

Identifying Patterns of Self-Reported Nonadherence Using Network Analysis in a Mixed German Cohort

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Purpose: Nonadherence is a complex behaviour that contributes to poor health outcomes; therefore, it is necessary to understand its underlying structure. Network analysis is a novel approach to explore the relationship between multiple variables.

Patients and Methods: Patients from four different studies (N = 1.746) using the self-reported Stendal Adherence to Medication Score (SAMS) were pooled. Network analysis using EBICglasso followed by confirmatory factor analysis were performed to understand how different types of nonadherence covered in the SAMS items are related to each other.

Results: Network analysis revealed different categories of nonadherence: lack of knowledge about medication, forgetting to take medication, and intentional modification of medication. The intentional modification can further be sub-categorized into two groups, with one group modifying medication based on changes in health (improvement of health or adverse effects), whereas the second group adjusts medication based on overall medication beliefs and concerns. Adverse effects and taking too many medications were further identified as most influential variables in the network.

Conclusion: The differentiation between modification due to health changes and modification due to overall medication beliefs is crucial for intervention studies. Network analysis is a promising tool for further exploratory studies of adherence.

Keywords: medication adherence, older adults, polypharmacy, Stendal adherence to medication score, network analysis

Introduction

Adherence describes the degree to which a person complies with recommendations agreed with healthcare providers. These recommendations may contain medical recommendations, such as medication, diet, or physical activity.^{1–3} Especially in older adults or in patients with chronic disorders, adherence to medication is crucial, because it has a direct influence on (adverse) health outcomes, readmissions to hospital, length of stay, and overall quality of life.^{3–5} However, nonadherence to medication is common,³ and the reasons for this nonadherence can be divided into patient characteristics, disease-related factors, financial and health-care system barriers, patient–provider relationship factors, and treatment-related factors.² Patient-related factors are especially important for adherence and can roughly be categorized as intentional (when the patient purposefully decides not to adhere to the recommended treatment) or unintentional (when the patient cannot follow the recommendations, eg due to cognitive problems).^{2,3,6} Reasons for nonadherence are complex, and often a combination of several factors influence a person's medication adherence.^{3,7,8} To fully understand and improve nonadherence, it is crucial to comprehend the different types and reasons of nonadherence. Measuring adherence, however, remains challenging as numerous objective and subjective measurement methods exist, such as self-report questionnaires, pill counting, prescription refill data from pharmacies, or electronic pill monitoring. All those measures vary in terms of their reliability, validity, and sensitivity to change.^{9–11} Thus, no gold standard exists to measure adherence.

Self-reports are an economically feasible method and are commonly used to estimate adherence and the personal reasons for nonadherence.¹¹ The Stendal Adherence to Medication Score (SAMS) is a German self-report questionnaire that measures various aspects of medication adherence. The 18 SAMS items can be assigned to three different factors: 1)

modification of medication, ie intentionally changing dosages or leaving medications out, 2) *lack of knowledge about medication*, and 3) *forgetting to take medication*.^{7,12,13} *Modification* refers to intentional changes in medication made without consulting the treating physicians. *Lack of knowledge* refers to missing knowledge about one's own medication (eg reasons for prescription and effect, time-point, dosage). *Forgetfulness* includes forgetting to take the medication properly. This three-factor structure of the SAMS was previously demonstrated with exploratory and confirmatory factor analyses in patients with Parkinson's disease, chronic pain, kidney transplantation, and neurogeriatric patients.^{7,12–14}

Network analysis is a relatively new and promising method for modeling interactions between large numbers of variables. Instead of trying to reduce the structure of the variables to their shared information, as is done in classical regression modeling, network analysis estimates the relation between all variables directly.^{15,16} With this approach, network analysis can visualize the association between different variables without assuming a direction of effects. In this study, we used network analysis as an exploratory approach to describe the complex interactive relationship among the SAMS items. We first aimed to confirm the previously described factor structure. Secondly, we aimed to gain deeper insight into the underlying SAMS structure to understand the different clusters of nonadherence in a large group of patients.

