * BDI		0 [a]				
Modification * MoCA		0.008	0.025	−0.040	0.056	0.755
Missing Knowledge * MoCA		−0.099	0.024	−0.145	−0.053	<0.001
Forgetting * MoCA		0 [a]				

[a] Set to 0, since this parameter is redundant. Significant predictors and interactions in bold. BDI II: Beck Depression Inventory II, HCCQ: Health Care Climate Questionnaire, BFI: Big Five Inventory, MoCA: Montreal Cognitive Assessment, TuG: Timed Up and Go test. Dependent variable: factor score. Model: (Constant), Sex, BFI, Factor, Education level, Diagnosis group, Living situation, Use of nonmedical treatment, Medication change in last 6 months, Age, Number of medications/day, BDI. HCCQ, MoCA, Timed Up and Go duration in seconds, Sex * Factor, BFI * Factor, Education Level * Factor, Diagnosis group * Factor, Use of nonmedical treatment * Factor, Medication change * Factor, Living situation * Factor, Age * Factor, Number of medications/day * Factor, BDI * Factor, HCCQ * Factor, MoCA * Factor, TuG * Factor

4. Discussion

This cross-sectional study examined the predictors of self-reported nonadherence in hospitalized older patients with neurological diseases. Sociodemographic variables, personality, depression, cognition, mobility, and satisfaction with healthcare providers were related to adherence, which conforms to the findings of other studies [6,8,9,31,32]. Furthermore, although depression and number of medications remained influential in all analyses, the different subfactors of nonadherence were influenced differently by the parameters considered. This is of enormous importance for developing interventions to improve adherence. The results and methodological features of the study are discussed below.

According to the results obtained for the SF-36, the cohort studied showed poorer QoL in all domains compared with a German reference cohort, the German Health Interview and Examination Survey for Adults (DEGS1), confirming that having one or more chronic diseases was associated with lower values in all QoL domains [28]. The largest difference between our cohort and the reference cohort was observed for physical function and role limitations due to physical problems. This finding is mirrored in other studies linking multimorbidity or chronic illness to worse functional status, disability, and reduced QoL [33,34].

This study revealed several predictors of global nonadherence and different types of nonadherence, which can broadly be divided into patient factors, interpersonal factors, and medication factors [6]. As in our previous work, we used the SAMS to detect *modification*, *missing knowledge*, and *forgetting* to take medication [13,14,25]. These factors were influenced differently by clinical and demographic variables.

The main patient factors associated with changes in adherence were depression, gender and cognitive function. This conforms to many other adherence studies in older adults [6]. Mirroring the literature, depression was identified as one of the main factors influencing adherence for all domains. Interestingly, in this study, depression was most closely linked to *modification*. One possible explanation for the effect on modification in depressed patients may be the reduced belief in the efficacy of medication, as depression is associated with reduced self-efficacy and patients may no longer believe in their ability to influence their illness [35–37]. A failure to perceive the benefit of medication, a general perception of illness, and illness burden reduce adherence, all of which depressed patients may be more sensitive to [6,36,38].

Furthermore, higher cognitive ability was associated with higher adherence in the missing knowledge category, as it is easier for cognitively unimpaired patients to understand and remember information about medication. Similarly, increased age was associated with more missing knowledge. These results conform to those found in the existing literature, highlighting the effect of cognitive impairments on reducing adherence [39,40].

Regarding the influence of age, previous studies have reported differing results, but, often, increased age is found to be detrimental to adherence due to its relation with cognitive decline [6]. This interpretation is supported by our results, which showed that increase in age was associated with reduced adherence, especially for the missing knowledge subfactor, which was also influenced by cognition. Of note, the influence of age on nonadherence has been found to be most pronounced when studies include participants that span a wide age range, as advanced age is associated with declines in cognition and health, with older patients differing strongly from their younger counterparts [41]. In our analysis, the selective inclusion of only patients of advanced age potentially resulted in reduced influence of age as a predictor.

In contrast to studies showing that neuroticism is associated with reduced adherence [6,39], in our study, neuroticism was associated with increased adherence for the *modification* group. A possible explanation is that other studies did not differentiate between different types of nonadherence, and neurotic patients may be too afraid to willfully change their medications without consulting their doctor.

Interestingly, we found gender differences, with women reporting better adherence than men, especially in the *missing knowledge* group. There are mixed results in the literature regarding sex differences in adherence [40], although most studies have not reported differences [37]. Further studies are needed to understand where these differences stem from and how they can be overcome.

Education is often cited as an influential factor for nonadherence [6,14] and our data confirmed this. Lower education was associated with nonadherence in the *missing knowledge* group, and, interestingly, it decreased the chances of *forgetting* medication. Patients with lower education may be more careful with their medication if they do not feel equipped to deal with possible complications or worsening of symptoms, for various reasons, spanning both cognition and socioeconomic status. Although education is often discussed as an intervention method for increasing adherence [2,9], it is important to keep in mind that the education level measured in this study was not medication-specific.

Regarding interpersonal factors, we found that trust in health care providers was a predictor of increased adherence [6,42]. Similarly, living alone was associated with better adherence. This was also observed in an early study of hypertensive patients [43]. However, according to another study on older adults, living alone was associated with lower adherence, although this study focused on cognitively impaired patients [44]. Since the majority of our patients evidenced normal cognition, it is possible that, for them, living alone and being solely responsible for their health led to more accountability and thus higher adherence.

In terms of medication factors, reports in the literature suggest increased nonadherence when patients take more medications or report frequent changes [6,45]. Furthermore, it is important to keep in mind that the number of medications per day is also an indicator of

multimorbidity, and therefore of worse health in general. Several studies have highlighted the connection between nonadherence and the number of medications or the complexity of the medication regime [46,47]. Our analyses showed that the number of medications was primarily related to *modification* and *missing knowledge*; thus, we argue that such complex medication plans are either too complicated for patients to understand or are accompanied by adverse side-effects leading to nonadherence [38,46]. This idea is supported by studies showing that education on medication can improve knowledge and adherence [48], and that simpler dosing regimens lead to increased adherence [47]. Interestingly, our analyses revealed reverse effects for patients in the *modification* group, where an increased number of medications reduced nonadherence. One possible explanation for this seemingly contradictory finding is that patients no longer dare to modify their medication regime when it becomes too complex, for fear of interfering with the intricate interplay of different agents.

Another interesting medication-related factor is the use of non-medical treatments, such as physiotherapy, which was revealed as a relevant factor increasing nonadherence in the *forgetting* group but not in the other groups. This seemingly contradictory finding may be explained by a busier schedule which may lead to forgetting medication before or after therapy sessions. Alternatively, patients may place less value on pharmacological treatment when also using nonpharmacological approaches, thus forgetting to take their medication often enough. However, our data does not allow for any explanation of this finding and further studies are needed to analyze the relationship between pharmacological and nonpharmacological treatments.

Our original hypothesis was that underlying neurological disorder impacts adherence [11]. Our data partially support this hypothesis, as diagnosis was a relevant factor in the elastic net model, especially for neuromuscular disorders. Of note, the listed diagnoses were not mutually exclusive, as many older patients suffer from multiple illnesses and may therefore share underlying diagnoses [34], which may effectively eliminate differences caused by individual diagnoses. For example, a patient diagnosed with Parkinson's disease may also previously have suffered a stroke, thus sharing characteristics with patients classified as 'cerebrovascular' in our dataset. The diagnoses listed in our data represent the most recent main diagnoses that patients were treated for at the time of recruitment; however, due to the presence of secondary diagnoses, this classification is not conclusive, which may explain the lack of support for our hypothesis. Due to the high occurrence of multimorbidity in the older population [34], it is rarely possible to find patients suffering exclusively from one health issue; this complexity should be taken into account when undertaking research on this patient population.

To summarize these complex results, our findings mirror the previous literature in highlighting the detrimental influence of depressive symptoms on adherence across all subfactors [6]. We were also able to confirm the number of medications as an influential factor [47], although our data suggest a differential influence on certain sub-factors of nonadherence, with a higher number of medications potentially protecting against intentional *modification* of medication. Other influential parameters, such as cognition, education and gender, mainly influenced *missing knowledge* and *forgetting*, with female gender increasing adherence for both subfactors. Cognitive deficits were most closely linked to *missing knowledge* but not *forgetting* of medication [6].

4.1. Limitations

This study has several limitations. Although the observed predictors and prevalence of nonadherence are comparable to other studies, the results are restricted to hospitalized neurogeriatric patients. As we were interested in personal factors, we used self-reports to assess nonadherence. Although this is a common and legitimate approach [49], it does not allow for statements to be made about the actual medication adherence ratio or the correctness of drug intake. Furthermore, we also collected other information through self-reports, which are prone to biases [50]. However, all the questionnaires used are widely reported in the clinical literature and have been validated. Although we have

collected a large amount of clinical data, capturing all relevant factors is inevitably not possible. In our opinion, significantly increasing the number of assessments made of this patient group risks creating datasets that are incomplete or invalid, as older adults grow tired or lose focus. As mentioned above, there were some necessary adaptations made to the study protocol because of the COVID-19 pandemic. Furthermore, the prevalence of nonadherence mainly depends on the threshold used to determine nonadherence [51]. In many studies using electronic pill monitoring or the medication possession ratio, a value of 20–25% is commonly regarded as the threshold for clinically relevant nonadherence. In addition, for self-reported adherence, several cutoff values have been used in previous studies [14,52]. According to the SAMS, using one point as an indicator of nonadherence, 78.9% of the screened patients reported some degree of nonadherence. However, not every degree of nonadherence is clinically relevant, and the threshold value at which nonadherence becomes clinically relevant has not yet been sufficiently investigated [51]. For the cohort studied in this study, there is no clear external criterion against which the effect of nonadherence can be measured, such as blood pressure during antihypertensive therapy. Therefore, we did not use a cutoff value for the SAMS but instead used it as a continuous variable.

4.2. Conclusions

Overall, the aim of our analysis was to detect factors pertaining to nonadherence to medication in geriatric patients with neurological disorders, with a special focus on different subfactors of nonadherence. Our data suggest a complex interplay of various factors relating to nonadherence, with depression and the number of medications being the most influential parameters. Highly complex medication regimes may lead to nonadherence, especially due to missing knowledge, but, at the same time, a higher number of medications reduces the chance of patients intentionally modifying their medication. Depression increases the chances of nonadherence across all subfactors. Therefore, both depressive symptoms and the complexity of medication should be targeted in interventions to assist patients with their medication. In addition, our results highlight the need to differentiate between different types of nonadherence, as other influential parameters, such as cognition or gender, influence different adherence subfactors to varying degrees. These results once more highlight the complexity of adherence and underline the necessity of assessing individual reasons for nonadherence to provide patients with the most effective support.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11185353/s1. Figure S1: Screening Procedure, Table S1: Assessments and questionnaires [53,54], Table S2: Specification of neurological diagnoses, Table S3: Principal Component Analysis of Stendal Adherence to Medication Score (SAMS), Supplement Table S4A–C: Predictors of Stendal Adherence to Medication Score (SAMS) subfactors.

Author Contributions: Conceptualization, T.P.; formal analysis, T.P., T.L. and A.S.; investigation, A.S. and H.M.M.; resources, T.P.; data curation, T.P., T.L. and A.S.; writing—original draft preparation, A.S.; writing—review and editing, T.P. and H.M.M.; funding acquisition, T.P. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was approved by the local ethics committee of the Jena University Hospital, approval number 5290-10/17. The study was registered at the German Clinical Trials Register http://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00016774. Registered 19 February 2019.

Informed Consent Statement: Written informed consent has been obtained from the patients.

Data Availability Statement: The data used in this study is freely available for noncommercial scientific purposes from: Prell, T., & Schönenberg, A. (2022). Data on medication adherence in adults with neurological disorders: The NeuroGerAd study. OSF. doi:10.17605/OSF.IO/KUAPH.

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Conflicts of Interest: The authors declare no conflict of interest.

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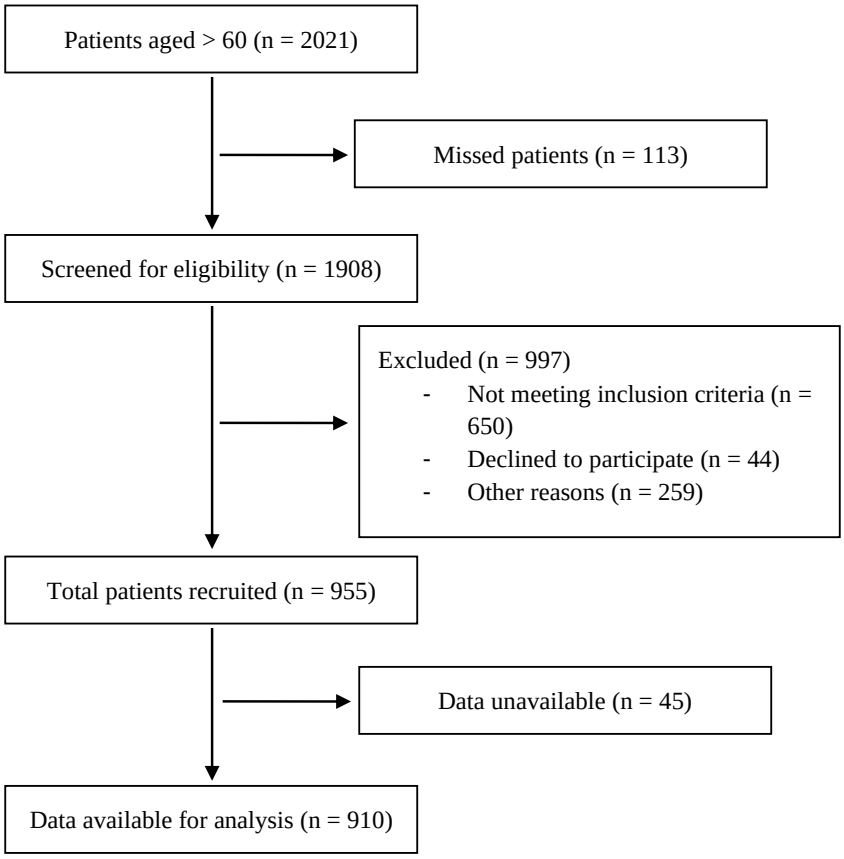
Supplementary Materials for Publication I

Supplement Figure 1. Screening procedure



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Supplement Table 1: Assessments and questionnaires

Domain	Score	Rating	Reference
Depression	Beck-Depression-Inventory II (BDI II)	The BDI-II is scored by summing the highest ratings for each of the 21 symptoms. Each symptom is rated for the past two weeks including the present day on a four-point rating scale (0–3). Sum scores range from 0 to 63. The following severity levels are suggested in the manual: Scores between 0 and 13 indicate minimal, between 14 and 19 mild, between 20 and 28 moderate, and between 29 and 63 severe depression	(1, 2)
Cognition	Montreal Cognitive Assessment (MoCA)	The MoCA is a common screen that targets the differentiation between normal aging and MCI and has gained worldwide traction among healthcare professionals. The MoCA test is straightforward to administer and easy to access (downloaded without cost from www.mocatest.org). It is scored out of 30 points, with higher scores reflecting better performance. The MoCA examines the following cognitive abilities: visuospatial/executive function, naming, episodic memory, attention, language, abstraction, and orientation. Nasreddine *et al.* (2005) suggested a cutoff score of 26, with those scoring 25 or below suspected of having MCI. A current meta-analysis indicated that a cutoff score of 23 on the MoCA offered better diagnostic accuracy than the originally recommended cutoff score of 26 (3) .	(3, 4)
Mobility	Timed up and Go Test (TUG-test)	The timed up and go test (TUG-test) is an effective method of assessing mobility and quantifying locomotor performance. The TUG-test is objective, quick and easy to perform. The test includes basic mobility skills, such as rising from a chair, walking 3 meters, turning and sitting down on the same chair. Subjects were observed and timed from the instant they rose from an armchair,walked 3 metres, and returned to a fully seated position in the chair. Subjects wore their regular footwear and were allowed to use the arms of the chair to get up. Subjects began the test on the word, 'go' and were instructed to 'walk at a comfortable fast and secure pace'. The score is the time in seconds that the subject needed to complete the test.	(5)
Personality	Big Five Inventory 10 (BFI-10)	The BFI-10 has five subscales with two bidirectional items for each of the big-five personality factors. The items are rated on a five-point Likert scale wherein the subjects choose from responses ranging from "strongly disagree "to "strongly agree". Scale scores are then calculated as the participant's mean response.	(6) (7)
Autonomy support/ health care climate	Health Care Climate Questionnaire (HCCQ)	The HCCQ is made up of 15 items using a Likert scale ranging from 1 = strongly disagree to 7 = strongly agree, with item 13 being coded in reverse. The HCCQ analyses patients' perception of support for autonomy, competence, and relatedness, enabling the researcher to gauge a patients' perception of healthcare providers' support in preserving their autonomy. The score is calculated s a mean score, with higher scores indicating a higher level of autonomy support.	(8)
Health related quality of life	Short Form Health Survey (SF-36)	The SF-36 is a disease-unspecific questionnaire to assess health-related quality of life in the last 4 weeks prior to testing. It encompasses 8 different domains in 36 items, including problems regarding both physical and social activity due to health, limitations in daily life due to physical or emotional problems, pain, mental health, vitality, and general health perception. Each domain is analyzed as the weighted sum of the corresponding items, with lower scores indicating less disability.	(9)
Adherence to medication	Stendal Adherence to Medication Score (SAMS)	The questionnaire comprises 18 items adding up to a cumulative adherence scale, with 0 indicating complete adherence and 72 complete non-adherence. Different aspects of adherence are covered, such as intentional modification of medication, lack of knowledge and forgetting to take the medication.	(10)

