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Effects of a remotely delivered group-format epilepsy self-management program on adverse health outcomes in vulnerable people with epilepsy: a causal mediation analysis.

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Abstract

Background—People with epilepsy frequently experience negative health events (NHEs), such as emergency room visits or hospitalizations for epilepsy-related complications despite significant advances in care. We developed a novel remotely delivered group-format epilepsy self-management program ("Self-management for people with epilepsy and a history of negative health events"; SMART). In a 6-month randomized controlled trial (RCT), SMART participants had significant decreases in NHEs, as well changes in attitudes and behaviors compared to a wait-list (Sajatovic et al., 2018). This secondary analysis from the RCT characterizes the indirect causal effects of SMART on NHE improvements that may be mediated by specific improvements in self-management, self-efficacy, social support, quality of life, and depression symptom severity.

Methods—Participants were adults with epilepsy and a NHE in the prior 6 months. There were 60 participants in each RCT arm (SMART versus wait-list) and assessments were conducted at baseline, 10 weeks and 24 weeks. The outcome was a binary variable measuring NHE improvement at week 24. A counterfactual-based mediation framework was used to determine whether improvements or changes in attitudes and behaviors at specific time points or across the study period, mediated the impact of SMART on NHE improvements.

Results—At week 24, SMART contributed to significant improvements in NHEs compared to those in wait-list (odds ratio=3.2, p=0.015). SMART was significantly associated with improvements and changes in aspects of self-management, self-efficacy, quality of life, and

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depression symptom severity at week 10, and significant improvements between baseline and week 24 in overall self-management and quality of life. Mediation analyses demonstrated that a portion of the effect (~20–30%; $p<0.05$) of SMART on NHE improvement was also indirectly mediated by early improvements in depression symptom severity and quality of life.

Conclusions—This mediation analysis of the SMART intervention demonstrates that in addition to its direct effect on improving NHEs in people with epilepsy, early improvements in depression symptom severity and quality of life indirectly mediated ~20–30% of the intervention's effect. These results demonstrate the promise of self-management approaches as a key component of an optimal healthcare model for people with epilepsy, particularly those with a recent history of NHEs.

1. Introduction

There have been marked advances in biological therapies for people with epilepsy, however many persons still experience frequent adverse outcomes, such as negative health events (NHEs), including seizures, accidents, self-harm attempts, emergency department visits, and hospitalizations (Begley et al., 2011; Chong et al., 2010; Ferguson et al., 2008; Hesdorffer and Begley, 2013). There is evidence demonstrating only 44% of those on antiepileptic drugs had their seizures controlled in the prior year (Tian et al., 2018), that people with epilepsy experience high rates of medical comorbidity (Centers for Disease Control and Prevention MMWR, 2005; Kobau et al., 2004), and report diminished occupational and personal satisfaction (Kobau et al., 2012), which collectively influence the frequency of NHEs experienced by people with epilepsy. Thus, there is a need for additional care strategies to optimize the health of those living with epilepsy, including evidence-based self-management approaches which have been shown to improve outcomes (DiIorio et al., 2011; Sajatovic et al., 2018; Sajatovic et al., 2016; Thompson et al., 2015; Thompson et al., 2010).

We developed a novel multidimensional epilepsy self-management intervention (**S**elf-**ma**nagement for people with epilepsy and a histo**r**y of negative health even**t**s; SMART) which successfully reduced epilepsy-related complications and improved quality of life, as well as physical and mental health functioning in a randomized controlled trial (RCT) of 120 individuals living with epilepsy (Sajatovic et al., 2018). SMART was designed to remotely share information in an accessible and interactive group format by a nurse educator-peer educator dyad to promote active self-management. At the end of the 24 weeks of the RCT, 82% of individuals in SMART compared to 60% of those in a wait-list (WL) control group had decreases in their total number of NHEs over 6 months ($p=0.015$), as well as a greater reduction in total NHEs over this same time period ($p=0.04$) (Sajatovic et al., 2018).

Considering the multidimensional nature of SMART and its positive impact on reducing NHEs in vulnerable persons with epilepsy, we sought to characterize the mechanisms that may mediate the effect of SMART. Given the diverse curriculum that SMART spans, it is not clear the extent to which improvements or changes in specific attitudes and behaviors versus the combined intervention resulted in NHE improvements in our RCT. Here we present results from a secondary data analysis of our RCT data examining the extent to which the causal effect of SMART on NHE improvements is direct or indirectly mediated by

improvements in self-management, self-efficacy, quality of life, social support, and depression symptom severity.