Materials and Methods

Samples

As a base for the network analysis, four large datasets using the SAMS were combined:

1. The NeuroGerAdh study, a longitudinal, observational study of hospitalized older adults with neurological disorders (mainly movement disorders, cerebro-vascular disorders, and neurodegenerative disorders) was conducted from 2019–2021 and contains data on 910 patients regarding quality of life, cognition, depression, adherence and overall health behaviour.^{17,18}
2. Between 2007 and 2008, medication adherence, coping and the transplantation-specific distress were examined in 418 kidney transplanted patients at the Essen University Hospital, Germany in the NTX Study.¹⁹
3. In an observational, cross-sectional study of 260 chronic pain patients from three pain and orthopedic facilities in Germany between 2017 and 2018, adherence, psychological distress and personality traits were assessed.²⁰
4. The association between health locus of control (HLC) and the SAMS was assessed in an observational, cross-sectional study of 160 patients recruited from three primary care practices in Germany comprising a wide spectrum of common illnesses, including hypertension, diabetes and thyroid diseases.²¹

Across all datasets, we used the following data for the network analysis: age (metric, years), gender (binominal, female/male), SAMS items 1 to 18 (ordinal, Likert-scale), SAMS total score.

The descriptives of the entire study cohort and the single studies are given in [Table 1](#), [Supplement Figure 1](#) and [Supplement Tables 1–4](#).

Measuring Adherence – SAMS

The SAMS is a self-report questionnaire constructed for measurement of adherence independent of the underlying disease. The SAMS includes 18 questions forming a cumulative score (0 = complete adherence to 72 = complete non-adherence). For all items, a higher value indicates higher nonadherence. The SAMS covers aspects of intentional and non-intentional nonadherence. The development and psychometric properties of the SAMS are detailed in the SAMS manual, but in brief, its construction was inspired by the Morisky Score, of which four items were included. Additional items were added from a study by Rottlaender et al (2007) on poly medication and agreed upon in expert meetings.^{12,22,23} The SAMS has previously been validated in three different cohorts (N = 418, N = 779 and N = 260, total N = 1457) and showed good psychometric properties (overall internal consistency $\alpha = 0.83$). Floor effects are expected for this instrument, as it includes the value 0 as a measure of total adherence for each item.¹² Previous factor analysis¹² and principal component analysis¹⁴ suggested a three-factor solution: *intentional modification* of medication (items 4, 7–13, 17), *lack of knowledge* about reasons/dosage/timing of medication (items 1–3, 5), *forgetting* to take medication (items 6, 14–16, 18).¹² An overview of all SAMS items is given in [Figure 1](#).

Table 1 Summary Descriptive Statistics of the Study Cohorts

	NeuroGerAdh N = 910	NTX Cohort N = 418	Pain Cohort N = 260	HLC Cohort N = 160
Age				
Mean \pm SD	70.12 \pm 8.63	51.76 \pm 12.82	57.24 \pm 13.07	63.34 \pm 14.88
Min; max	55; 96	20; 81	19; 88	20; 95
Number of pills per day				
Mean \pm SD	5.6 \pm 3.60	13.97 \pm 4.95	4.30 \pm 3.04	4.25 \pm 2.91
Sex				
Male (n, %)	521, 57.3	237, 56.7	70, 26.9	62, 38.8
Female (n, %)	389, 42.7	181, 43.3	190, 73.1	98, 61.3
Married	621 (69.2%)	230 (55.0%)	153 (58.8%)	104 (65.8%)
Education				
Low/medium (n, %)	571 (63.7%)	322 (77%)	190 (73.1%)	97 (60.6%)
High (n, %)	325 (36.3%)	96 (23%)	70 (26.9%)	63 (39.4%)
Pensioned/not working (n, %)	756 (84.0%)	271 (64.8%)	127 (48.8%)	126 (67.0%)

Statistical Analyses

All analyses were conducted using IBM SPSS statistics (Version 25), JASP (Version 0.16), and R version 4.1.1, in particular the R packages *bootnet* (Version 1.5)¹⁵ and *qgraph* (Version 1.9).²⁴ Descriptive statistics were used to describe the cohort. For the network analysis, the SAMS items were used to understand how different aspects of nonadherence relate to each other.²⁵