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Supplement Table 2. Specification of neurological diagnoses

Diagnosis	**n**	**%**
PD	215	23.6
Atypical/Secondary PD	45	4.9
Tremor, Dystonia, Other	43	4.7
Acute infarction	173	19.0
Chronic neurovascular problem	25	2.7
Other neurovascular diagnosis	34	3.7
Epilepsy, idiopathic	4	.4
Structural epilepsy	19	2.1
Other epileptic problem/unclassified	25	2.7
ALS	21	2.3
Other neuromuscular disease	25	2.7
Peripheral neuropathy	123	13.5
OSAS	30	3.3
Spinal problems	18	2.0
Others	110	12.1
Total	910	100.0

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Supplement Table 3. Principal Component Analysis of Stendal Adherence to Medication Score (SAMS)

Item	Factor with factor loadings		
	Modification	**Missing knowledge**	**Forgetting**
If you think you have side effects due to of the medications (such as tremors, nausea etc.), do you not take the medication for a while, i.e. take a break?	.867		
If you think you have side effects due to of the medications (such as tremors, nausea etc.), do you reduce the dose without consulting a doctor?	.795		
If you feel you have to take too many tablets, do you stop taking those medications you consider to be less important than the others without consulting your doctor?	.791		
Do you stop taking your medication if you sometimes feel worse after taking the medication?	.677		
Do you stop taking your medication when you feel better?	.673		
Do you deliberately not take medications you do not consider important, but take the rest?	.584		
Do you take any wrong or other/unprescribed medications (such as those of your partner)?	.558		
Do you know the dosages of your medication?		.857	
Do you know the names of medications you are taking?		.790	
Do you know the reason for taking your medication?		.761	
Are you familiar with the timing for taking the medication?		.727	
If you forget or omit your medication, do you forget it in the evening?			.744
Do you forget to take your medication?			.738
If you forget or omit your medication, do you forget it at noon?			.708
If you forget or omit your medication, do you forget it in the morning?			.669
Eigenvalue	**3.756**	**2.57**	**2.343**
Variance explained	**25.038**	**17.131**	**15.62**
Cronbachs Alpha	**.851**	**.798**	**.731**

Both the Bartlett test ($p < 0.001$) and the Kaiser–Meyer–Olkin Measure of Sampling Adequacy ($p = 0.85$) indicated that the variables were suitable for factor analysis. Three items, items 4 (Do you take your medication regularly?), 7 (Are you untroubled about taking the medication?), and 18 (If you take medication from a syringe or in a weekly tablet, have you ever forgotten it?), exhibited a low communality score and were removed from the analysis.

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Supplement Table 4 A-C: Predictors of Stendal Adherence to Medication Score (SAMS) subfactors

A. Predictors of the factor Modification

	coefficient	**Standard error**	**95% CI lower limit**	**95% CI upper limit**	**p**
Constant	.321	.652	−.960	1.602	.623
Factor-1	0	.	.	.	.
BFI extraversion	.151	.199	−.241	.543	.449
BFI conscientiousness	.168	.179	−.185	.521	.350
BFI neuroticism	−.205	.217	−.632	.222	.345
BFI openness	.084	.206	−.320	.488	.683
BFI agreeableness	0	.	.	.	.
Gender female	−.062	.095	−.249	.125	.515
Gender male	0	.	.	.	.
Diagnosis movement disorder	.018	.132	−.241	.277	.890
Diagnosis cerebrovascular disorder	−.098	.146	−.384	.189	.503
Diagnosis epilepsy	−.237	.246	−.720	.246	.335
Diagnosis neuromuscular	.041	.142	−.237	.320	.770
Diagnosis others	0	.	.	.	.
Living situation alone	.033	.111	−.185	.251	.764
Living situation not alone	0	.	.	.	.
Education level high	−.064	.120	−.300	.172	.593
Education level middle	−.116	.121	−.355	.123	.340
Education level low	0	.	.	.	.
Age	−.011	.006	−.023	.001	.070
number of medications/day	**−.044**	**.013**	**−.070**	**−.018**	**.001**
BDI	**.047**	**.007**	**.033**	**.060**	**.000**
HCCQ-D	−.043	.043	−.126	.041	.315
MoCA	.012	.013	−.014	.038	.370
TuG	.018	.011	−.003	.039	.087

Note: BDI = Beck's Depression Inventory II, BFI = Big Five Inventory, HCCQ = Healthcare Climate Questionnaire, MoCA = Montreal Cognitive Assessment, TuG = Timed Up and Go, CI = Confidence Interval

B. Predictors of the factor Missing Knowledge

	coefficient	**Standard error**	**95% CI lower limit**	**95% CI upper limit**	**p**
Constant	.276	.552	−.809	1.362	.617
Factor-2	0	.	.	.	.
BFI extraversion	.074	.169	−.258	.406	.661
BFI conscientiousness	.100	.152	−.199	.399	.510
BFI neuroticism	.166	.184	−.196	.528	.367
BFI openness	.119	.174	−.224	.461	.496
BFI agreeableness	0	.	.	.	.
Gender female	**−.164**	**.081**	**−.322**	**−.005**	**.043**
Gender male	0	.	.	.	.
Diagnosis movement disorder	.001	.112	−.218	.221	.992
Diagnosis cerebrovascular disorder	.045	.124	−.198	.288	.715
Diagnosis epilepsy	.131	.208	−.279	.540	.531
Diagnosis neuromuscular	−.072	.120	−.308	.163	.547
Diagnosis others	0	.	.	.	.
Living situation alone	.011	.094	−.173	.196	.904
Living situation not alone	0	.	.	.	.
Education level high	−.114	.102	−.314	.086	.264
Education level middle	−.193	.103	−.395	.009	.061
Education level low	0	.	.	.	.
Age	.011	.005	.001	.021	.037
number of medications/day	**.055**	**.011**	**.033**	**.077**	**.000**
BDI	**.012**	**.006**	**3.477E-5**	**.023**	**.049**
HCCQ-D	−.023	.036	−.094	.048	.531
MoCA	**−.060**	**.011**	**−.083**	**−.038**	**.000**
TuG	.008	.009	−.010	.025	.382

Note: BDI = Beck's Depression Inventory II, BFI = Big Five Inventory, HCCQ = Healthcare Climate Questionnaire, MoCA = Montreal Cognitive Assessment, TuG = Timed Up and Go, CI = Confidence Interval

C. Predictors of the factor Forgetting

	coefficient	**Standard error**	**95% CI lower limit**	**95% CI upper limit**	**p**
Constant	−.079	.631	-1.319	1.162	.901
Factor-3	0	.	.	.	.
BFI extraversion	−.296	.193	−.675	.084	.126
BFI conscientiousness	−.185	.174	−.527	.156	.286
BFI neuroticism	−.230	.210	−.644	.183	.274
BFI openness	−.128	.199	−.520	.263	.521
BFI agreeableness	0	.	.	.	.
Gender female	−.153	.092	−.334	.028	.097
Gender male	0	.	.	.	.
Diagnosis movement disorder	.229	.128	−.022	.480	.073
Diagnosis cerebrovascular disorder	.012	.141	−.265	.290	.932
Diagnosis epilepsy	.082	.238	−.386	.550	.731
Diagnosis neuromuscular	−.149	.137	−.418	.121	.278
Diagnosis others	0	.	.	.	.
Living situation alone	**−.239**	**.107**	**−.450**	**−.028**	**.026**
Living situation not alone	0	.	.	.	.
Education level high	.193	.116	−.035	.422	.097
Education level middle	.156	.118	−.075	.387	.186
Education level low	0	.	.	.	.
Age	.001	.006	−.010	.012	.862
number of medications/day	.015	.013	−.010	.040	.237
BDI	**.014**	**.007**	**.001**	**.028**	**.032**
HCCQ-D	−.068	.041	−.149	.013	.101
MoCA	.010	.013	−.015	.036	.422
TuG	.002	.010	−.018	.022	.868

Note: BDI = Beck's Depression Inventory II, BFI = Big Five Inventory, HCCQ = Healthcare Climate Questionnaire, MoCA = Montreal Cognitive Assessment, TuG = Timed Up and Go, CI = Confidence Interval

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Impact of depressive symptoms on medication adherence in older adults with chronic neurological diseases

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Abstract

Background Nonadherence to medication contributes substantially to worse health outcomes. Especially among older adults with chronic illness, multimorbidity leads to complex medication regimes and high nonadherence rates. In previous research, depressive symptomology has been identified as a major contributor to nonadherence, and some authors hypothesize a link via motivational deficits and low self-efficacy. However, the exact mechanisms linking depressive symptomology and nonadherence are not yet understood. This is in part because the often-employed sum scores cannot do justice to the complexity of depressive symptomology; instead, it is recommended to assess the influence of individual symptoms.

Methods Following this symptom-based approach, we performed correlation, network and regression analysis using depressive symptoms as depicted by the items of the revised Beck Depression Inventory II (BDI) to assess their influence with nonadherence in $N = 731$ older adults with chronic neurological diseases. Nonadherence was measured with the self-report Stendal Adherence to Medication Score (SAMS).

Results Even when controlling for sociodemographic and health-related covariates, the BDI remained the most influential contributor to nonadherence. Across different methods, Loss of Interest and Difficulty with Concentration were identified as particularly influential for nonadherence, linking nonadherence with other affective or somatic BDI items, respectively. Additionally, Fatigue, Problems with Decision Making, Suicidal Thoughts, and Worthlessness contribute to nonadherence.

Conclusion Using a symptom-driven approach, we aimed to understand which depressive symptoms contribute to higher levels of nonadherence. Our results refine previous hypotheses about motivation and control beliefs by suggesting that it is not merely a lack of beliefs in the efficacy of medication that connects depressive symptoms and nonadherence, but rather an overall lack of interest in improving one's health due to feelings of worthlessness and suicidal tendencies. This lack of interest is further substantiated by already sparse resources caused by changes in concentration and fatigue. In order to improve health outcomes and reduce nonadherence, these associations between depressive symptoms must be further understood and targeted in tailored interventions.

Keywords Older adults, Medication adherence, Depression, Network analysis, Beck depression inventory

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Background

With advancing age, the prevalence of chronic diseases in general and neurological diseases in particular increases. The World Health Organization (WHO) estimates that more than 20% of adults aged 60 years have a mental or

neurological disease; other projections predict that the number of these older adults will double by 2050, leading to an increasing burden of age-related diseases worldwide [1, 2].

Importantly, most chronic conditions are treated with medication. According to the American Center for Disease Control and Prevention, in 2016, 85% of US citizens aged 60 or older received a prescription for medication [3]. Because older adults often have multiple conditions, they have to adhere to complex medication regimens [2, 4, 5]. To achieve optimal health outcomes, it is essential that patients take these medications as prescribed. Nonadherence describes a situation where patients do not take their medicines as agreed on with their healthcare providers [4, 6]. Nonadherence rates remain high, with a recent review estimating nonadherence at 43% [7]. As nonadherence reduces the effectiveness of medication and/or can lead to adverse health events due to side effects or inappropriate drug interactions [8], nonadherence is generally associated with poorer health outcomes and quality of life (QoL) [9, 10].

The reasons for nonadherence are multifaceted; in a review, Yap and colleagues summarize five overall domains of adherence barriers: medication factors such as medication complexity and frequency of change, physician factors such as communication and satisfaction, system factors including finances and availability, miscellaneous factors, and patient factors such as age and gender, cognition, personality, and overall health [11]. Among these, depressive symptoms as patient factors have been identified as particularly detrimental [12, 13]. This association between depressive symptoms and nonadherence is particularly harmful because poorer health and depressive symptoms are interrelated, leading to a downward spiral of poorer physical and mental health. As poorer health in old age is also associated with more medical prescriptions, the association between nonadherence and depressive symptoms makes the latter an ideal starting point for improving nonadherence rates. Thus, across many different studies, including different patient groups and measurement tools, depressive symptoms have been consistently identified as influential [11, 14, 15].

Of note, depression is a highly heterogeneous construct that includes both affective symptoms, such as loss of interest, hopelessness, sadness and lack of pleasure, and somatic symptoms concerning sleep, appetite and concentration [16–19]. Additionally, much like nonadherence, depressive symptoms are complex and may differ in their manifestation between individuals [20–23]. Because of this complexity, new efforts have been made to expand the view of depressive symptomology towards a symptom-based approach. Accordingly, researchers are proposing to move away from the traditional idea of depression being a single (latent) construct that causes its corresponding symptoms, and instead to focus on these very symptoms as a self-sustaining, interactive system [21, 23–25]. This approach suggests that symptoms influence and trigger each other in cyclic relationships that cannot be satisfactorily accounted for by summarizing depression in a single diagnostic criterion or total score. This symptom-based approach is based on research demonstrating a) significant associations between depressive symptoms, b) symptom overlap between depression and other psychiatric disorders, and c) the overall lack of a replicable (factor) structure of depression as an overall diagnostic term across individuals [20–23, 25–28]. This symptom-based approach not only recognizes the complexity of depressive symptoms, but also allows a better understanding of which of the many depressive symptoms have an impact on, for example, health, QoL, or adherence [29].

Despite the close association between nonadherence and depressive symptoms, it is not well understood how exactly depressive symptoms exert their influence. While several studies report an effect of higher depression sum score values on higher levels of nonadherence [11–13], for example a meta-analysis by Grenard et al. estimates an odds ratio of 1.76 for nonadherence in patients with depression compared to patients without depression [15], these studies cannot explain which aspects of depressive symptoms deliver this effect. Many authors hypothesize about potential effects of reduced concentration or motivation as a connecting factor [14, 15, 30]; however, the symptom-driven approach described above may shed light on which depressive symptoms contribute primarily to nonadherence. While this approach has been applied to depressive symptoms in other contexts [31–35], to the best of our knowledge, it has not yet been done to assess its relation with nonadherence. Therefore, we applied different methods to assess the relationship between nonadherence and individual depressive symptoms to understand by which mechanisms depressive symptomology is linked to nonadherence.

Methods

Study design, setting and participants

The data used for this secondary analysis were taken from the NeuroGerAd study, an observational study on medication adherence and related psychosocial factors conducted on the wards of Neurology at Jena University Hospital, Germany, from 2019 to 2020. Detailed information on the study design and collected data can be found in the published study materials [36–38]. Briefly, older patients with common neurological main diagnoses as confirmed by the hospital's leading physicians received

a comprehensive assessment during their hospital stay. Initial study inclusion criteria comprised age (≥60 years, or ≥55 years with multi-morbidity), cognition (no severe cognitive impairments as indicated by Montreal Cognitive Assessment >18 or diagnosis of dementia, no delirium), and absence of severe depression. Of the original 910 participants included in the study, $N=731$ completed both the dependent and independent variable of interest for this manuscript, and were thus included in the present analysis.

Variables

We extracted the following variables for the present analysis:

- The dependent variable was depressive symptomology as assessed with the revised Beck Depression Inventory (BDI) [39, 40]. The BDI encompasses 21 items assessing the presence and intensity of different depressive symptoms on a 4-point Likert scale.
- The key independent variable was medication adherence measured with the Stendal Adherence to Medication Score (SAMS), a self-report scale encompassing a sum score as well as the sub-scales *Modification* of medication, *Forgetting* to take medication, and *Missing Knowledge* about medication. Each of the 18 items is posed as a 4-point Likert scale ranging from 0 to 4, with higher scores indicating higher levels of nonadherence. The SAMS has undergone testing across a range of patient groups, such as neurological patients, chronic pain patients, and patients who have received kidney transplants, and the three sub-scales have been replicated in various studies [41–45]. In our study, we calculated the sub-scales as the mean of the respective items (Cronbach's α: *Total Score* = 0.83 [95% CI 0.82-0.85], *Forgetting* = 0.73 [95% CI 0.70-0.76], *Modification* = 0.84 [95% CI 0.82-0.86], and *Missing Knowledge* = 0.79 [95% CI 0.77-0.81]). As no universally accepted cut-off point for nonadherence is defined, we treated the SAMS as a continuous variable [46].