2. Material and methods

2.1 Study population and design

The study population consisted of 120 adults (≥18 years) with self-reported epilepsy and a NHE (seizure, accident, self-harm attempt, emergency department visit, or hospitalization) within the prior 6 months, recruited from an urban setting in northeastern Ohio. All participants continued treatment with their healthcare providers, but were randomized 1:1 to receive the SMART intervention or 6-month WL, which has been previously described in detail (Sajatovic et al., 2018).

SMART included an expansive curriculum developed with stakeholder input, and included general epilepsy management principles, coping with stigma, minimizing complications, problem-solving, stress-management approaches, social support, and other topics, that was remotely administered in an accessible and interactive group format by a nurse educator-peer educator dyad (Sajatovic et al., 2018). Peer educators were persons with epilepsy who had ≥3 life-time NHEs, and were recruited from previous epilepsy self-management pilot studies or were referred from the local Epilepsy Association. Educator dyads received in-person training over 2 days followed by regular in-person and telephone group meetings, which were similar to prior peer educator self-management trainings conducted by the study team (Blixen et al., 2015; Sajatovic et al., 2018). There were two phases to the intervention. The first phase consisted of 8 interactive group-format, 60 to 90 minute sessions, of up to 10 participants that spanned 8–10 weeks, progressively covering the self-management curriculum. The fidelity of presentations across groups were assessed by noninterventionist staff using a seven item checklist (Fraser, 2009). The second phase of SMART consisted of 6 telephone maintenance sessions approximately two weeks apart with the nurse educator and peer educator alternating calls. These semi-structured 10 to 15 minute calls were designed to briefly re-inforce themes from the first phase of SMART in the context of the participant's personal care plan.

2.3 Assessments

In-person self-reported assessments were conducted at baseline, week 10, and week 24 (6 months) (Sajatovic et al., 2018). The number of NHEs at 6-months after baseline was the primary outcome. To determine the possible mechanisms through which SMART positively impacted study participants through reductions in NHEs, attitudes and behaviors were measured at each time point, including: Epilepsy Self-Management Scale (ESMS; a sum of five subscales: medication management, information management, safety management, seizure management, and lifestyle management) (DiIorio et al., 2004), Epilepsy Self-Efficacy Scale (ESES) (DiIorio et al., 1996; DiIorio et al., 2003), 10-item Quality of Life in Epilepsy (QOLIE-10) (Cramer et al., 1996), 12-item Multidimensional Scale of Perceived Social Support (MSPSS) (Zimet et al., 1988), Montgomery-Asberg Depression Rating Scale (MADRS) (Fantino and Moore, 2009), and 9-item Patient Health Questionnaire (PHQ-9)

(Kroenke et al., 2001). Higher scores on ESMS, ESES, and MSPSS, and lower scores on QOLIE-10, MADRS, and PHQ-9 indicate better outcomes.

2.4 Statistical analyses

The objective of this analysis was to determine the extent to which the causal effect of SMART on improvements in NHEs was mediated by improvements or changes in attitudes and behaviors (i.e. self-management (ESMS), self-efficacy (ESES), quality of life (QOLIE-10), social support (MSPSS), or depression symptom severity (MADRS, PHQ-9)). First, demographic and baseline characteristics were compared between study arms using Fisher's exact test and non-parametric Wilcoxon rank-sum test (version 13.1; StataCorp, College Station, TX, USA; command *ranksum*). Second, the impact of SMART on improvements in the attitudes and behaviors (1 = improved scores; 0 = no change or worse scores) at week 10 compared to baseline, at week 24 compared to week 10, and at week 24 compared to baseline, were examined using logistic regression models. Linear regression models examined the impact of SMART on changes in the attitudes and behaviors. And third, a counterfactual-based mediation framework was used to test whether improvements in specific attitudes and behaviors at specific time points or across the study period, mediated the impact of SMART on improvements in NHEs reported in the previous 6 months at week 24 compared to baseline (1 = decrease in NHEs; 0 = increase or no change in NHEs) (Imai et al., 2010). Binary predictors that reflected improvements in the attitudes and behaviors were generated for week 10 compared to baseline, week 24 compared to week 10, and week 24 compared to baseline. Stata command *medeff* was used to separate the total effect of SMART on improvements in NHEs into independent direct effects and indirect effects for the binary measures for each attitude and behavior (Hicks and Tingley, 2011). Five thousand simulations were run for the quasi-Bayesian approximation of parameter uncertainty. The percentage of mediation by each attitude and behavior were calculated as a proportion of SMART's indirect effect to total effect on NHE improvement. Mediation analyses were repeated using continuous measures of change for the difference in attitudes and behaviors between time points (week 10 and baseline, week 24 and week 10, and week 24 and baseline).