Network Construction

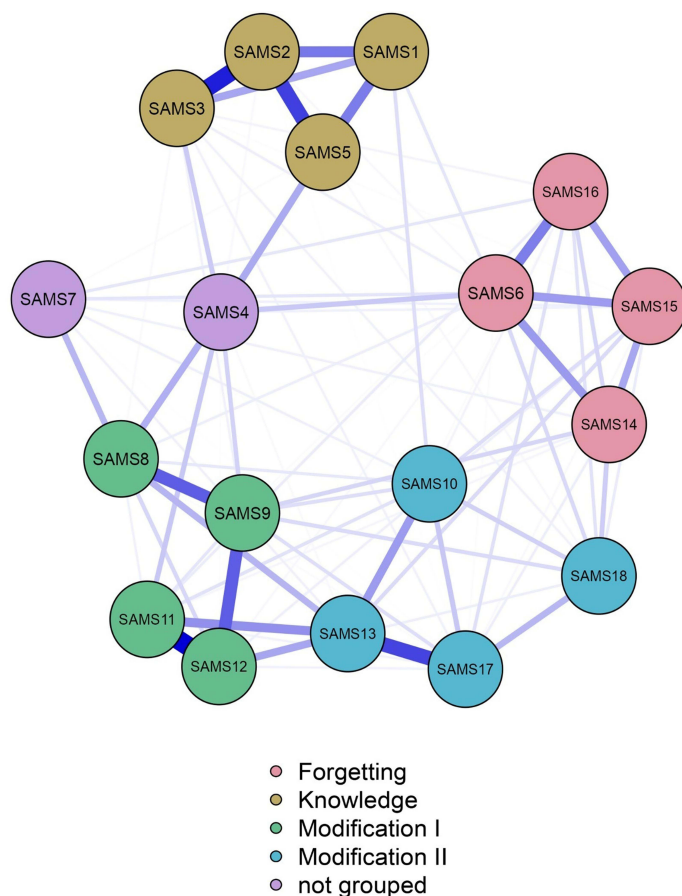
A network presents variables as nodes, connected to each other via lines (edges). In a simple correlation network, all significant and non-significant edges are shown, causing much noise ([Supplement Figure 2](#)). Therefore, instead of using correlations, we used a regularized estimation method called the Extended Bayesian Information Criterion Graphical Least Absolute Shrinkage and Selection Operator (EBICglasso).¹⁵ It estimates the partial correlations between all variables and shrinks the absolute weights towards zero. Hence, edge weights which were shrunken to exactly zero do not have to be tested against zero anymore, alleviating the problem of multiple testing. The extended Bayesian Information Criteria (EBIC) was used as an information criterion that takes both model complexity and model fit into account.²⁶ Missing values in EBIClasso were pairwise treated.

Network Visualization

The nodes are positioned using the Fruchterman-Reingold algorithm. It organizes the network based on the strength of the connections between nodes. Blue edges referred to positive associations, while red edges indicated negative ones. The thicker the edge, the stronger the association between two nodes.²⁴

We used the following centrality parameters to describe nodes and edges in the network:

1. Strength, which quantifies how well a node is directly connected to other nodes.²⁷
2. Edge betweenness centrality score, defined as the number of the shortest paths that go through an edge in a network. It refers to the edges that are most “between” domains, representing a bridge-like connector between



SAMS Items

- 1 Do you know the reasons for taking your medication?
- 2 Do you know the dosage of your medication?
- 3 Are you familiar with the time of taking for the medication?
- 4 Do you take your medication regularly?
- 5 Do you know the names of your medications?
- 6 Do you forget to take your medication?
- 7 Are you untroubled about taking your medication?
- 8 Do you stop taking your medication when you feel better?
- 9 Do you stop taking your medication if you sometimes feel worse after taking it?
- 10 Do you take wrong/unprescribed medication? (e.g. such as those of your partner?)
- 11 If you think you have side effects due to the medication, do you reduce the dosage without consulting a doctor?
- 12 If you think you have side effects due to the medication, do you not take it for a while, i.e. take a break?
- 13 If you feel like you have to take too many medications, do you stop taking those medications you consider less important without consulting a doctor?
- 14 If you forget or omit your medication, do you forget it in the morning?
- 15 If you forget or omit your medication, do you forget it at noon?
- 16 If you forget or omit your medication, do you forget it in the evening?
- 17 Do you deliberately not take medications you do not consider important, but take the rest?
- 18 If you take medication as a syringe or a weekly tablet, have you ever forgotten it?

Figure 1 Network plot and SAMS items.

two parts of a network.²⁸ The removal of this edge may affect the communication between many pairs of nodes through the shortest paths between them.