In addition, to evaluate the relative contribution of the BDI, we included the following covariates:

- Age (years), Sex (Male/Female), Living Situation (Alone/not Alone), Marital State (Married or in a relationship/not Married), Education (low ≤8 years, medium 9 – 11 years, high ≥12 years corresponding to the German education system)
- Type of medical main diagnosis as given by physicians during the patients' hospital stay (Movement Disorder, Cerebrovascular Disorder, Neuromuscular Disorder, Epilepsy, Miscellaneous Disorders) and number of different medications taken daily
- Self-Rated Health (SRH) according to item 1 of the SF-36. This item asks patients to rate their general health ("in general, would you say your health is…?") on a scale of 1 = excellent to 5 = poor [47, 48].
- Satisfaction with healthcare indicated by Healthcare Climate Questionnaire (HCCQ) The HCCQ utilizes 15 Likert-Scale items to assess patients' perception of support for autonomy, competence, communication, and empathetic support. It is summarized as a mean score, with higher scores indicating a higher overall satisfaction with the provided care. It has been tested and validated in previous studies [49–51].
- Cognition assessed with the Montreal Cognitive Assessment (MoCA). The MoCA is one of the most commonly used cognitive screenings with high sensitivity especially for differentiation between unimpaired cognition and mild cognitive impairment. It incorporates not only memory and orientation but also abstraction, language/fluency, and visuospatial tasks. A maximum of 30 points can be received, with higher scores reflecting better performance. In addition to utilizing the overall sum score as a continuous variable, different cutoffs are proposed in various patient populations [52–55].
- As we included not only patients with movement disorders but generally older adults, we measured Mobility as indicated by the Timed Up and Go (TuG) test. During the TuG, patients are asked to stand up from a chair, walk a set distance, turn around and retake their seat, assessing overall mobility required for every-day tasks [56]. The TuG is a validated and reliable measure for mobility also in impaired populations [57, 58].
- Personality according to the Big Five Inventory-10 (BFI) [59]. The BFI is the most commonly used and validated questionnaire to assess personality based on the Big Five theory including the traits openness, neuroticism, agreeableness, conscientiousness, and extraversion. The BFI-10 has five subscales with two Likert-scale items for each of the traits. Scale scores are then calculated as the participant's mean response. Its validity has been confirmed previously in extensive German samples [60].

Statistical methods

We used descriptive statistics (Mean and SD or Median and IQR) to describe the included patients. Using linear regression, we initially confirmed the association between BDI and SAMS while controlling for covariates. Subsequently, we performed network analysis (NA)

[61–63] using the R-package *bootnet* [61] as an exploratory tool to map out the relation between the SAMS sum score and sub-scales, and depressive symptoms represented by the BDI items. Unlike traditional modelling approaches, NA does not assume an underlying latent factor to account for links between variables, but rather assumes that the included variables influence each other in a cyclic relationship. Especially for psychosocial items, this approach is beneficial as it assumes that items, e.g. symptoms in a questionnaire such as the BDI, are interrelated and assesses their interplay rather than reducing a phenomenon as complex as depressive symptomology down to one latent factor [21, 24–26].

This approach has recently been employed to study the complexity of mental health disorders, especially depression [22, 31, 32, 35, 61, 64]. The Gaussian Graphical Model (GGM) based on polychloric correlation for ordinal variables maps the relationships between two variables while controlling for all other variables in the network [65]. Consequently, the network plot does not contain mere correlations; two items can be strongly correlated but unconnected in the network if their association is delivered via other variables. Thus, NA can help understand the potential flow of information between different variables [66]. Of note, NA is an exploratory tool that we mainly used to visualize the complex interactions between the BDI items and the SAMS, allowing for the assessment of interconnection between items rather than reducing the data down into (orthogonal) factors or single latent constructs [66]. Although centrality measures exist to assess the influence of particular items within the network, we intentionally do not report them, mainly because centrality indices only indicate the importance of items relative to all items in the network, but not relative to specific constructs such as the SAMS. Thus, centrality indices do not provide useful information for our specific purpose [61, 67, 68].

Visually, NA displays two components: the variables (BDI items and SAMS scores), called *nodes*, and their connecting *edges.* Edges display the strength of the association with their thickness and the direction with their color, with red edges depicting negative associations. present edge indicates that, when conditioning on all other inter-item relationships in the network, a relation between two items remains. In contrast, the absence of an edge between two nodes indicates independence of those two nodes after conditioning on all other nodes. The nodes are then depicted graphically using the Fruchterman-Reingold algorithm, placing the nodes within the network based on the strengths of their associations. This means that nodes with strong connections are positioned in close proximity [69].

In NA with multiple variables, all edges are drawn per default, leading to a network that is difficult to interpret. Therefore, we used the Extended Bayesian Information Criterion with Graphical Least Absolute Shrinkage and Selection Operator (EBICgLasso) to shrink the absolute weights of the correlations towards zero, effectively reducing the number of edges to produce a sparse network [61, 70]. The hyper-parameter was set to 0.5. The stability of NA can be assessed using a case-dropping nonparametric bootstrap: if the correlation stability coefficient (CS-C) remains above 0.5, a proportion of the study sample can be dropped without major changes in the NA properties [61].

Lastly, we used linear regression with elastic net regularization to assess the contribution of the different BDI items on the SAMS variance. When using the BDI items as regressors, we performed Elastic Net Regularization with tenfold cross-validation to detect the optimal alpha and lambda combination [71, 72]. Elastic Net is a penalty-based combination of Ridge and Lasso regression to perform variable selection and prevent overfitting. This makes elastic net a beneficial approach when a multitude of independent variables is included in a model, when these variables are correlated, and/or sample sizes are small [71, 72]. The variables identified as relevant based on a reduction of the mean squared error (MSE) in the elastic net can then be entered into a final linear model. All elastic net models were compared to regular linear regression models with all included variables using the *performance*-package to detect the best-fitting model. Elastic Net was performed with the *glmnet* package in R [71].

Assumptions for linear regression were assessed with the *performance*-package in R [73]. All analyses were performed in R Version 4.3.1. [74]. P-values below 0.05 denote statistical significance, 95% confidence intervals (CIs) are given where possible. All visualizations were computed using *ggplot2* [75] or *qgraph* for the NA [69].

Results

The included 731 patients had a mean age of 70.2 years (SD ± 8.61), ranging from 55 to 96 years. Of these, 326 patients (44.6%) were female (see Tables 1 and 2 for a descriptive overview).

As a first step, we confirmed the association between the BDI and the SAMS that we reported in previous manuscripts as a basis for subsequent analyses (Supplement Table 1A).

In a univariate linear regression model ($F(1, 729) = 52.23$, $p < 0.001$, adjusted $R^2 = 0.07$), the BDI was significantly associated with the SAMS sum score (est = 0.26, $p < 0.001$, 95% CI [0.19; 0.33]).

Table 1 Sociodemographic information on included patients

Variable	Mean (SD)	Median (IQR)	N
Age	**70.2 (8.61)**	**70 (14)**	**731**
	N	**%**	**N**
Gender: female	326	44.6	731
Education			724
Low	224	30.9	
Medium	249	34.4	
High	251	34.7	
Marital Status: married	496	68.7	722
Living Situation: not alone	527	75.4	699
Diagnosis			731
Movement Disorder	237	32.4	
Cerebrovascular	191	26.1	
Neuromuscular	143	19.6	
Epilepsy	35	4.8	
Miscellaneous	125	17.1	

IQR interquartile range, *SD* standard deviation

Table 2 Descriptive statistics of included variables

Variable	Mean (SD)	Median (IQR)	N
BDI	9.68 (7.51)	8 (9)	731
SAMS	6.16 (7.59)	4 (8)	731
Modification	0.219 (.53)	0 (0.17)	731
Missing Knowledge	.446 (.79)	0 (0.75)	731
Forgetting	.418 (.57)	0.25 (0.50)	731
MoCA	23.50 (2.71)	23 (4)	731
HCCQ	5.62 (1.13)	5.9 (1.3)	692
TuG	10.60 (4.48)	10 (4)	477
Number of Drugs	5.74 (3.68)	5 (5)	697
	N	**%**	**N**
BFI			701
Neurotic	81	11.8	
Open	114	16.3	
Extroverted	148	21.1	
Conscientious	298	42.5	
Agreeable	60	8.7	
SRH (SF-36 Item 1)			721
1—Excellent	4	0.6	
2 – Very Good	18	2.5	
3 – Good	209	29.0	
4 – Fair	356	49.4	
5 – Poor	134	18.6	

BDI Beck Depression Inventory II, *BFI* Big Five Inventory, *HCCQ* Healthcare Climate Questionnaire, *MoCA* Montreal Cognitive Assessment, *SAMS* Stendal Adherence to Medication Scale, *SRH* Self-Rated Health, *TuG* Timed Up and Go

When adding the covariates to the model ($F(23, 386) = 5.62$, $p < 0.001$, adjusted $R^2 = 0.201$), the BDI remained a significant predictor of the SAMS (est = 0.36, $p < 0.001$, 95% CI [0.26; 0.45]) along with sex, HCCQ, and SRH (see Supplement Table 1B, Model 1). The BDI was also identified as a significant contributor to all the SAMS sub-scales even with adjustment for covariates (Supplement Table 1B, Models 2–4). Having confirmed the general relationship between SAMS and BDI, we aimed to understand which aspects of depressive symptomology as described by the BDI items deliver this influence. For this purpose, we performed subsequent analyses using the BDI items.

Spearman correlations between the BDI items and the SAMS in the sum score (Fig. 1) and in the SAMS sub-scales (Supplement Figs. 1–3) were low to moderate but statistically significant for most items. However, for the Missing Knowledge sub-scale, only items 1–3 (Sadness, Pessimism and Failure), 10–14 (Crying, Restlessness, Loss of Interest, Decision Making, Worthlessness), and 18–19 (Appetite, Concentration) reached statistical significance. *Forgetting* was significantly associated with all items except for items 7 (Self-Rejection), 10 (Crying), 16 (Sleep) and 21 (Sexual Interest). The *Modification* scale was significantly correlated with all BDI items. The SAMS sum score is most strongly correlated with item 12 (Loss of Interest), 19 (Problems with Concentration), 20 (Fatigue), 14 (Worthlessness), and 13 (Decision Making). Looking at the SAMS sub-scales, the *Forgetting* sub-scale showed highest correlation with BDI items 12 (Loss of Interest), 19 (Concentration), 20 (Fatigue) and 13 (Decision Making) as well, although with lower loadings than for the SAMS sum score. For the *Missing Knowledge* sub-scale, items 19, 14 and 12 still showed highest associations, as well as item 18, and for the *Modification* sub-scale again items 12, 13, 14, and 20 as well as item 17 (Irritability) showed highest correlations.

Correspondingly, in the Network for the total SAMS (Fig. 2), direct connections were present between the SAMS sum score and items 19 (Concentration) and 12 (Loss of Interest). Additionally, the SAMS was directly connected to BDI-II item 9 (Suicidal Thoughts), and weakly with items 17 (Irritability) and 20 (Fatigue). Visually, item 19 appears to connect the SAMS with other somatic BDI-items, while item 12 serves as a gateway to other affective BDI symptoms. Case-dropping bootstrap revealed the network to be sufficiently stable with a CS-C of 0.595, displaying 132/231 possible edges. Having established an overall relationship between the SAMS sum score and the BDI, we then used the SAMS sub-scales to provide more refined information about how the various BDI symptoms are related to aspects of nonadherence.

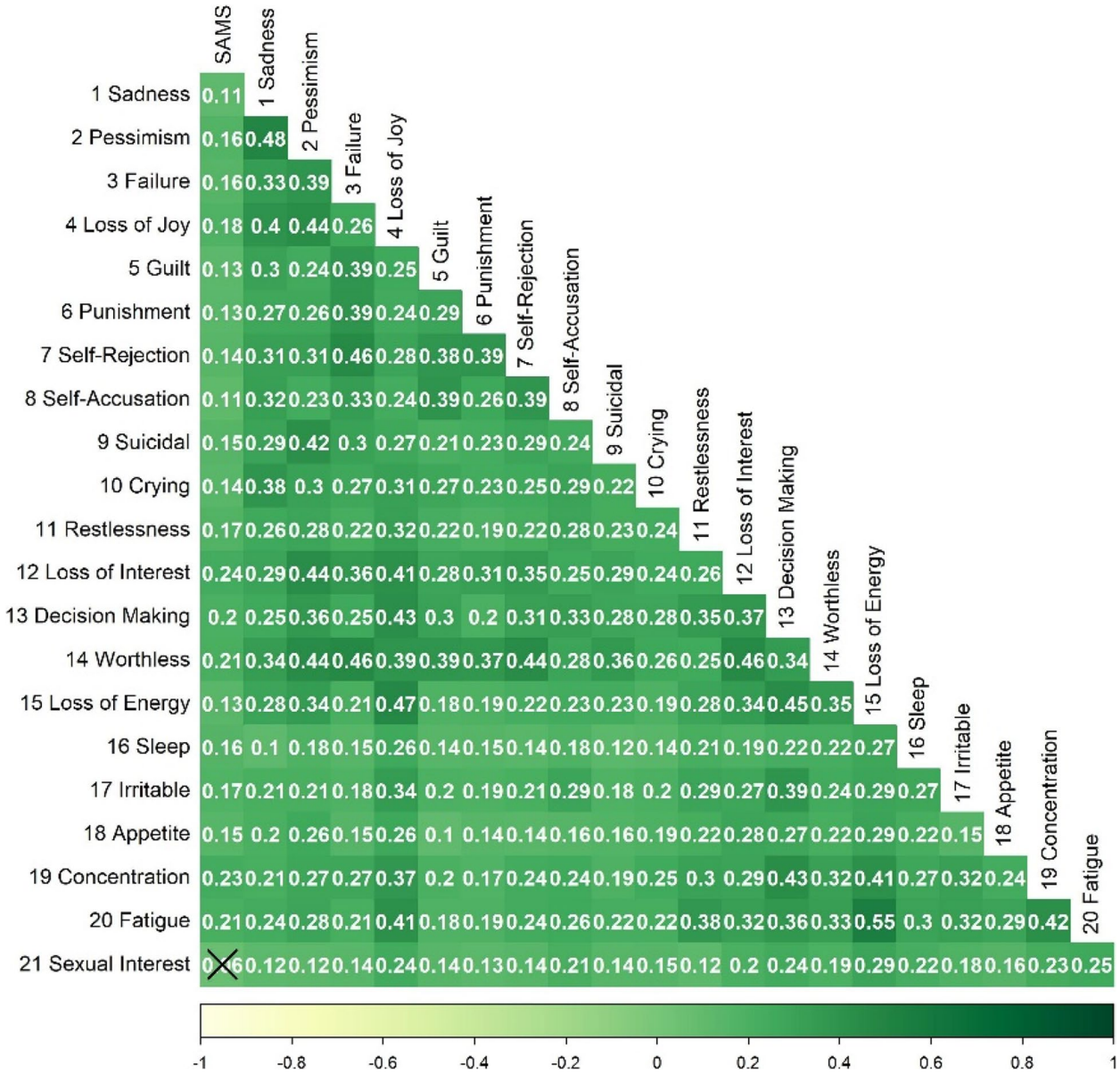

Fig. 1 Spearman correlation for SAMS and BDI-II Items based on significance level of .05. Note: Values give correlation coefficients. Crossed-out values did not reach significance

(Supplement Figs. 4–6). All networks revealed CS-Cs above the required 0.5.

The Network for the *Forgetting* sub-scale confirmed direct associations between forgetting and items 12 (Loss of Interest), 9 (Suicidal Thoughts), and 20 (Fatigue), as well as weakly with item 19 (Concentration). Again, items 12 and 9 connect nonadherence with other affective BDI items, while items 19 and 20 link *Forgetting* with the somatic symptoms. The network for *Missing Knowledge* generally showed weaker relations, direct connections for knowledge were present with item 15 (Loss of Energy) as a connection to somatic BDI symptoms, and items 12, 14 (Worthlessness), and 3 (Failure). In the network for *Modification*, this sub-scale was directly connected to somatic symptoms via items 16 (Sleep) and 20, as well as weakly with 15 and 21 (Sexual interest). Weaker direct links were present with affective symptoms via items 12, 10 (Crying) and 8 (Self-Accusation).