3. Results

At baseline the participants in SMART and WL study arms did not differ by age, sex, race/ethnicity, education, income, NHEs in the prior 6 months (data not shown) (Sajatovic et al., 2018). There were also no differences in baseline scores for ESMS, ESES, QOLIE-10, MADRS, and PHQ-9, however MSPSS was slightly higher in the SMART group (p=0.047; Table 1). By week 10, the SMART and WL groups significantly differed across all attitude and behavior measures, with improved ESMS, ESES, MSPSS, QOLIE-10, MADRS and PHQ-9 scores observed in the those receiving the SMART intervention (Table 1). Similar relationships were observed at week 24, including significance differences for the information, seizure, and lifestyle self-management subscales. Notable reductions in the SMART arm was observed for depression symptom severity as measured by MADRS (15.5 at baseline to 7.5 at week 24) and PHQ-9 (10 at baseline to 6 at week 24). At week 24, participants receiving SMART had 3.2 (95% confidence interval [CI]: 1.3, 8.0; p=0.015)

fold greater odds of reporting improvements (reductions) in NHEs in the prior 6 months compared to those on the WL (Table 2) as we have previously reported (Sajatovic et al., 2018).

Between baseline and week 10, SMART led to marked improvements in information management, ESES, QOLIE-10, MADRS and PHQ-9 (Table 2). Those on the WL reported an increase in safety management at week 10 (Table 1), while those in SMART arm reported no change, which resulted in an OR<1 for SMART compared to WL at week 10 (Table 2). Interestingly, between 10 and week 24, there were no additional improvements amongst those participating in SMART for the above attitudes and behaviors (Table 2). When assessing the impact of SMART from baseline to week 24, the intervention led to significant improvements in ESMS (odds ratio [OR]=2.6, 95% CI: 1.1, 6.0; p=0.027), information management subscale (OR=2.5, 95% CI: 1.1, 5.8; p=0.029), and QOLIE-10 (OR=3.5, 95% CI: 1.5, 8.0; p=0.0037). Similar patterns across all time points were observed when evaluating quantitative changes in the attitudes and behaviors (Table 3), which suggest that SMART had a positive impact on participants by week 10, and this effect was sustained through the second phase of the intervention.

To determine the extent to which the effect of SMART on improvements in NHEs at week 24 was mediated through improvements in specific attitudes and behaviors, we conducted mediation analyses using measures for each time point (i.e. improvements from baseline to week 24, baseline to week 10, and week 10 to week 24; Supplementary Table 1). Similar models were conducted for changes in attitudes and behaviors (Supplementary Table 2). Improvements in QOLIE-10 from baseline to week 10 significantly mediated 21.6% (95% CI: 11.6%, 87.9%) of the effect of SMART on improvements in NHEs (Table 4). Near significant associations were observed for improvements in MADRS and PHQ-9 at week 10 (CIs for the indirect effect ORs just spanned the null: 0.99–1.115 and 0.99–1.106, respectively). When investigating quantitative changes in attitudes and behaviors, there was evidence that 28.5% effect of SMART was significantly mediated by changes in PHQ-9 (Table 4), with near significant indirect effects for QOLIE-10 (OR=1.065, 95% CI: 0.999, 1.156) and MADRS (OR=1.067, 95% 0.996, 1.159). Across all time points, the scores for PHQ-9, MADRS, and QOLIE-10 were highly correlated (r^2:0.72–0.87; p<0.0001; data not shown). Considered collectively, these results suggest that the effect of the SMART intervention on improvements in NHEs was driven by the multidimensional nature of the intervention itself, with a significant influential indirect effect (~20–30%) mediated by early improvements in depression symptom severity and/or quality of life.

4. Discussion

While it is known that epilepsy self-management can reduce epilepsy burden, the mechanism by which these interventions work has not been well-studied (Luedke et al., 2019). This secondary analysis from the SMART epilepsy self-management RCT, sought to refine our understanding of how SMART led to improvements in NHEs, specifically the causal extent to which improvements or changes in specific attitudes and behaviors at specific points in time versus the combined intervention resulted in NHE improvements in our RCT. We observed that ~20–30% of the significant impact of SMART on NHEs was

indirectly mediated by the early improvements in depression symptom severity and/or quality of life in the first phase of the intervention.