Network Stability and Accuracy

A case-dropping bootstrap procedure was used to examine the node strength stability. A network is stable if a large proportion of the sample can be excluded from the dataset without observing significant changes in the indices. For a stable network, the Correlation Stability Coefficient (CS-C) is preferably above 0.5. A nonparametric bootstrap procedure based on 95% confidence intervals (95% CIs) was used to assess the edge weights stability, with narrower 95% CIs indicating a more trustworthy network. Bootstrap stability difference test was used to test between edge-weights that were non-zero, and to assess whether the nodes in the network differed significantly in terms of strength centrality edge-weights.¹⁵

Confirmatory factor analyses (CFA) using JASP (Version 0.16) were conducted with a diagonally weighted least square (DWLS) estimator. Goodness-of-fit was evaluated using the χ^2 statistic of exact fit, comparative fit index (CFI), Tucker–Lewis index (TLI), and root mean square error of approximation (RMSEA). TLI and CFI should be >0.90 , and RMSEA <0.08 for an acceptable fit.²⁹

Results

Network Structure

The network of SAMS items is shown in Figure 1. Strength as a centrality measure is summarized in Figure 2. On a global level, the network can visually be divided into four domains: items about *forgetting to take medication* (SAMS 6, 14, 15, 16), items covering *lack of knowledge* about medication (SAMS 1, 2, 3, 5), and items about *modification of medication*, which can

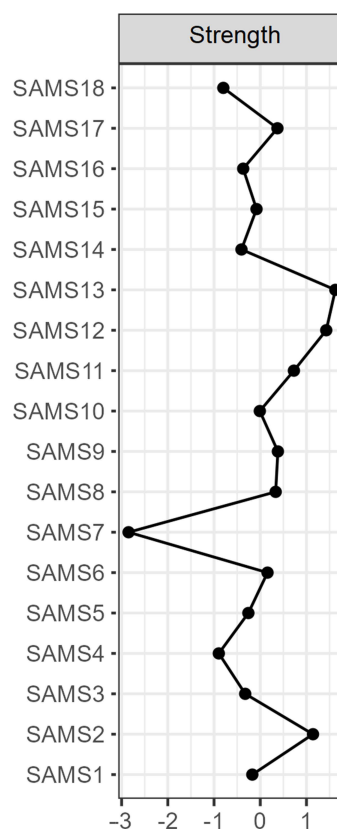


Figure 2 Centrality plot.

be further divided into two subdomains containing SAMS items 8, 9, 11, 12 and items 10, 13, 17, and 18. Two items (4, 7) cannot be categorized into one of these domains (see [Figure 1](#) for a description of the SAMS items).

Various cross-domain associations bridge the borders between these domains. Within-domain associations were stronger than between-domain associations. The edge SAMS 11–12 (dose change or stop intake due to side effects) shows the strongest association, followed by the edge SAMS 2–3 (knowledge about dose and timing of medication), and SAMS 2–5 (knowledge about dose and names of medication) (see [Supplement Table 5](#) for the weights matrix). As provided in [Supplement Table 6](#), highest edge betweenness centrality was observed for SAMS 4–5 (regular medication intake, knowing names of medication), SAMS 4–6 (regular medication intake – forgetting medication), and SAMS 4–8 (regular medication intake – stop medication intake when feeling better).

As shown in [Figure 2](#), the SAMS item 13 (change of medication when feeling that one takes too many drugs) has the highest node strength in the network, followed by SAMS 12 (change of medication due to side effects) and SAMS 2 (knowing doses). The values for expected influence were equal to strength.

Network Stability

[Supplement Figures 3–6](#) show the results of the accuracy and stability checks. Overall, the network model is stable, many of the identified edges and centrality measures are significantly different from each other. All findings are interpretable. The case-dropping bootstrap procedure shows that CS-Cs of both node strength and edge were 0.75. Network plots for each of the individual datasets are given in [Supplement Figure 7A–D](#). As expected, certain edges differ slightly between the datasets, although the overall structure of the network and the subcategorization of the modification domain is comparable.

Various CFAs were calculated to assess the model fit of a four-factor solution (with two factors for modification) with and without the items 4 and 7. The best model fit was reached when item 4 and 7 were excluded from the four factors and when the modification domain was separated into a factor with items 8, 9, 11, 12 and a factor with items 10, 13, 17 and 18 ([Table 2](#) and [Supplement Table 7](#) for all analyses).