Because NA is primarily an exploratory approach, we used linear regression with elastic net regularization to identify the BDI items most relevant in explaining SAMS variance. Regression analysis for the SAMS sum score

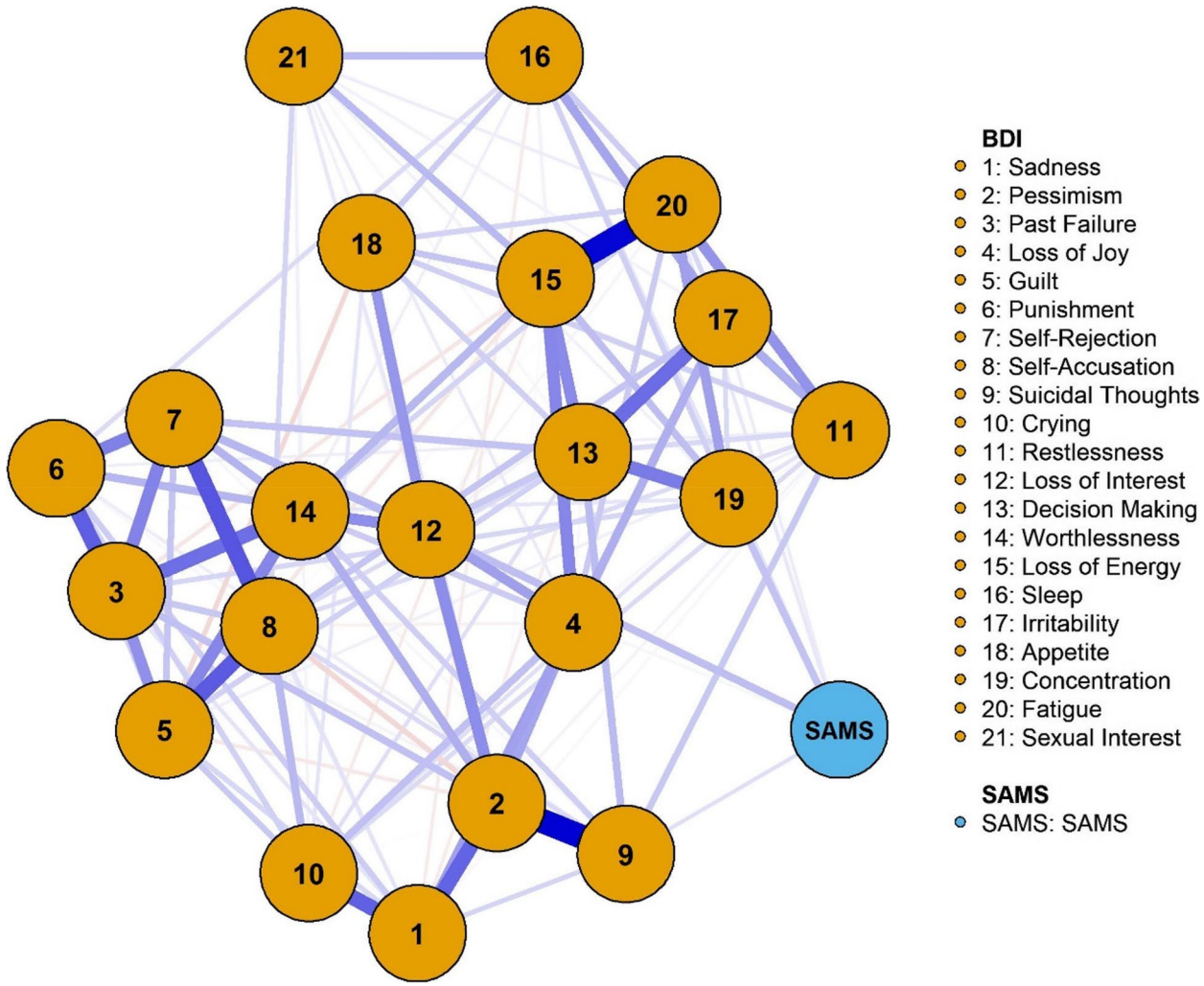

Fig. 2 Network Analysis of SAMS Sum Score and BDI items

and sub-scales yielded similar results as the NA. Accordingly, for the SAMS sum score, the BDI items 12 (Loss of Interest) and 19 (Concentration) were identified as main contributors to SAMS variance (Table 3).

When looking at the *Forgetting* sub-scale (see Supplement Table 2, Model 1), only item 12 significantly contributed to explained variance of the sub-scale, while items 12, 15 and 19 contribute significantly to the *Missing Knowledge* (Supplement Table 2, Model 2) subscale. Finally, *Modification* (Supplement Table 2, Model 3) was related only to item 12.

Discussion

Depressive symptomology has previously been identified as closely related to nonadherence, both in our data and in other studies [11, 14, 15, 36]. However, new approaches suggest that depressive symptomology needs to be considered at the symptom level rather than using

Table 3 Linear Regression with Elastic Net Regularization for SAMS sum score with all BDI items as predictors

Predictors	**SAMS**		
	Estimates	***CI***	***p***
(Intercept)	3.56	2.61 – 4.51	**< 0.001**
bdi 3	1.01	-0.17 – 2.18	0.093
bdi 5	0.41	-1.07 – 1.90	0.584
bdi 11	0.61	-0.23 – 1.45	0.154
bdi 12	1.56	0.54 – 2.58	**0.003**
bdi 14	0.11	-1.11 – 1.33	0.858
bdi 16	0.35	-0.26 – 0.96	0.259
bdi 19	1.07	0.16 – 1.97	**0.021**
bdi 20	0.44	-0.49 – 1.36	0.354

BDI Beck Depression Inventory, *CI* confidence interval, *Sams* Stendal Adherence to Medication Scale

N 730, R^2 / R^2 adjusted 0.091 / 0.081

$F(8, 721) = 9.02$, $p < .001$

sum scores [21, 24–26]. Therefore, we set out to examine the impact of depressive symptoms, as measured by the BDI, on medication nonadherence using correlation, network and regression analysis.

Overall, our data confirm that depressive symptoms and nonadherence are closely related, with the BDI sum score alone explaining 7% of SAMS variance. When socio-demographic and health-related covariates were included, the BDI still retained the strongest explanatory value in the model. Therefore, we used item-level correlation, network and regression analyses to explore this relationship between the BDI and SAMS in depth.

Both for the SAMS sum score and the sub-scales, BDI item 12 (Loss of Interest) has been identified as influential across all methods. The associations between depressive symptoms and adherence vary slightly depending on which sub-scale, i.e. which type of nonadherence, is considered, but overall items 12 and 19 (Problems with Concentration) were found to be directly related to nonadherence. Additionally, items 20 (Fatigue), 14 (Worthlessness) and 13 (Problems with Decision Making) were identified to contribute to nonadherence. In the NA, item 9 (Suicidal Thoughts) also showed direct associations with nonadherence for SAMS sum score and *Forgetting*.

Although there is no replicable structure of the BDI due to the high complexity and individuality [76], the BDI is often thought to incorporate both cognitive-affective and somatic symptoms [39, 77, 78]. Generally, higher levels of nonadherence as measured by the SAMS sum score were associated with other affective symptoms via Loss of Interest (Item 12) and with other somatic symptoms via Concentration (Item 19) and Fatigue (Item 20), indicating a multi-component association between depressive symptoms and nonadherence.

The effect of cognitive problems such as lack of concentration and unintentional forgetting of medication has been reported in previous studies [11, 14, 15, 79]; our data again indicate that not taking medication may be associated with concentration deficits as well as with a general physical weakness. Of note, the *Forgetting* sub-scale representing unintentional nonadherence was associated with both Concentration and Fatigue, as well as with a lack of interest and a feeling of worthlessness. The *Modification* sub-scale was primarily related to loss of interest, indicating a general carelessness about the correctness of medication intake. In the NA, also items 8 and 10 (Crying and Self-Accusation) were linked with higher levels of *Modification*; however, for this sub-scale the somatic symptoms appear to be more influential. Thus, the NA shows links with Fatigue (item 20) and Sleep Problems (item 16), which together with the influence of item 12 point towards a general lack of care and interest in one's medication. This is in line with the association found between nonadherence and item 9 (Suicidal Thoughts), as well as item 14 (Worthlessness) that has been reported in the NA and regression for SAMS sum score as well as *Knowledge* and *Forgetting* sub-scales. These associations suggest an underlying general belief that taking care of one's health is not worth the effort. Our results indicate overall that patients with higher levels of depressive symptomology may care less about their own well-being and survival due to general feelings of worthlessness and loss of interest in their well-being; and accordingly do not invest in their own health, especially when cognitive and energy resources are already scarce.

In their review, Grenard and Colleagues propose a "lack of energy, motivation, […], feelings of hopelessness and changes in cognition […]" [15] as pathways linking depressive symptoms with nonadherence. Our results confirm this hypothesis. Similarly, Goldstein and colleagues even suggest psychological counseling using motivational interviewing as a means to improve medication nonadherence [30], pointing to the importance of motivation and control beliefs in illness. Similarly, Schüz et al. identified the beliefs in efficacy and necessity of medication as predictors of nonadherence [80, 81], suggesting that the beliefs in the ability and necessity to improve one's health are essential for adherence [41, 82]. In contrast, self-efficacy and locus of control are often reduced in persons with higher levels of depressive symptoms [83–85], and depressive symptoms have been shown to influence expectations and interpretations of health in older adults [86]. These results indicate an association between depressive symptomology and nonadherence via lack of beliefs in the ability to influence health; our present result substantiate these findings with the addition of worthlessness and loss of interest, suggesting that it is not only a lack of self-efficacy and control but also a lack of willingness to devote resources to the improvement of one's own health in particular due to not feeling worthy. Additionally, our results highlight that these resources may also be scarce in the first place due to lack of concentration and problems with fatigue and sleep.

According to NA, this overall lack of interest (item 12) seems to bundle the other affective symptoms to culminate in nonadherence, while concentration (item 19) bundles somatic symptoms. Although with cross-sectional data, it is not possible to assess whether other affective symptoms result in lack of interest or whether lack of interest causes the other symptoms. While NA differs from traditional modelling by allowing the co-presence of connections and plotting the potential flow of information rather than taking into account the individual contribution of each variable separately, it remains an exploratory analysis especially when using

cross-sectional data. Longitudinal analyses using symptom-based approaches such as NA that include more fine-tuned data such as motivation, self-efficacy and control perceptions as covariates may provide a more detailed understanding of the association between nonadherence and the broad bandwidth of depressive symptomology.

Limitations

Our study is not free of limitations. Firstly, the single-center study design and specific study population hinders generalizability, although we did choose this particular cohort of older adults with neurological chronic diseases due to its high relevance and predisposition for depressive symptoms [2]. Although NA can provide useful insight into the structure of data, it requires large datasets in order to be sufficiently stable; thus subgroup-analyses concerning very specific patient populations, age groups or gender differences are not always feasible. Additionally, cross-sectional data cannot indicate causality, thus the analyses should be repeated with longitudinal data in different settings. Furthermore, both the depressive symptoms and nonadherence questionnaires are based on self-report; although self-reported measurements carry a risk of bias, they offer an opportunity to evaluate various forms of nonadherence and their underlying causes, which cannot be achieved through the use of more objective measures [46, 87]. Furthermore, when using valid scores, self-reports can provide reliable information on nonadherence behavior. Of note, the patients included in our study did not receive a psychiatric assessment, thus the depressive symptoms reported in our data are not indicative of Major Depressive Disorders. While the use of a questionnaire such as the BDI is useful as it provides an assessment of various different symptoms, it would be beneficial to repeat these analyses with patients at different intensities of depressive symptomology after professional psychiatric assessment.

Conclusion

Modern research approaches highlight the need to assess depressive symptomology on symptom level to do justice to its high complexity. Based on this approach, we utilized several methods to assess the association between depressive symptoms and nonadherence to medication. Our results are in line with previous hypotheses suggesting a lack of cognitive resources and motivation or control beliefs. Additionally, they refine these hypotheses by highlighting that it is not merely a lack of beliefs in the efficacy of medication that connects depressive symptoms and nonadherence, but rather an overall lack of interest in improving one's health due to feelings of worthlessness and suicidal ideas. This lack of interest is further substantiated by already sparse resources caused by changes in concentration and fatigue on the other hand.

Abbreviations

BDI	Beck Depression Inventory II
BFI	Big Five Inventory
CI	Confidence Interval
CS-C	Correlation Stability Coefficient
EBICgLasso	Extended Bayesian Information Criterion with Graphical Least Absolute Shrinkage and Selection Operator
GGM	Gaussian Graphical Model
HCCQ	Healthcare Climate Questionnaire
IQR	Interquartile Range
M	Mean
MoCA	Montreal Cognitive Assessment
MSE	Mean Squared Error
NA	Network Analysis
SAMS	Stendal Adherence to Medication Score
SD	Standard Deviation
SRH	Self-Rated Health
TuG	Timed Up and Go

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12888-024-05585-7.

Additional file 1: Supplement Table 1. Linear Regression for SAMS and SAMS sub-scales using the BDI (A) and Covariates (B). **Supplement Table 2.** Linear Regression after Elastic Net Regularization for SAMS sub-scales using BDI items as predictors. **Supplement Figure 1.** Spearman Correlations for SAMS Forgetting and BDI Items. **Supplement Figure 2.** Spearman Correlations for SAMS Missing Knowledge and BDI Items. **Supplement Figure 3.** Spearman Correlations for SAMS Modification and BDI Items. **Supplement Figure 4.** Network for SAMS Forgetting and BDI Items. **Supplement Figure 5.** Network for SAMS Missing Knowledge and BDI Items. **Supplement Figure 6.** Network for SAMS Modification and BDI Items.

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Authors' contributions

AS was involved in data collection and curation, performed the analysis, and wrote the original draft. KGH assisted with data analysis and reviewed and edited the manuscript. TP was involved in the study conception and design, as well as review and editing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

An anonymized version of the dataset used in this analysis is available from: Prell, T., & Schönenberg, A. (2022). Data on medication adherence in adults with neurological disorders: The NeuroGerAd study. OSF. 10.17605/OSF.IO/KUAPH.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Jena University Hospital, approval number 5290–10/17. All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Publisher's Note

Supplementary Materials for Publication II

Supplement Table 1. Linear Regression for SAMS and SAMS sub-scales using the BDI (A) and Covariates (B)

Predictors	**Est.**	**CI**	**p**	**Est.**	**CI**	**p**	**Est.**	**CI**	**p**	**Est.**	**CI**	**p**
A Model with BDI Only	Model 1A: SAMS			Model 2A: Forgetting			Model 3A: Missing Knowledge			Model 4A: Modification		
Intercept	3.63	2.76 – 4.50	**<0.001**	0.28	0.21 – 0.34	**<0.001**	0.31	0.22-0.40	**<0.001**	0.08	0.01-0.14	**0.014**
BDI	0.26	0.19 – 0.33	**<0.001**	0.01	0.01 – 0.02	**<0.001**	0.01	0-01-0.02	**<0.001**	0.01	0.01-0.02	**<0.001**
Model Fit	N = 731, R^2/R^2 adjusted = 0.067 / 0.066, F(1, 729) = 52.23, p < .001			N = 731, R^2/R^2 adjusted 0.037 / 0.035, F(1, 729) = 27.87, p < .001			N= 731, R^2/R^2 adjusted = 0.018 / 0.016, F(1, 729) = 13.12, p < .001			N = 731, R^2/R^2 adjusted = 0.045 / 0.043, F(1, 729) = 34.12, p < .001		
B Model with Covariates	Model 1B: SAMS			Model 2B: Forgetting			Model 3B: Missing Knowledge			Model 4B: Modification		
	Est.	**CI**	**p**	**Est.**	**CI**	**p**	**Est.**	**CI**	**p**	**Est.**	**CI**	**p**
Intercept	9.31	-0.43 – 19.04	0.061	-0.05	-0.86 – 0.76	0.906	0.45	-0.58 – 1.48	0.388	0.61	-0.14 – 1.35	0.111
BDI	0.36	0.26 – 0.45	**<0.001**	0.01	0.00 – 0.02	**0.009**	0.02	0.01 – 0.03	**<0.001**	0.03	0.02 – 0.03	**<0.001**
Age	0.01	-0.06 – 0.09	0.776	0.00	-0.01 – 0.01	0.842	0.01	0.00 – 0.02	**0.028**	-0.00	-0.01 – 0.00	0.291
Gender [male]	1.85	0.65 – 3.05	**0.003**	0.13	0.03 – 0.23	**0.013**	0.15	0.02 – 0.28	**0.021**	0.07	-0.03 – 0.16	0.159
Education [medium]	-0.88	-2.38 – 0.63	0.253	0.12	-0.00 – 0.25	0.056	-0.18	-0.34 – -0.02	**0.028**	-0.05	-0.17 – 0.06	0.385
Education [high]	-0.14	-1.64 – 1.35	0.851	0.12	0.00 – 0.25	**0.049**	-0.13	-0.29 – 0.03	0.108	0.01	-0.10 – 0.12	0.860
Marital [married]	1.55	-0.48 – 3.58	0.134	0.14	-0.03 – 0.31	0.098	-0.05	-0.27 – 0.16	0.625	0.16	0.00 – 0.31	0.046
Living [not alone]	-0.41	-2.62 – 1.80	0.715	-0.03	-0.21 – 0.16	0.762	0.08	-0.16 – 0.31	0.521	-0.10	-0.27 – 0.07	0.247
MoCA	-0.11	-0.35 – 0.12	0.337	0.01	-0.01 – 0.03	0.218	-0.04	-0.07 – -0.02	**0.001**	0.00	-0.02 – 0.02	0.833
TuG Seconds	0.12	-0.01 – 0.26	0.076	0.00	-0.01 – 0.01	0.698	0.01	-0.00 – 0.03	0.092	0.01	-0.00 – 0.02	0.067
BFI [Openness]	1.67	-0.63 – 3.97	0.153	0.06	-0.13 – 0.25	0.521	0.02	-0.22 – 0.26	0.862	0.12	-0.05 – 0.30	0.171
BFI [Agreeableness]	1.45	-1.30 – 4.20	0.299	0.09	-0.14 – 0.32	0.438	-0.06	-0.35 – 0.23	0.696	0.11	-0.10 – 0.33	0.284
BFI [Conscientiousness]	1.32	-0.66 – 3.31	0.191	0.03	-0.14 – 0.19	0.759	-0.01	-0.22 – 0.20	0.947	0.12	-0.03 – 0.27	0.119
BFI [Extraversion]	0.28	-1.99 – 2.54	0.812	-0.03	-0.21 – 0.16	0.787	-0.02	-0.26 – 0.21	0.839	0.03	-0.14 – 0.20	0.738
HCCQ	-0.74	-1.28 – -0.20	**0.007**	-0.06	-0.10 – -0.01	**0.014**	-0.03	-0.08 – 0.03	0.354	-0.02	-0.06 – 0.02	0.283
Number of Drugs	0.07	-0.10 – 0.23	0.430	0.01	-0.01 – 0.02	0.315	0.04	0.02 – 0.06	**<0.001**	-0.01	-0.03 – -0.00	0.023
Diagnosis [Cerebrovasc.]	-0.87	-2.54 – 0.80	0.308	-0.07	-0.21 – 0.07	0.314	-0.01	-0.19 – 0.16	0.881	-0.02	-0.15 – 0.11	0.792
Diagnosis [Neuromusc.]	-0.55	-2.16 – 1.06	0.505	-0.13	-0.27 – -0.00	**0.050**	-0.08	-0.25 – 0.09	0.334	0.09	-0.03 – 0.21	0.145
Diagnosis [Epilepsy]	-0.55	-3.54 – 2.45	0.720	-0.09	-0.34 – 0.16	0.498	0.11	-0.21 – 0.43	0.492	-0.12	-0.35 – 0.11	0.319
Diagnosis [Misc.]	-0.67	-2.37 – 1.03	0.438	-0.08	-0.22 – 0.06	0.243	-0.02	-0.20 – 0.16	0.791	0.03	-0.10 – 0.16	0.631
SRH [1 - Excellent]	-15.68	-23.28 – -8.09	**<0.001**	0.22	-0.42 – 0.85	0.504	-0.24	-1.04 – 0.56	0.556	-1.73	-2.31 – -1.15	**<0.001**
SRH [2 - Very good]	9.65	3.26 – 16.03	**0.003**	-0.19	-0.72 – 0.34	0.484	-0.00	-0.68 – 0.67	0.998	1.27	0.78 – 1.75	**<0.001**
SRH [3 - Good]	-5.88	-10.32 – -1.45	**0.009**	0.11	-0.25 – 0.48	0.544	-0.10	-0.57 – 0.37	0.681	-0.76	-1.10 – -0.42	**<0.001**
SRH [4 - Poor]	1.00	-1.39 – 3.38	0.412	-0.07	-0.27 – 0.13	0.502	0.04	-0.22 – 0.29	0.778	0.19	0.01 – 0.38	**0.038**
Model Fit	N = 410, R^2/R^2 adjusted = 0.251 / 0.206, F(23, 386) = 5.624, p < .001			N = 410, R^2/R^2 adjusted 0.121 / 0.068, F(23, 386) = 2.30, p < .001			N = 410, R^2/R^2 adjusted 0.223 / 0.177, F(23, 386) = 4.815, p < .001			N = 410, R^2/R^2 adjusted = 0.237 / 0.191, F(23,386) = 5. 202, p < .001		