Luedke et al (Luedke et al., 2019) suggested a conceptual model for epilepsy self-management interventions in which improving epilepsy knowledge, self-efficacy, self-management skills and life-style modifications can all mediate improved outcomes amongst people with epilepsy. Multidimensional evidence based self-management interventions, such as SMART, aim to provide people with epilepsy a framework through which they acquire skills to improve seizure control, minimize the adverse effects of a seizure, and hopefully become empowered to be more engaged in healthcare decisions (Bennett et al., 2016). SMART offered a remotely administered, interactive, group format curriculum over an 8 to 10 week period, with brief individual follow-up calls over the latter half of the intervention. It was perhaps not surprising that improvements in self-management (ESMS) did not indirectly mediate the effect of SMART (see indirect ORs in Supplementary Tables 1 and 2), since the direct effect of SMART is primarily due to specific training and support in self-management. Thus, disentangling the *additional* indirect effect of self-management training is likely not possible. However, in evaluating the additional indirect effects for other attitudinal and behavioral variables from the direct effect of SMART, our results show that improvements/changes in depressive symptom severity and quality of life (which are overlapping traits) mediates up to a third of SMART's effect on improving NHEs.

Depression is an important and common comorbid condition in people with epilepsy to consider. In studies published in the last two decades, the average prevalence of depression in people with epilepsy ranged between 17–37%, with higher burden amongst those with drug-refractory epilepsy (Blaszczyk and Czuczwar, 2016; Kwon and Park, 2014). In fact, the prevalence of depression may be >50% in people with epilepsy who have poorly controlled seizures or who have been hospitalized (Kwon and Park, 2013; Piedad et al., 2012). Depression and severity of depression symptoms demand attention considering their relationships with increased seizure activity and suicide risk amongst people with epilepsy (Chen et al., 2018; Christensen et al., 2007). We demonstrate that the early improvements in depression specifically contributed to improvements in NHEs for those participating in SMART. We hypothesize that as individuals with epilepsy are less burdened by depression and the lack of motivation and energy that accompany more severe depression, they are better able to engage in self-care and these benefits accumulate over time.

We also observed a similar indirect effect for quality of life, as we did for depression symptom severity. This was not unexpected, as quality of life is a multidimensional construct, and depression appears to be the leading factor influencing quality of life in people with epilepsy (Whatley et al., 2010). We observed exceptionally high correlation amongst measures of depression symptom severity and quality of life across all time points. Thus, reaffirming their interrelatedness. Our results suggest that as improvements in quality of life are accrued over time, individuals may gain skills and confidence in their ability to manage their epilepsy and health.

This study has several strengths, and a few limitations that merit discussion. The first strength to acknowledge is that the study population was diverse and balanced across

intervention arms, which supports the internal and external validity of our RCT, and the generalizability to other vulnerable populations. Another key strength of this study is the availability of measures for several attitudes and behaviors across the study period, which granted us a unique opportunity to comprehensively investigate and identify mechanisms facilitating the effect of the intervention. Our limitations include sample size, which impeded us from considering more complex causal relationships (i.e. as discerning the independent indirect effects of SMART by depression symptom severity versus quality of life), the single site methodology, and the fact that people with epilepsy who enroll in a self-management RCT may not be entirely representative of the larger population of individuals with epilepsy.

5. Conclusions

This mediation analysis of a novel self-management intervention demonstrated that in addition to its direct effect on improving NHEs in people with epilepsy, early improvements in depression symptom severity and quality of life indirectly mediated ~20–30% of the intervention's effect. These results demonstrate the promise of self-management approaches as a key component of an optimal healthcare model for people with epilepsy, particularly those with a recent history of NHEs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	confidence interval
ESES	Epilepsy Self-Efficacy Scale
ESMS	Epilepsy Self-Management Scale
MADRS	Montgomery-Asberg Depression Rating Scale

MSPSS	12-item Multidimensional Scale of Perceived Social Support
NHE	negative health event
OR	odds ratio
PHQ-9	9-item Patient Health Questionnaire
QOLIE-10	10-item Quality of Life in Epilepsy
WL	wait-list

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Highlights

- A novel self-management approach positively impacted outcomes in people with epilepsy
- 20-30% of improvements in adverse outcomes was mediated by improvements in mood
- Results encourage closer attention to depression severity and quality of life in epilepsy

Table 1.