Table 2 Confirmatory Factor Analysis

	χ^2	Df	p	CFI	TLI	RMSEA	RMSEA CI
Baseline	21,163.709	120					
Factor Model	194,491	98	< 0.001	0.995	0.994	0.025	0.020, 0.031
Factor Loadings							
Factor	Indicator	Est.	Std. Error	z-value	p	Lower CI	Upper CI
Modification I	SAMS 8	0.781	0.016	48.597	< 0.001	0.750	0.813
	SAMS 9	0.843	0.015	57.084	< 0.001	0.814	0.872
	SAMS 11	0.876	0.014	60.845	< 0.001	0.848	0.904
	SAMS 12	0.928	0.014	66.171	< 0.001	0.900	0.955
Knowledge	SAMS 1	0.793	0.018	44.928	< 0.001	0.759	0.828
	SAMS 2	0.922	0.019	49.458	< 0.001	0.886	0.959
	SAMS 3	0.867	0.020	43.616	< 0.001	0.828	0.906
	SAMS 5	0.768	0.019	41.204	< 0.001	0.732	0.805
Forgetting	SAMS 6	0.754	0.018	40.887	< 0.001	0.717	0.790
	SAMS 14	0.653	0.020	31.966	< 0.001	0.613	0.693
	SAMS 15	0.726	0.021	34.592	< 0.001	0.685	0.767
	SAMS 16	0.723	0.019	37.120	< 0.001	0.685	0.761
Modification II	SAMS 10	0.758	0.023	32.658	< 0.001	0.713	0.084
	SAMS 13	0.907	0.019	46.717	< 0.001	0.868	0.945
	SAMS 17	0.792	0.019	41.218	< 0.001	0.754	0.830
	SAMS 18	0.549	0.020	27.696	< 0.001	0.510	0.588

Abbreviations: CI, confidence interval; CFI, comparative fit index; Df, degrees of freedom; RMSEA, root mean squared error of approximation; TLI, Tucker-Lewis-index.

Discussion

To the best of our knowledge, this was the first study that characterized a self-reported adherence questionnaire using network analysis.

One property of a node in a network is its strength, which refers to the number of connections it has with other nodes. Network analysis revealed that SAMS items 13 (change of medication when feeling that one's takes too many drugs), 12 (change of medication due to side effects), and 2 (knowing medication dose) had the highest node strength in the network. This identifies the listed items as putative network hubs, which is in line with previous research as both high number of drugs (eg, polypharmacy) and adverse effects have been repeatedly identified as influential factors contributing to nonadherence.^{2,5,30,31} Additionally, the expected influence, which assesses the cumulative influence within the network, indicates that items 13, 12 and 2 are highly influential nodes in the network.³² Therefore, our network analysis was able to detect commonly identified influential factors for nonadherence, namely taking too many medications, adverse effects and lack of knowledge.² The edge betweenness centrality refers to the edges that represent a bridge-like connector between two parts of a network. The edge between item 4 (taking medication regularly) and item 5 (knowing names of medication), between item 4 and item 6 (forgetting to take medication), and between item 4 and 8 (stop taking medication when feeling better) may affect the communication between many pairs of nodes through the shortest paths between them.

In line with previous studies, the network revealed that the SAMS consists of different domains: non-intentional nonadherence (*forgetting*), *lack of knowledge* about medication, and intentional nonadherence (*modification of medication*).^{7,12,14} The present network analyses, however, showed that intentional nonadherence (*modification of medication*) can be further categorized into two different domains, which was also confirmed by CFA. Persons in the group modification I modify their medication due to adverse effects (items 9, 11, 12) or when they believe that medication is no longer necessary (item 8). These modifications seem reasonable to the patient and can be interpreted as a behavior to regain control.³³ As stated in previous research, nonadherence is closely related to health beliefs and concerns,^{34,35} and it seems that as health either improves or worsens due to sudden adverse effects, patients modify their medication accordingly.^{30,31} In contrast, people in the modification II group deliberately do not take medication (item 17), consider medication to be less important (item 13), or take wrong or other/unprescribed medications (item 10). Unlike modification group I, this behavior suggests that medication is not adjusted as a response to recent changes in health such as improvement after a hospital stay or sudden adverse effects, but rather based on overall mistrust and concerns regarding medication.^{34,36}