Note: BDI = Beck Depression Inventory II, BFI = Big Five Inventory, MoCA = Montreal Cognitive Assessment, HCCQ = Healthcare Climate, Questionnaire, SAMS = Stendal Adherence to Medication Score, SRH = Self-Rated Health according to SF-36 Item 1, TuG = Timed Up and Go

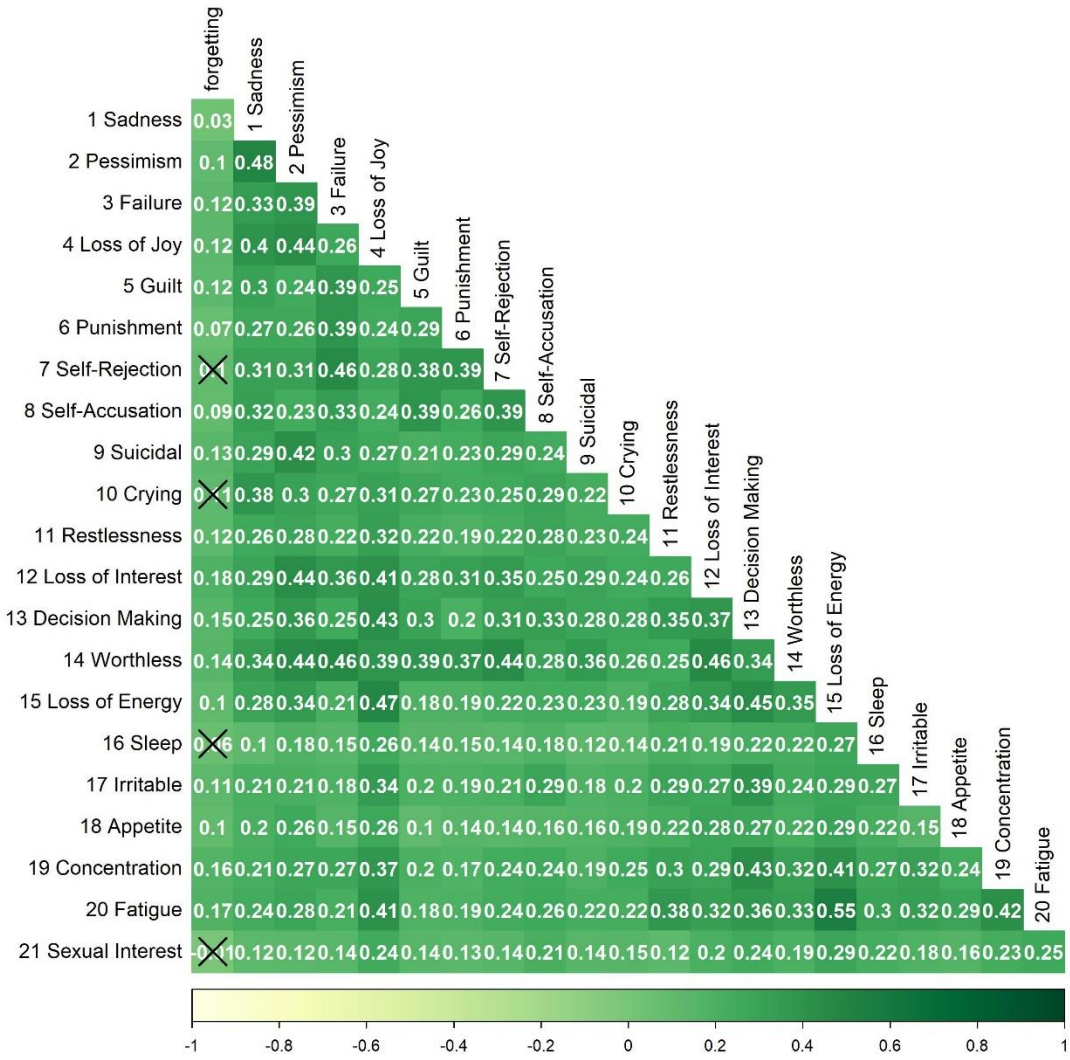
Supplement Table 2. Linear Regression after Elastic Net Regularization for SAMS sub-scales using BDI items as predictors

Variable	**Est.**	**CI**	**p**	**Est.**	**CI**	**p**	**Est.**	**CI**	**p**
Outcome	Model 1: SAMS: Forgetting			Model 2: SAMS: Missing Knowledge			Model 3: SAMS: *Modification*		
Intercept	0.28	0.21 – 0.34	<0.001	0.38	0.28 – 0.49	**<0.001**	0.06	-0.00 – 0.13	0.063
BDI 1							0.03	-0.05 – 0.10	0.465
BDI 3	0.04	-0.05 – 0.13	0.357	0.09	-0.03 – 0.21	0.127			
BDI 4				-0.08	-0.18 – 0.02	0.101	0.07	-0.03 – 0.17	0.144
BDI 5									
BDI 9	0.07	-0.05 – 0.18	0.263						
BDI 10				0.04	-0.05 – 0.13	0.353			
BDI 11	0.02	-0.05 – 0.08	0.640				0.03	-0.03 – 0.09	0.305
BDI 12	0.09	0.01 – 0.17	**0.029**	0.14	0.03 – 0.25	**0.013**	0.07	-0.00 – 0.14	**0.056**
BDI 14	0.04	-0.05 – 0.13	0.417	0.07	-0.06 – 0.20	0.283			
BDI 15				-0.13	-0.23 – -0.02	**0.018**			
BDI 16							0.03	-0.01 – 0.07	0.158
BDI 17	0.02	-0.07 – 0.10	0.699				0.04	-0.04 – 0.12	0.302
BDI 18				0.04	-0.04 – 0.13	0.330			
BDI 19	0.03	-0.04 – 0.10	0.375	0.16	0.06 – 0.25	**0.001**	0.02	-0.04 – 0.08	0.561
BDI 20	0.06	-0.01 – 0.13	0.093				0.05	-0.02 – 0.11	0.144
Model Fit	N = 730, R^2 / R^2 adjusted = 0.058 / 0.047 F(8, 721) = 5.509, p < .001			N = 730, R^2 / R^2 adjusted = 0.058 / 0.047 F(8, 721) = 5.54, p < .001			N = 730, R^2 / R^2 adjusted = 0.058 / 0.047 F(8, 721) = 5.52, p < .001		

Note: BDI = Beck Depression Inventory II; CI = Confidence Interval; SAMS = Stendal Adherence to Medication Score. Grey fields indicate that the variable was excluded from the model during elastic net regularization

Schönenberg, A., Heimrich, K.G. & Prell, T. (2024). Impact of depressive symptoms on medication adherence in older adults with chronic neurological diseases. *BMC Psychiatry* 24, 131. doi.org/10.1186/s12888-024-05585-7

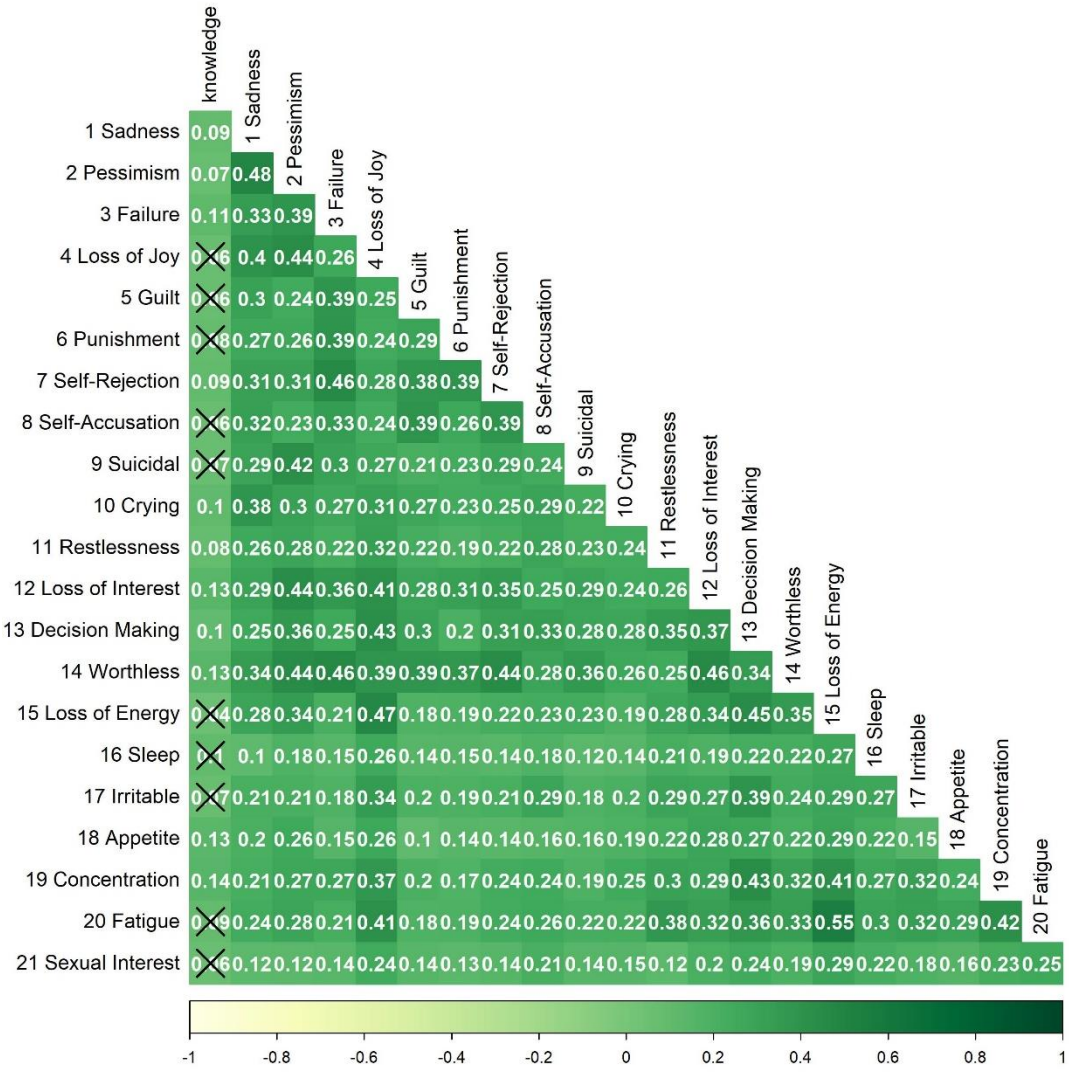
Supplement Figure 1. Spearman Correlations for SAMS Forgetting and BDI Items



Note: BDI = Beck Depression Inventory II; SAMS = Stendal Adherence to Medication Score

Schönenberg, A., Heimrich, K.G. & Prell, T. (2024). Impact of depressive symptoms on medication adherence in older adults with chronic neurological diseases. *BMC Psychiatry* 24, 131. doi.org/10.1186/s12888-024-05585-7

Supplement Figure 2. Spearman Correlations for SAMS Missing Knowledge and BDI Items



Note: BDI = Beck Depression Inventory II; SAMS = Stendal Adherence to Medication Score

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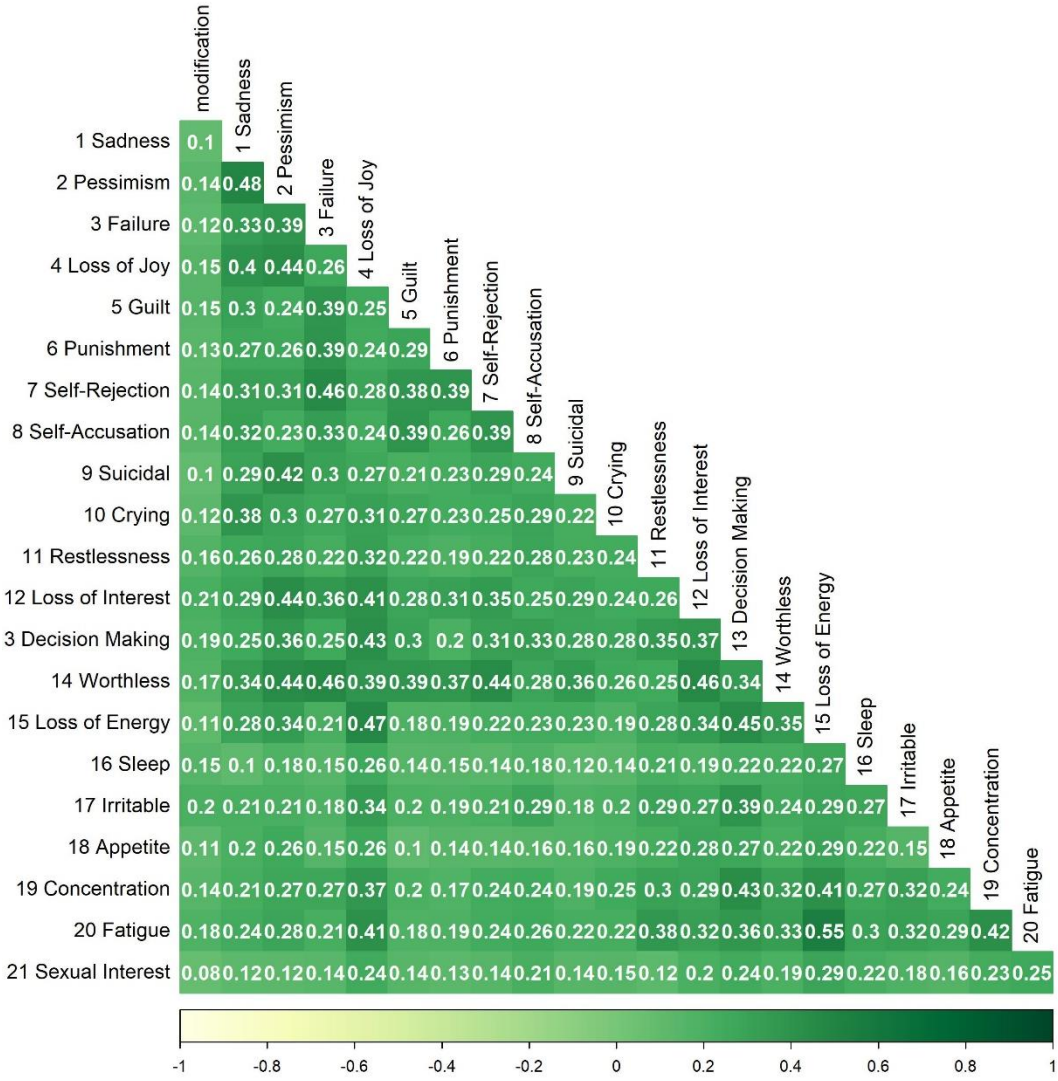
Supplement Figure 3. Spearman Correlations for SAMS Modification and BDI Items



Note: BDI = Beck Depression Inventory II; SAMS = Stendal Adherence to Medication Score