Medians and interquartile ranges for attitudinal and behavioral outcomes across the study period[1].

	Baseline			Week 10			Week 24		
	SMART (n=60)	**WL (n=60)**	**p**	**SMART (n=53)**	**WL (n=58)**	**p**	**SMART (n=50)**	**WL (n=52)**	**p**
ESMS	141 (130, 154)	140 (127, 151)	0.45	150.5 (139, 159)	143.5 (131, 155)	**0.026**	156 (142.5, 162.5)	143 (127, 152)	**0.0001**
Medication management	44 (39, 47.5)	44 (39, 48)	0.84	46 (42.5, 49)	45 (40, 48)	0.10	47 (42, 49)	45 (41, 48)	0.10
Information management	20 (16, 25)	18.5 (24, 14)	0.45	23.5 (18.5, 29.5)	20.5 (14, 25)	**0.0063**	26 (19.5, 29)	21 (16, 25)	**0.0009**
Safety management	34 (30.5, 36)	32.5 (36, 29)	0.26	34 (31.5, 36.5)	34 (31, 38)	0.68	35 (32, 37)	33 (29, 37)	0.079
Seizure management	26.5 (22.5, 29)	26.5 (28.5, 23.5)	0.87	27 (24, 29)	26.5 (23, 29)	0.56	28 (26, 30)	26 (23, 28)	**0.035**
Lifestyle management	19 (16, 23)	19 (16, 22)	0.47	20 (17.5, 24.5)	18 (14, 22)	**0.0045**	21.5 (17, 24)	18 (14, 21)	**0.0011**
ESES	256 (227, 289)	246.5 (211, 289)	0.36	275 (236, 298)	245 (198, 290)	**0.020**	280 (255, 319)	257 (200, 308)	**0.014**
MSPSS	72 (62, 79)	67 (52.5, 73.5)	**0.047**	71 (59, 81)	65.5 (50, 74)	**0.049**	75 (60, 83)	67 (46, 75)	**0.0067**
QOLIE-10	2.9 (2.5, 3.7)	3.1 (2.2, 3.7)	0.98	2.4 (1.8, 3.1)	2.8 (2.5, 3.7)	**0.0046**	2.4 (1.7, 2.9)	3.0 (2.4, 3.8)	**0.0083**
MADRS	15.5 (7.5, 26)	19.5 (9.5, 29.5)	0.13	10 (4, 16)	22 (10, 29)	**0.0001**	7.5 (2, 15)	17 (8, 28)	**0.0008**
PHQ-9	10 (5, 14)	10 (5, 18)	0.39	7 (2, 12)	11 (6, 18)	**0.0043**	6 (2, 11)	10 (5, 15)	**0.0061**

[1]Higher scores on ESMS (self-management), ESES (self-efficacy), and MSPSS (social support), and lower scores on QOLIE-10 (quality of life), MADRS (depression symptom severity), and PHQ-9 (depression symptom severity) indicate better outcomes.

Table 2.

The effect of SMART on improvements in NHEs and attitudinal/behavioral outcomes.

Outcome assessed	From Baseline to Week 24		From Baseline to Week 10		From Week 10 to Week 24	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
NHE in prior 6 months	3.17 (1.25, 7.99)	**0.015**	-	-	-	-
ESMS	2.59 (1.12, 6.00)	**0.027**	1.92 (0.86, 4.29)	0.11	1.39 (0.62, 3.14)	0.80
Medication management	1.45 (0.66, 3.19)	0.36	0.93 (0.44, 1.97)	0.86	0.83 (0.37, 1.87)	0.65
Information management	2.53 (1.10, 5.79)	**0.029**	2.30 (1.04, 5.08)	**0.039**	1.17 (0.521, 2.64)	0.70
Safety management	1.05 (0.48, 2.32)	0.90	0.24 (0.11, 0.53)	**0.0005**	1.97 (0.86, 4.55)	0.11
Seizure management	1.83 (0.82, 4.11)	0.14	1.07 (0.51, 2.27)	0.86	1.68 (0.70, 4.03)	0.24
Lifestyle management	1.69 (0.76, 3.74)	0.20	1.63 (0.76, 3.51)	0.21	1.09 (0.49, 2.45)	0.84
ESES	2.16 (0.92, 5.09)	0.079	2.31 (1.06, 5.05)	**0.035**	1.22 (0.53, 2.77)	0.64
MSPSS	1.27 (0.58, 2.78)	0.55	1.28 (0.61, 2.70)	0.52	1.00 (0.45, 2.22)	0.99
QOLIE-10	3.45 (1.50, 7.97)	**0.0037**	2.71 (1.24, 5.91)	**0.012**	1.19 (0.53, 2.70)	0.68
MADRS	2.09 (0.90, 4.82)	0.085	3.18 (1.46, 6.92)	**0.0035**	0.67 (0.30, 1.48)	0.32
PHQ-9	1.25 (0.56, 2.80)	0.59	3.07 (1.41, 6.68)	**0.0047**	0.92 (0.41, 2.06)	0.84