The subcategorization of the factor *modification of medication* underlines the complex nature of self-reported intentional nonadherence. This distinction is crucial for clinical practice, because it has different implications for health outcomes and requires different treatments in intervention studies. Previous intervention studies to improve medication adherence only have weak or modest effect sizes, partially because the complexity of adherence is not fully taken into account.^{2,37} Our results again highlight the need to identify the underlying reasons for non-adherence, as different aspects of nonadherence may differentially influence patient behavior and require different interventional approaches. For example, while forgetting may require habit-building interventions and constant reminders, a patient with high scores in modification factor II may instead benefit from motivational interviewing and interventions targeted at cognitive/belief changes.³⁷ In contrast, patients with intentional nonadherence according to the modification factor I may profit from education approaches (ie, how to proceed correctly in case of adverse effects). Patient-centeredness is an often-cited but often lacking approach for adherence interventions,^{2,3,37} and the results of our network analysis once more imply that a closer look at the individual composition of each patients' nonadherence profile is required for optimal intervention design. Further studies are necessary to explore which parameters (eg, psychological, socio-economic) are relevant for the two subcategories of intentional adherence.

Interestingly, item 18 (forgetting medication which has to be taken as a syringe or a weekly tablet) was closer related to the modification domain than to forgetting domain, which may be rooted in patients perceiving medication as less important if it has to be taken less frequently. However, the estimate of item 18 in the CFA was lower, indicating that this item is less strongly correlated with the modification II factor.

Limitations

Although a broad spectrum of patients with varying diseases was represented in the data, patterns of adherence may vary depending on diagnosis and age.² We therefore calculated the stability of the network by using a case-dropping bootstrap procedure.¹⁵ This re-estimates strength and edge with an increasingly higher percentage of dropped-out cases. Afterwards, the correlation between the original index and those from the subsamples were calculated. These analyses showed that the network model is stable. Of note, to incorporate disease-specific differences between the merged datasets, a network was calculated for each individual dataset. However, due to small sample sizes, these network analyses cannot be considered stable and only serve as an initial overview to show that the structure of the SAMS does not differ significantly between the samples included in the respective datasets.

Since the study was limited to the SAMS and therefore German samples, the findings cannot be generalized to other adherence questionnaires or patient groups. Although self-reported questionnaires have been shown to be comparable to objective measures of adherence,¹¹ no other measures of adherence were employed in this study. Thus, the SAMS scores should be interpreted with caution, as self-reports may be subject to biases.³⁸ However, as this analysis merely describes categories of nonadherence and does not aim to predict its relationship with health outcomes, we believe that a statement on the structure of the SAMS can be made on the basis of our data. Further studies using different self-report adherence questionnaires are required to confirm the subcategorization of

intentional nonadherence. This is necessary, because patterns and subdomains may vary depending on diagnoses and other cohort characteristics.^{39–41} Of note, network analysis is an exploratory approach and causal statements cannot be drawn from cross-sectional datasets.

Conclusion

Using network analysis followed by CFA, we were able to show that nonadherence can be grouped into different categories: *forgetting to take medication*, *lack of knowledge* about medication, and intentional *modification of medication*. Of note, the last category can be further divided into modification group I and II, with the first group adjusting medication based on changes in health and the second group modifying medication due to mistrust in or concerns about medication. In addition to those categories, taking too many medications, lack of basic knowledge of medication (such as dosage) and having adverse effects were identified as particularly influential variables for nonadherence in the network. Network analysis proved to be a valuable tool for gaining a deeper insight into the complex interplay between elements of nonadherence, especially as it is able to visualize the bidirectional relationships between different items and hidden subdomains of adherence measures. The datasets analyzed in the present manuscript serve as an example of how subcomponents of adherence can be detected. This is essential to fully understand patient barriers and resources, as patients may differ in the individual constellation of these subcomponents. Taking a closer look at the interplay between different facets of adherence might help to pave the way toward individualized interventions.

Data Sharing Statement

The dataset used in Study 1 (NeuroGerAdh Study) is freely accessible for scientific purposes at: Prell, T., & Schönberg, A. (2022). Data on medication adherence in adults with neurological disorders: The NeuroGerAd study. doi: 10.17605/OSF.IO/KUAPH. Retrieved from osf.io/kuaph. All other datasets can be requested from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

All datasets included in the present analysis were approved by the respective ethics committee and all patients gave written informed consent. Study 1 and 4 were approved by the local ethics committee of Jena University Hospital, Germany, approval number 5290-10/17. Study 2 and 3 were approved by the local ethics committee of the Department of Applied Human Sciences of the University of Applied Science Magdeburg-Stendal, approval number AZ 4973-8.

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Disclosure

The authors report no conflicts of interest in this work.

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