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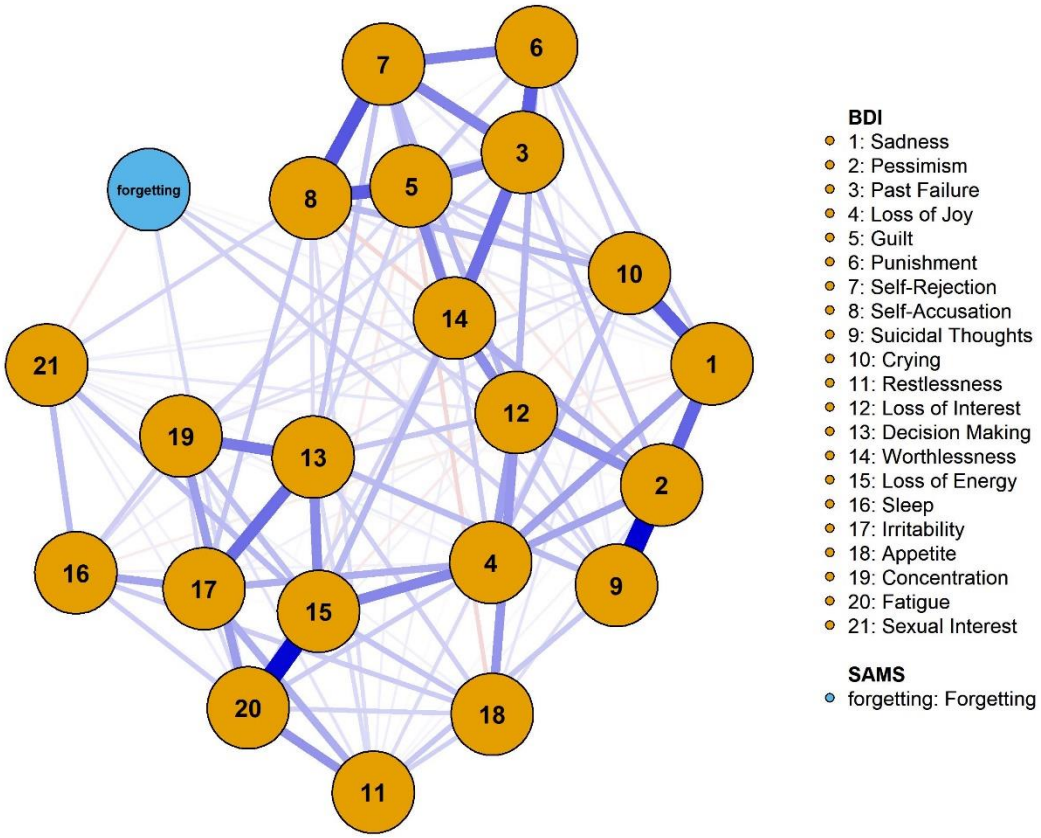
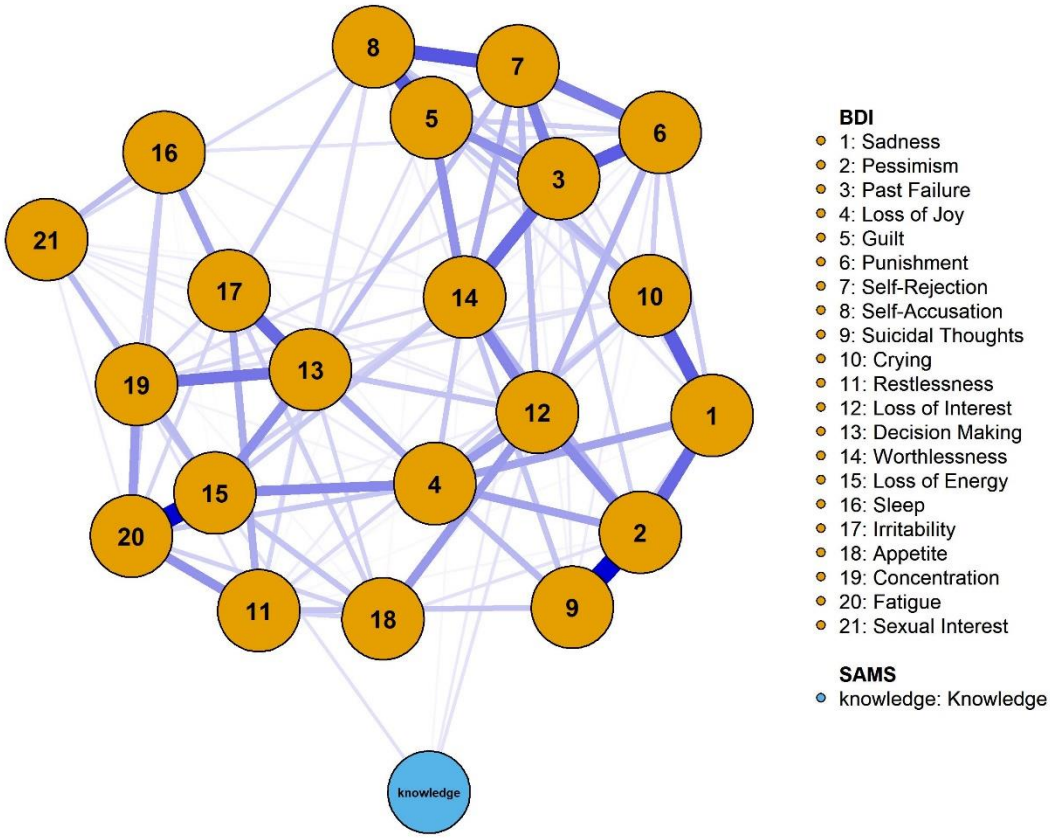
Supplement Figure 4. Network for SAMS Forgetting and BDI Items



Note: CS-C = .595., displaying 133/231 edges. BDI = Beck Depression Inventory II; SAMS = Stendal Adherence to Medication Score

Schönenberg, A., Heimrich, K.G. & Prell, T. (2024). Impact of depressive symptoms on medication adherence in older adults with chronic neurological diseases. *BMC Psychiatry* 24, 131. doi.org/10.1186/s12888-024-05585-7

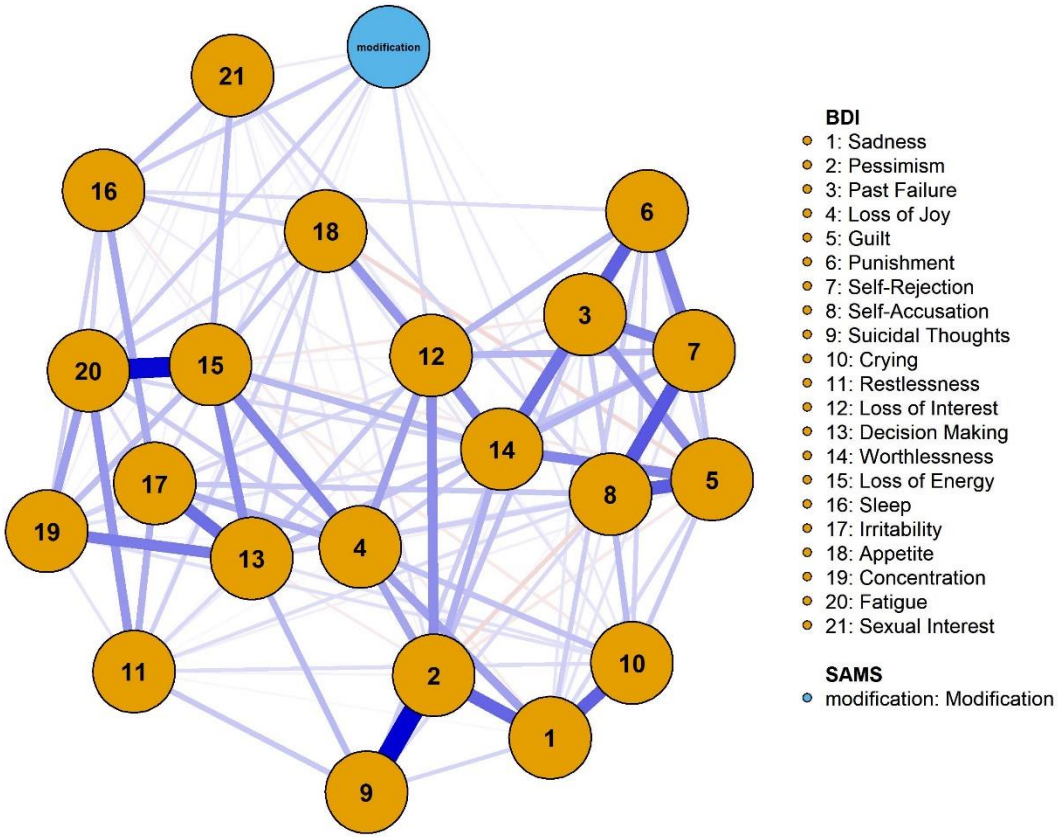
Supplement Figure 5. Network for SAMS Missing Knowledge and BDI Items



Note: CS-C = .595., displaying 116/231 edges. BDI = Beck Depression Inventory II; SAMS = Stendal Adherence to Medication Score

Schönenberg, A., Heimrich, K.G. & Prell, T. (2024). Impact of depressive symptoms on medication adherence in older adults with chronic neurological diseases. *BMC Psychiatry* 24, 131. doi.org/10.1186/s12888-024-05585-7

Supplement Figure 6. Network for SAMS Modification and BDI Items



Note: CS-C = .516., displaying 136/231 edges. BDI = Beck Depression Inventory II; SAMS = Stendal Adherence to Medication Score

BMJ Open

Using a generic quality of life measure to determine adherence thresholds: a cross-sectional study on older adults with neurological disorders in Germany

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ABSTRACT

Objectives Measuring the degree of adherence to medication is essential in healthcare However, the cut-offs provided for adherence scales are often arbitrary and disease-specific, and need to be validated against a clinical outcome. Here, we used health-related quality of life (QoL) to determine cut-offs for a self-report adherence questionnaire in patients with neurological diagnoses.

Design Cross-sectional study.

Participants 910 patients (age 70±8.6 years) with neurological disorders were recruited from the wards of neurology at a local university hospital. All patients received a comprehensive geriatric assessment, including assessments of adherence (Stendal Adherence to Medication Score, SAMS) and QoL (Short Form Survey SF-36).

Outcome measures The main aim of the study was to define a cut-off for non-adherence at which QoL is significantly impaired. Thus, we used Spearman's rank correlation, multivariate and univariate analyses of variance to test the impact of different adherence levels on QoL. Receiver operating characteristics and area under curve measures were then used to determine cut-off scores for adherence based on significant differences in QoL.

Results Correlations between SAMS and SF-36 domains were weak (ranging between r=−0.205 for emotional well-being and r=−0.094 for pain) and the effect of non-adherence on QoL disappeared in the multivariate analysis of variance (p=0.522) after adjusting for demographical and clinical factors. SAMS cut-offs in terms of SF-36 domains varied greatly, so that an overall SAMS cut-off for this cohort could not be defined.

Conclusions QoL as measured by the SF-36 is not suitable as a single outcome parameter to study the impact of non-adherence on QoL in a mixed neurological cohort. Since both QoL and adherence are heterogeneous, multifaceted constructs, it is unlikely to find an overarching cut-off applicable for all patients. Thus, it may be necessary to use disease or cohort-specific external outcome parameters to measure the indirect effect of interventions to enhance adherence.

Trial registration number DRKS00016774.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We used a commonly applied quality of life questionnaire to define clinically relevant cut-off scores for non-adherence using receiver operating characteristic (ROC) and area under curve analysis.
⇒ Our comprehensive data on 910 older adults provides ample information on adherence and its influence of quality of life when controlling for relevant covariates such as depression, cognition and health.
⇒ Our data and results are limited to the cohort of older adults with neurological disorders; however, in this particular cohort, the problem of non-adherence is particularly relevant.

BACKGROUND

Adherence describes the extent to which a person's behaviours correspond with agreed recommendations from their healthcare provider. However, many people cannot or do not want to take medications as prescribed. This non-adherence contributes to poorer health outcomes, higher healthcare costs and lower quality of life (QoL).[1 2] Measuring adherence is important for several reasons, for example, determining the influence of non-adherence on outcome parameters in clinical trials, identifying patients' needs or determining the effect of interventions to improve adherence and thus health. Non-adherence can be detected with objective and subjective methods, which both have their drawbacks.[3] Objective measures include methods such as dose counts, pharmacy records, electronic monitoring of medication administration (eg, the Medication Event Monitoring System) and drug concentrations in plasma. Subjective measures of adherence include patient interviews and self-report adherence scales. These subjective measures are simple to use and can identify personal reasons for non-adherence.[3 4] In addition to the question of which instrument to use, another issue with measuring adherence is the question

of an appropriate cut-off to determine non-adherence. Most subjective adherence scales provide cut-offs for identifying non-adherence. However, the arbitrary nature of the cut-offs provided for most self-report adherence scales needs to be kept in mind.[5] Oftentimes, the cut-off point to identify non-adherence is based on the respective distribution of scores, or determined in comparison to objective measures, such as the score that corresponds to patients that took 80% of their medication as ascertained by an objective measure of adherence. However, these cut-off scores do not necessarily determine whether the identified level of non-adherence is clinically relevant. A small number of scales have assessed the sensitivity and specificity of their cut-off against an external clinical parameter.[6 7] These external clinical outcomes are oftentimes disease-specific (eg, blood pressure, cardiovascular events). However, to define an adherence cut-off in mixed cohorts with more than one disorders is challenging. This is especially true in older adults, where multimorbidity is common[8] and one single clinical endpoint is not feasible. Given that non-adherence was also found to be associated with poor health-related QoL,[1 9 10] we aimed to test if a generic QoL measure can be used to determine adherence cut-off in a cohort of older patients with mixed neurological diagnoses.

METHODS

Setting and participants

This paper reports explorative analyses of the cross-sectional dataset from the NeuroGerAd study,[11] which is a longitudinal observational study in older hospitalised adults with neurological disorders (registered in the German Clinical Trials Register DRKS00016774; registered on 19 February 2019).[12 13] Briefly, from February 2019 to March 2020, elderly patients with neurological disorders received a comprehensive geriatric assessment during their stay in the Department of Neurology at the Jena University Hospital. We included patients (age>55 with multimorbidity or age>60) with a common neurological disorder (cerebrovascular disorders, movement disorders, epilepsy and neuromuscular or peripheral neurological disorders). Patients with dementia, acute psychotic symptoms and delirium were excluded.

Detailed information on the study can be found in the corresponding data descriptor.[13] In short, 2021 patients aged 55 years and above were admitted to the department during the data collection phase, of which 113 could not be approached before discharge. Of the remaining 1908 patients, 997 were excluded because they did not meet the inclusion criteria, were physically unable or declined to participate. A total of 995 patients were deemed eligible, and 910 patients completed the assessments. The following assessments were used for this analysis: age, gender, main neurological diagnosis, medication regime at admission and discharge, marital status (single/divorced/widowed or married), living condition (alone, not alone), level of education (high, middle, low), number of medications per day, medical diagnoses, depression (Beck's Depression Inventory II, BDI,[14] personality (Big Five Inventory, BFI,[15] Healthcare Climate Questionnaire (HCCQ),[16] QOL (SF-36),[17] adherence (Stendal Adherence to Medication Score, SAMS),[18] Timed-Up-and-Go Test (TuG),[19] and Montreal Cognitive Assessment (MoCA).[20]

The Short Form Survey (SF-36) is a general health-related QoL questionnaire with eight different domains: problems regarding both physical and social activity due to health, limitations in daily life due to physical or emotional problems, pain, mental health, vitality and general health perception. Each domain is summarised as the weighted sum of the respective items, with lower scores indicating less disability. A physical and mental compound score as well subscores can be calculated.[17]

The SAMS is a questionnaire with 18 items summed up in a cumulative adherence score, with 0 indicating complete adherence and 72 complete non-adherence.[21] One if its advantages is that different facets of adherence are included, namely modification of medication, lack of knowledge and forgetting to take medication.[18 22] The SAMS has previously been validated in neurological patients, patients with chronic pain and patients with kidney transplants, and has been used in a variety of studies since.[18 23–27]

All self-report questionnaires were checked for completeness by study staff, which was available in case of questions. The face-to-face approach allowed us to assess if patients were cognitively able to participate and give valid information.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Statistical analysis

Descriptive statistics (mean and SD for continuous data, absolute and relative frequencies for categorical data) were used to describe the overall study population. Spearman's rank correlation coefficient was calculated to assess the association between SAMS and the SF-36 domains. In order to adjust for sociodemographic factors and clinical parameters, multivariate analysis of variance (MANOVA) was performed. Here, the SF-36 domains served as dependent variables and the SAMS as well as the following covariates were included as independent variables: gender, living condition, diagnosis, personality according to BFI, number of daily medication, HCCQ, MoCA and TuG in seconds. The mean difference in the SF-36 domains was analysed for different cut-offs of the SAMS score and area under curve (AUC) with 95% CI was calculated to evaluate the discrimination between the groups defined by the cut-off value. The significance level was set at 0.05 for all statistical tests.