Table 3.

The effect of SMART on changes in attitudinal/behavioral outcomes.

	From Baseline to Week 24		From Baseline to Week 10		From Week 10 to Week 24	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
ESMS	7.95 (2.42, 13.48)	**0.005**	4.97 (−0.23, 10.18)	0.061	3.79 (−1.31, 8.90)	0.14
Medication management	2.09 (−0.32, 4.50)	0.088	1.44 (−0.58, 3.47)	0.16	0.10 (−1.55, 1.75)	0.91
Information management	3.14 (0.73, 5.56)	**0.011**	2.36 (0.04, 4.68)	**0.046**	1.61 (−0.69, 3.91)	0.17
Safety management	0.01 (−1.58, 1.60)	0.99	−1.54 (−2.71, −0.36)	**0.011**	1.52 (−0.12, 3.16)	0.069
Seizure management	0.97 (−0.37, 2.32)	0.15	0.74 (−0.56, 2.03)	0.26	0.65 (−0.68, 1.98)	0.33
Lifestyle management	1.73 (−0.20, 3.67)	0.078	1.97 (0.04, 3.90)	**0.046**	−0.09 (−1.70, 1.53)	0.92
ESES	21.37 (1.90, 40.83)	**0.032**	19.63 (4.79, 34.46)	**0.010**	0.13 (−17.45, 17.71)	0.99
MSPSS	0.63 (−5.04, 6.31)	0.83	0.94 (−4.19, 6.06)	0.72	0.93 (−4.88, 6.74)	0.75
QOLIE-10	−0.45 (−0.74, −0.17)	**0.0019**	−0.51 (−0.80, −0.22)	**0.0007**	−0.06 (−0.31, 0.19)	0.63
MADRS	3.69 (−0.04, 7.42)	0.052	−5.85 (−8.63, −3.07)	**6×10^{-5}**	1.28 (−1.86, 4.43)	0.42
PHQ-9	2.13 (−0.48, 4.75)	0.11	−2.96 (−5.01, −0.91)	**0.005**	0.53 (−1.59, 2.65)	0.62

Table 4.

Results for significant (p<0.05) and near-significant (p~0.05) indirect effects of the association between SMART and improvements in NHEs mediated by improvements/change in attitudinal/behavioral outcomes.

Improvements (Baseline to Week 10)	**Total effect OR (95% CI)**	**Direct effect OR (95% CI)**	**Indirect effect OR (95% CI)**	**Total effect mediated (95% CI)**
QOLIE-10	1.246 (1.046, 1.489)	1.188 (0.992, 1.424)	1.049 (1.001, 1.124) [1]	21.6% (11.6%, 87.9%) [1]
MADRS	1.235 (1.04, 1.476)	1.186 (0.988, 1.423)	1.042 (0.992, 1.115)	19.2% (10%, 84.8%)
PHQ-9	1.246 (1.047, 1.491)	1.201 (1.001, 1.442)	1.037 (0.992, 1.106)	16.6% (8.8%, 69.5%)
Change (Baseline to Week 10)	Total effect OR (95% CI)	Direct effect OR (95% CI)	Indirect effect OR (95% CI)	Total effect mediated (95% CI)
QOLIE-10	1.249 (1.043, 1.484)	1.173 (0.977, 1.418)	1.065 (0.999, 1.156)	27.9% (15.3%, 126.9%)
MADRS	1.236 (1.033, 1.466)	1.159 (0.962, 1.405)	1.067 (0.996, 1.159)	30.1% (16.1%, 145.9%)
PHQ-9	1.244 (1.037, 1.485)	1.168 (0.977, 1.406)	1.065 (1.005, 1.155) [1]	28.5% (15.4%, 125.9%) [1]

[1] Significant mediated effects for a two-sided alpha of 0.05.