Table 1 Clinical and demographical characteristics (N=910)

	n	%	Missing
Sex			
Female	389	42.7	0
Male	521	57.3	
Marital			
Single/widowed/divorced	277	30.8	12
Married	621	69.2	
Living situation			
Alone	204	24.1	65
Not alone	641	75.9	
Education			
High	325	36.3	14
Middle	306	34.2	
Low	265	29.6	
Occupation status			
Not working/retired	756	84.0	10
Working	144	16.0	
Diagnosis group			
Movement disorder	303	33.3	0
Cerebrovascular disorder	233	25.6	
Epilepsy	48	5.3	
Neuromuscular	168	18.5	
Others	158	17.4	
	M	**SD**	**Missing**
Age	70.1	8.6	0
Beck Depression Inventory II	9.8	7.6	1
Healthcare Climate Questionnaire	5.6	1.1	79
Montreal cognitive assessment	22.5	4.4	0
Timed-Up-and-Go duration in seconds	10.5	4.3	325*
Stendal Adherence to Medication Score	6.3	7.6	0
No of Medications/day	5.6	3.7	67
SF-36 Physical Component Scale	33.9	11.0	61
SF-36 Mental Component Scale	48.6	11.2	61

*Timed-Up-and-Go not performed in 325 subjects for medical reasons.
M, mean; SF-36, Short Form Survey.

RESULTS

Demographical data of the 910 adults (42.75% or 389 female, 57.25% or 521 male, mean age 70±SD = 8.6 years) are given in table 1. Health-related QoL as measured by the SF-36 was substantially impaired in this sample of older ill adults in comparison with the general German population[28] (figure 1).

There were weak negative correlations between the SAMS and the SF-36 domains physical functioning (r=−0.129, p<0.001), social functioning (r=−0.176, p<0.001), role limitations due to physical health (r =−0.144, p<0.001), role limitations due to emotional problems (r=−0.177, p<0.001), emotional well-being (r=−0.205, p<0.001), energy/fatigue (r=−0.184, p<0.001), pain (r=−0.097, p=0.004), general health (r=−0.191, p<0.001), Physical Component Scale (r=−0.135, p<0.001) and Mental Component Scale (r=−0.200, p<0.001). An MANOVA with the 8 SF-36 domains as dependent variables showed a significant influence of the SAMS on the combined dependent variables, $F(8, 840) = 5.891$, p<0.001, partial Wilk's $\Lambda=0.947$. Post hoc univariate analysis of variances were conducted for every dependent variable. The SAMS was significantly associated with all SF-36 domains except pain: physical functioning (p=0.014), social functioning (p<0.001), role limitations due to physical health (p<0.001), role limitations due to emotional problems (p<0.001), emotional well-being (p<0.001), energy/fatigue (p<0.001), general health (p<0.001), pain (p=0.176). However, after adjustment for sociodemographic and clinical factors, the SAMS was no longer significantly associated with the SF-36 domains (p=0.522) (table 2).

We then explored how the SF-36 domains differed between subjects below and above the possible SAMS cut-offs (ranging from 0 to 72 points). By doing so, we determined how the SF-36 domains change as a function of the SAMS, that is, at which SAMS cut-off the influence on the SF-36 is maximal. For the two compound SF-36 scales, a mixed picture emerges. For the Physical Component Scale, the maximum mean difference was 3.2 points when the SAMS cut-off was set at two points (ie, comparing groups with SAMS ≤2 vs >2). For a SAMS cut-off of 31 or higher, the SF-36 Physical Component Scales were even higher than in the other group, which can certainly be attributed to the small sample with SAMS >31 and the increased sampling error (figure 2).

In contrast, for the SF-36 Mental Component Scale, the differences of the means at all SAMS cut-offs were greater than zero. The maximum difference of 8.4 points in the SF-36 was reached at a SAMS cut-off of 41 points (AUC=0.713, 95% CI: 0.453 to 0.973, p<0.001) (figure 3). The detailed SAMS thresholds for the SF-36 component scales and 8 SF-36 domains are given in figures 2 and 3. All SAMS cut-offs and the corresponding AUCs are detailed in online supplemental tables 1 and 2.

DISCUSSION

According to the SF-36, the studied cohort showed poorer health-related QoL in all domains in comparison to a German reference cohort, the German Health Interview and Examination Survey for Adults.[28] This is in line with other studies linking chronic illness and multimorbidity to worse functional status, disability and thus reduced QoL,[29] indicating that the SF-36 measured our cohort's

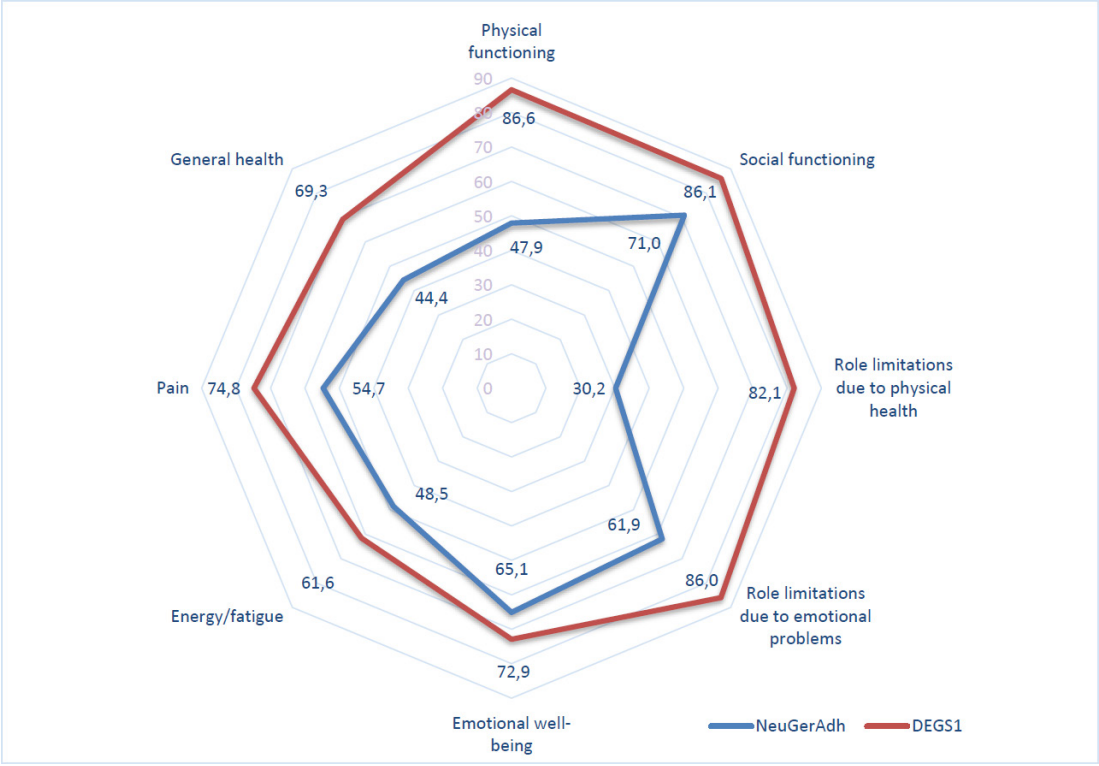

Figure 1 Comparison of mean health-related quality of life as measured in the Short-Form Survey (SF-36) domains between the NeurGerAdh cohort and German reference cohort (DEGS1). DEGS1, German Health Interview and Examination Survey for Adults.

QoL somewhat accurately. Despite a well-documented link between non-adherence and QoL,[30–32] some studies found only weak univariate associations between adherence and QoL domains[9 10] that match our own results. This weak association is also the reason why some of the cut-offs for the SAMS found are so variable and high. The difficulty in finding a concrete connection between adherence and QoL may stem from the heterogeneity of the two constructs themselves. The factors associated with adherence are numerous, complex and vary between patients.[1 33] Similarly, as health-related QoL is essentially a patients' interpretation of the current health status, it is a highly individual construct with varying factors, leading to different scales measuring different concepts without covering all aspects of QoL.[34 35] Therefore, for each patient, different aspects may influence both QoL and non-adherence, leading to heterogeneity in the association between both constructs. Therefore, our results contradict our initial hypothesis and instead suggest that QoL as an overarching and relevant clinical endpoint is

Table 2 Results from the MANOVA with the eight SF-36 domains as dependent variables

	Wilk's Λ	F	dF	Error df	P value	Partial Eta²
Constant	0.654	28.717	8.000	435.000	0.000	0.346
Sex	0.954	2.636	8.000	435.000	0.008	0.046
Living situation	0.963	2.098	8.000	435.000	0.035	0.037
Diagnosis	0.886	1.674	32.000	1605.796	0.011	0.030
Personality (BFI)	0.879	1.423	40.000	1898.916	0.042	0.025
SAMS	0.984	0.894	8.000	435.000	0.522	0.016
No of medications per day	0.877	7.639	8.000	435.000	0.000	0.123
BDI	0.565	41.866	8.000	435.000	0.000	0.435
HCCQ	0.987	0.740	8.000	435.000	0.656	0.013
MoCA	0.951	2.799	8.000	435.000	0.005	0.049
TuG	0.840	10.376	8.000	435.000	0.000	0.160

BDI, Beck Depression InventoryII; BFI, Big Five Inventory; HCCQ, Healthcare Climate Questionnaire; MANOVA, multivariate analysis of variance; MoCA, Montreal Cognitive Assessment; SAMS, Stendal Adherence to Medication Score; TuG, Timed-Up-and-Go.

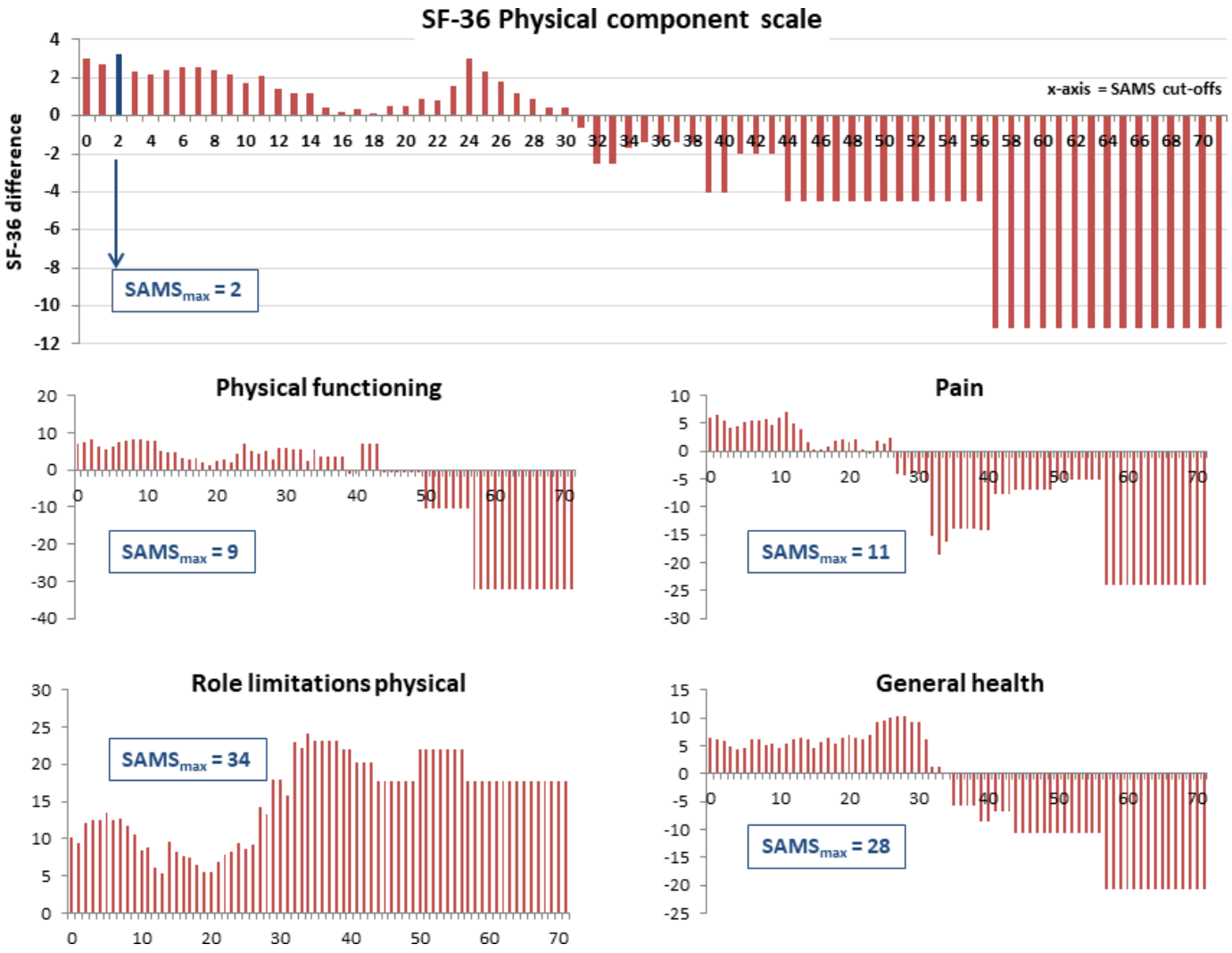

Figure 2 Change of Short-Form Survey (SF-36) domains and component scales as a function of different SAMS cut-offs the Physical Subscale. Note: The x-axis shows the possible SAMS cut-offs based on sum scores ranging from 0 to 72. The y-axis shows how the SF-36 changes depending on the SAMS cut-off. By doing so, we determined at which SAMS cut-off the influence on the SF-36 is maximal. SAMS, Stendal Adherence to Medication Score.

not sufficiently clear-cut to serve as an indicator of non-adherence cut-offs.

While clinical outcomes are the ultimate aim of any intervention to enhance adherence, the use of clinical outcomes as a proxy of adherence can be confounded by disease-specific factors independent of real adherence. The connection between QoL and adherence in our study vanished after controlling for demographical and clinical factors, which all contribute individually to both adherence and QoL.[1] It is possible that measuring such complex constructs with a single questionnaire falls short when each contributing component, such as age, diagnosis or depression, is considered individually. The many dimensions and subscales may interact in individual ways for each patient, thus effectively annihilating any overall effect for wider populations.[36]

As shown in this study, the SF-36 is not suitable as a single external outcome parameter to define a reasonable cut-off of the SAMS in a mixed neurological cohort. Therefore, it is also not possible to determine a general SAMS cut-off that differentiates between adherent and non-adherent patients with respect to QoL. Due to the heterogeneity of both constructs, it seems unlikely to find an overarching cut-off for adherence that is applicable to all patients, and it may be more appropriate to use specific outcome parameters for individual patients or specific cohorts (eg, Unified Parkinon's Disease Rating Scale in Parkinson's disease) to estimate the effect of non-adherence or the effect of interventions to improve adherence.[33]

Limitations

This study has several limitations. This is an explorative study of a dataset, which was intended to study predictors of non-adherence in elderly people with neurological disorders. Therefore, confirmatory statements cannot be made. Another limitation is that we evaluated many symptoms exclusively through self-reports, which are known to be prone to systematic and unsystematic biases.[37] However, the questionnaires used are valid in the clinical

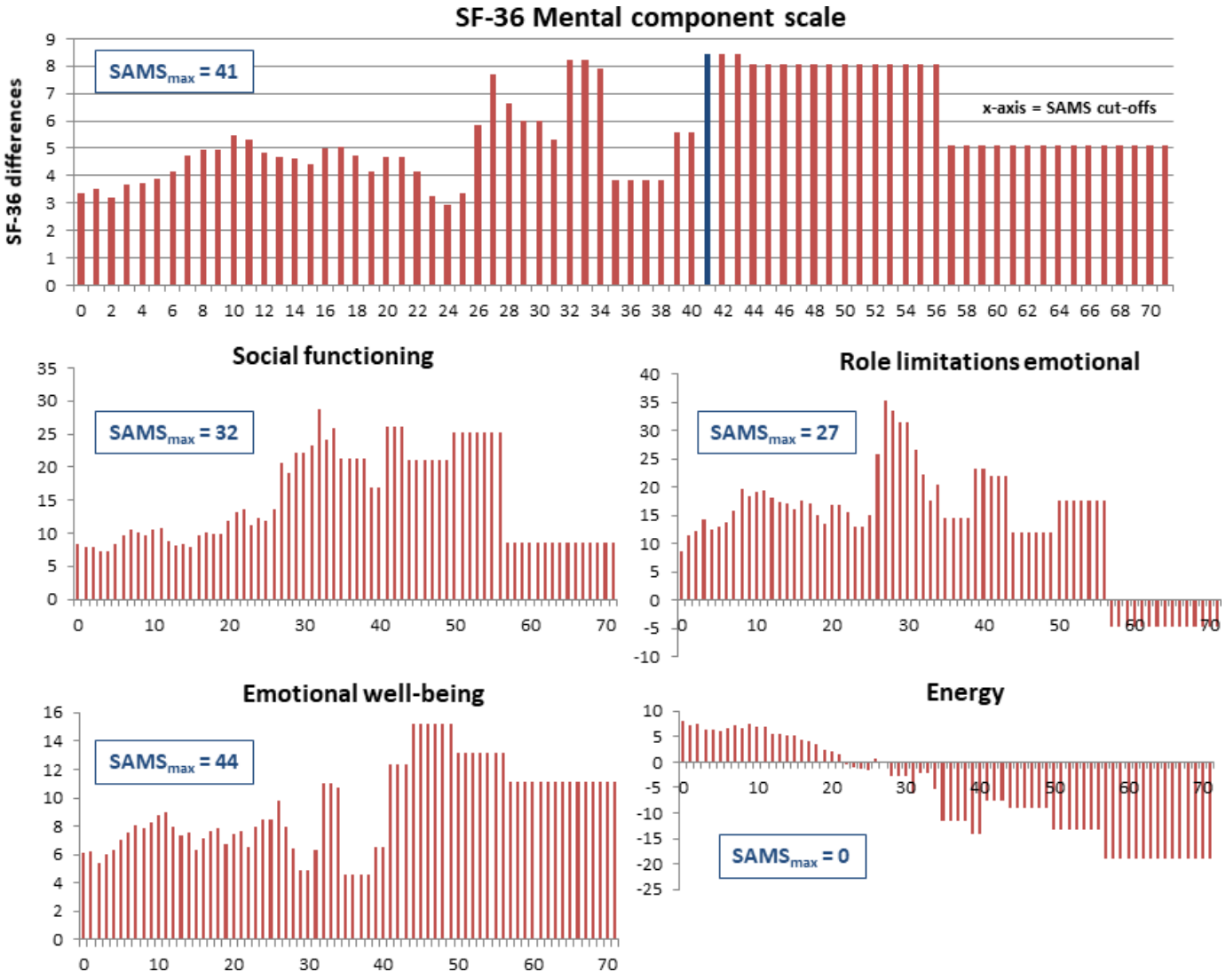

Figure 3 Change of Short-Form Survey (SF-36) domains and component scales as a function of different SAMS cut-offs the Mental Subscale. Note: The x-axis shows the possible SAMS cut-offs based on sum scores ranging from 0 to 72. The y-axis shows how the SF-36 changes depending on the SAMS cut-off. By doing so, we determined at which SAMS cut-off the influence on the SF-36 is maximal. SAMS, Stendal Adherence to Medication Score.

literature.[22 35 38] Furthermore, we only used one measure for adherence and QoL each, and several others exist which were not used in this study. There are more than 40 different self-report scales for measuring adherence, and while those scales differ greatly, none of them perform appropriately in all aspects.[5]

Although research suggests that there are no best practice instruments available that cover all important aspects of adherence and QoL,[5] a general statement about QoL and adherence using different scales cannot be made and further research is needed to validate our results in different groups of patients and using different adherence measures.

Conclusion

Our data suggest that using a general QoL-measurement to determine cut-off scores for adherence levels is not feasible in a mixed patient group, as the multiple dimensions and subscales of the two complex constructs may interact individually for each patient. Therefore, to determine adherence scores that are clinically relevant, disease-specific and patient-specific aspects must be determined to identify clinically relevant adherence.

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Contributors Design of the study: TP. Collection of data: AS and HMM. Analysis: TP, TL. Writing of the paper: TP and HMM. Writing—editing and revision: AS. All authors read and approved the final manuscript. TP is the guarantor for this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (ethics committee of the Jena University Hospital, 4572-10/15) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the local ethics committee (approval number 5290-10/17) of Jena University Hospital. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The anonymous data from the study can be freely requested from: Prell, T., Schönenberg, A., Mühlhammer, H.M. &Teschner, U (2022). *Data on Medication Adherence in Adults with Neurological Disorders: The NeuroGerAd Study* [Data Collection]. Colchester, Essex: UK Data Service. 10.5255/UKDA-SN-856032

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Supplementary Materials für Publication III

Supplement Table 1: SAMS cut-off and corresponding SF-36 scores

SAMS Cut-off	Physical component scale	Mental component scale	Physical functioning	Social functioning	Role lim. Physic. health	Role lim. Emot. problems	Emot. Well-being	Energy/ fatigue	Pain	General health
0	3.00	3.38	7.24	8.44	10.14	8.73	6.08	***8.00***	6.12	6.34
1	2.70	3.53	7.30	7.83	9.48	11.49	6.18	7.30	6.49	6.20
2	***3.24***	3.18	8.18	8.00	12.16	12.22	5.41	7.42	5.52	5.85
3	2.31	3.69	6.42	7.28	12.44	14.26	6.01	6.48	4.18	4.94
4	2.16	3.73	5.58	7.31	12.50	12.51	6.35	6.26	4.42	4.27
5	2.39	3.86	6.32	8.44	13.39	13.10	7.02	6.09	5.38	4.55
6	2.57	4.16	7.36	9.75	12.43	13.80	7.51	6.73	5.60	6.15
7	2.54	4.75	7.66	10.64	12.78	15.92	8.03	7.15	5.48	6.22
8	2.43	4.95	8.27	10.00	11.79	19.63	7.88	6.77	5.75	5.08
9	2.16	4.94	***8.32***	9.70	10.50	18.44	8.22	7.58	4.82	5.46
10	1.71	5.46	7.73	10.56	8.47	19.08	8.81	6.98	5.97	4.48
11	2.09	5.31	7.97	10.75	8.76	19.34	8.98	6.94	***6.97***	5.45
12	1.40	4.85	5.28	8.74	5.99	18.10	7.95	5.62	5.02	6.21
13	1.21	4.66	4.89	8.20	5.34	17.22	7.38	5.40	3.84	6.53
14	1.15	4.64	4.88	8.25	9.64	17.11	7.51	5.35	1.67	6.11
15	0.43	4.40	3.10	7.83	8.22	15.96	6.35	5.25	0.41	4.58
16	0.19	4.99	2.88	9.62	7.70	17.61	7.16	4.28	0.28	5.54
17	0.37	5.05	3.09	10.21	7.38	17.00	7.66	4.21	0.87	6.35
18	0.16	4.74	2.04	9.79	6.55	15.06	7.87	3.45	1.91	5.44
19	0.47	4.13	1.15	9.80	5.50	13.37	6.74	2.39	2.26	6.46
20	0.48	4.68	2.45	11.79	5.44	16.70	7.45	2.02	1.67	6.85
21	0.88	4.68	2.79	13.11	6.91	16.90	7.66	1.67	2.23	6.49
22	0.83	4.14	1.96	13.56	7.84	15.64	6.55	-0.50	0.16	6.20
23	1.53	3.26	4.33	11.09	8.24	12.96	7.91	-0.91	-0.43	6.88
24	2.98	2.93	6.99	12.23	9.48	12.98	8.48	-1.30	1.84	9.20
25	2.35	3.37	5.29	11.84	8.57	15.14	8.43	-1.52	1.50	9.40
26	1.81	5.82	4.48	13.59	9.17	25.87	9.77	0.75	2.35	10.12
27	1.22	7.72	4.99	20.73	14.31	***35.18***	7.93	-0.15	-4.03	10.18
28	0.86	6.66	2.70	19.17	13.26	33.39	6.38	-2.60	-4.24	***10.21***
29	0.43	5.98	5.71	22.22	17.99	31.37	4.90	-2.68	-4.05	9.12
30	0.43	5.98	5.71	22.22	17.99	31.37	4.90	-2.68	-4.05	9.12
31	-0.63	5.31	5.33	23.27	15.84	26.44	6.30	-6.11	-5.25	6.27
32	-2.50	8.22	5.51	***28.84***	22.97	22.20	11.02	-2.06	-15.15	1.26
33	-2.50	8.22	2.41	24.03	22.10	17.68	11.02	-2.06	-18.47	1.26
34	-1.69	7.92	5.49	25.93	***24.18***	20.46	10.73	-5.28	-16.33	0.09
35	-1.39	3.84	3.69	21.18	23.25	14.44	4.60	-11.58	-13.89	-5.66
36	-1.39	3.84	3.69	21.18	23.25	14.44	4.60	-11.58	-13.89	-5.66
37	-1.39	3.84	3.69	21.18	23.25	14.44	4.60	-11.58	-13.89	-5.66
38	-1.39	3.84	3.69	21.18	23.25	14.44	4.60	-11.58	-13.89	-5.66
39	-4.03	5.56	-1.23	16.96	22.02	23.21	6.51	-14.08	-14.07	-8.67
40	-4.03	5.56	-1.23	16.96	22.02	23.21	6.51	-14.08	-14.07	-8.67
41	-2.01	***8.42***	6.98	26.16	20.32	22.07	12.40	-7.53	-7.76	-6.91
42	-2.01	***8.42***	6.98	26.16	20.32	22.07	12.40	-7.53	-7.76	-6.91
43	-2.01	***8.42***	6.98	26.16	20.32	22.07	12.40	-7.53	-7.76	-6.91
44	-4.49	8.07	-0.81	21.11	17.79	12.00	***15.20***	-9.03	-7.03	-10.66
45	-4.49	8.07	-0.81	21.11	17.79	12.00	***15.20***	-9.03	-7.03	-10.66
46	-4.49	8.07	-0.81	21.11	17.79	12.00	***15.20***	-9.03	-7.03	-10.66
47	-4.49	8.07	-0.81	21.11	17.79	12.00	***15.20***	-9.03	-7.03	-10.66
48	-4.49	8.07	-0.81	21.11	17.79	12.00	***15.20***	-9.03	-7.03	-10.66
49	-4.49	8.07	-0.81	21.11	17.79	12.00	***15.20***	-9.03	-7.03	-10.66
50	-4.49	8.07	-10.42	25.27	21.95	17.56	13.18	-13.20	-5.15	-10.66
51	-4.49	8.07	-10.42	25.27	21.95	17.56	13.18	-13.20	-5.15	-10.66
52	-4.49	8.07	-10.42	25.27	21.95	17.56	13.18	-13.20	-5.15	-10.66
53	-4.49	8.07	-10.42	25.27	21.95	17.56	13.18	-13.20	-5.15	-10.66
54	-4.49	8.07	-10.42	25.27	21.95	17.56	13.18	-13.20	-5.15	-10.66
55	-4.49	8.07	-10.42	25.27	21.95	17.56	13.18	-13.20	-5.15	-10.66
56	-4.49	8.07	-10.42	25.27	21.95	17.56	13.18	-13.20	-5.15	-10.66

57	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
58	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
59	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
60	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
61	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
62	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
63	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
64	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
65	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
66	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
67	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
68	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
69	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
70	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67
71	-11.20	5.11	-32.13	8.54	17.75	-4.73	11.16	-19.03	-23.89	-20.67

SF-36 scales: Physical component scale, mental component scale, physical functioning, social functioning, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, energy/fatigue, pain, general health

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Supplement Table 2: Area Under Curve (AUC)

SAMS Cut-off	Physical component scale	Mental component scale	Physical functioning	Social functioning	Role lim. Physic. Health	Role lim. Emot. Problem	Emot. Well-being	Energy/ fatigue	pain	General health
0	0.579	0.584	0.568	0.588	0.556	0.555	0.594	0.609	0.555	0.609
1	0.573	0.590	0.568	0.581	0.553	0.568	0.596	0.599	0.559	0.608
2	0.588	0.583	0.576	0.583	0.566	0.573	0.584	0.601	0.551	0.602
3	0.563	0.597	0.560	0.574	0.572	0.585	0.592	0.587	0.538	0.587
4	0.560	0.596	0.552	0.573	0.573	0.572	0.595	0.582	0.541	0.575
5	0.566	0.600	0.559	0.583	0.579	0.575	0.607	0.580	0.549	0.580
6	0.571	0.607	0.569	0.597	0.572	0.578	0.615	0.590	0.552	0.608
7	0.571	0.622	0.571	0.607	0.577	0.590	0.623	0.597	0.551	0.608
8	0.568	0.624	0.577	0.601	0.571	0.611	0.620	0.593	0.554	0.589
9	0.562	0.622	0.577	0.596	0.560	0.604	0.625	0.605	0.546	0.598
10	0.549	0.634	0.572	0.607	0.548	0.610	0.633	0.594	0.556	0.579
11	0.558	0.632	0.574	0.610	0.552	0.612	0.635	0.597	0.566	0.592
12	0.539	0.625	0.549	0.589	0.542	0.607	0.622	0.582	0.548	0.608
13	0.534	0.619	0.546	0.580	0.535	0.602	0.613	0.578	0.538	0.610
14	0.532	0.619	0.546	0.581	0.563	0.599	0.612	0.576	0.518	0.604
15	0.516	0.617	0.529	0.575	0.556	0.594	0.597	0.576	0.506	0.579
16	0.512	0.633	0.527	0.594	0.554	0.605	0.606	0.563	0.505	0.591
17	0.518	0.636	0.529	0.598	0.554	0.601	0.613	0.561	0.511	0.607
18	0.488	0.628	0.519	0.589	0.549	0.592	0.614	0.549	0.520	0.590
19	0.484	0.613	0.511	0.586	0.543	0.584	0.599	0.530	0.522	0.610
20	0.478	0.622	0.523	0.599	0.541	0.604	0.605	0.532	0.518	0.623
21	0.470	0.619	0.526	0.613	0.549	0.606	0.611	0.528	0.521	0.614
22	0.475	0.603	0.518	0.615	0.553	0.600	0.587	0.495	0.501	0.604
23	0.549	0.575	0.541	0.588	0.556	0.584	0.603	0.490	0.504	0.615
24	0.584	0.562	0.566	0.597	0.563	0.585	0.607	0.485	0.517	0.651
25	0.567	0.572	0.549	0.590	0.556	0.598	0.603	0.481	0.515	0.653
26	0.554	0.633	0.542	0.617	0.555	0.664	0.618	0.506	0.524	0.665
27	0.540	0.675	0.547	0.695	0.588	0.714	0.606	0.506	0.534	0.675
28	0.529	0.650	0.525	0.680	0.579	0.705	0.583	0.473	0.535	0.672
29	0.485	0.629	0.554	0.709	0.604	0.695	0.559	0.474	0.538	0.648
30	0.485	0.629	0.554	0.709	0.604	0.695	0.559	0.474	0.538	0.648
31	0.513	0.602	0.549	0.709	0.584	0.670	0.575	0.419	0.546	0.596
32	0.565	0.674	0.551	0.751	0.620	0.642	0.643	0.477	0.631	0.516
33	0.565	0.674	0.522	0.723	0.609	0.619	0.643	0.477	0.662	0.516
34	0.538	0.659	0.552	0.733	0.636	0.623	0.629	0.426	0.646	0.488
35	0.476	0.602	0.535	0.699	0.624	0.591	0.576	0.347	0.628	0.594
36	0.476	0.602	0.535	0.699	0.624	0.591	0.576	0.347	0.628	0.594
37	0.476	0.602	0.535	0.699	0.624	0.591	0.576	0.347	0.628	0.594
38	0.476	0.602	0.535	0.699	0.624	0.591	0.576	0.347	0.628	0.594
39	0.597	0.642	0.489	0.661	0.608	0.644	0.608	0.688	0.626	0.655
40	0.597	0.642	0.489	0.661	0.608	0.644	0.608	0.688	0.626	0.655
41	0.465	0.713	0.565	0.762	0.586	0.641	0.704	0.374	0.570	0.613
42	0.465	0.713	0.565	0.762	0.586	0.641	0.704	0.374	0.570	0.613
43	0.465	0.713	0.565	0.762	0.586	0.641	0.704	0.374	0.570	0.613
44	0.605	0.699	0.490	0.721	0.447	0.590	0.741	0.648	0.563	0.681
45	0.605	0.699	0.490	0.721	0.447	0.590	0.741	0.648	0.563	0.681
46	0.605	0.699	0.490	0.721	0.447	0.590	0.741	0.648	0.563	0.681
47	0.605	0.699	0.490	0.721	0.447	0.590	0.741	0.648	0.563	0.681
48	0.605	0.699	0.490	0.721	0.447	0.590	0.741	0.648	0.563	0.681
49	0.605	0.699	0.490	0.721	0.447	0.590	0.741	0.648	0.563	0.681
50	0.605	0.699	0.599	0.747	0.608	0.592	0.704	0.715	0.537	0.681
51	0.605	0.699	0.599	0.747	0.608	0.592	0.704	0.715	0.537	0.681
52	0.605	0.699	0.599	0.747	0.608	0.592	0.704	0.715	0.537	0.681
53	0.605	0.699	0.599	0.747	0.608	0.592	0.704	0.715	0.537	0.681
54	0.605	0.699	0.599	0.747	0.608	0.592	0.704	0.715	0.537	0.681
55	0.605	0.699	0.599	0.747	0.608	0.592	0.704	0.715	0.537	0.681
56	0.605	0.699	0.599	0.747	0.608	0.592	0.704	0.715	0.537	0.681
57	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
58	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
59	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
60	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
61	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877

62	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
63	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
64	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
65	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
66	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
67	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
68	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
69	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
70	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877
71	0.789	0.610	0.802	0.636	0.448	0.464	0.652	0.803	0.714	0.877

SF-36 scales: Physical component scale, mental component scale, physical functioning, social functioning, role limitations due to physical health, role limitations due to emotional problems, emotional well-being, energy/fatigue, pain, general health

Declaration

(1) Ich erkläre, dass ich mich an keiner anderen Hochschule einem Promotionsverfahren unterzogen bzw. eine Promotion begonnen habe.

(2) Ich erkläre, die Angaben wahrheitsgemäß gemacht und die wissenschaftliche Arbeit an keiner anderen wissenschaftlichen Einrichtung zur Erlangung eines akademischen Grades eingereicht zu haben.

(3) Ich erkläre an Eides statt, dass ich die Arbeit selbstständig und ohne fremde Hilfe verfasst habe. Alle Regeln der guten wissenschaftlichen Praxis wurden eingehalten; es wurden keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt und die den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht.

Datum, 06.11.2024 Unterschrift

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A., im Juli 2025