Study protocol with statistical analysis plan

What drives the effects of exposure therapy and healthy lifestyle promotion for psychological distress related to persistent somatic symptoms? Secondary analysis of effect mediators and process variables in a randomized controlled trial in primary care

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Background

Persistent physical symptoms lead to substantial levels of distress and social costs. Exposure therapy and healthy lifestyle promotion have been found to reduce somatic symptom burden and psychological distress in a large number of conditions where persistent physical symptoms are common, but little is known about the mechanisms responsible for these beneficial effects. Mainstream theoretical models emphasize the role of various forms of symptom preoccupation – the tendency to respond strongly to, and engage in behaviors contingent on, somatic symptoms – in exacerbating somatic symptom burden over time [1-5]. Especially in exposure therapy, but also to some degree in healthy lifestyle promotion, the observed reduction in somatic symptom burden may be likely to be mediated by a reduction in symptom preoccupation. There are also many other processes likely to contribute to the observed treatment effects. Noteworthy examples include increased physical activity [6], the degree to which patients engage with the treatment for example by conducting exposure exercises, and also common factors, i.e., mechanisms common to most psychotherapies, notable examples being the relationship with the therapist [7-10], treatment credibility and the expectancy of future improvement [11, 12].

Aim of this study

This study aims to evaluate potential mediators, and correlates of key process variables, that could be important for understanding the effects of exposure therapy and healthy lifestyle promotion when delivered to reduce somatic symptom burden and symptom preoccupation in individuals suffering from persistent physical symptoms.

Hypotheses

Main hypotheses are listed in Table 1.

Table 1. Hypotheses pertaining to tests of mediation.

Note	Outcome	Potential mediator	Hypothesis		
			Exposure	HLP	Between-group
Primary model	Overall somatic symptom burden	Overall symptom preoccupation	Yes, mediation (+)	Yes, mediation (+)	Yes, mediation ([a])
Sensitivity analysis 1: general factor	General somatic symptom burden	Overall symptom preoccupation	Yes, mediation (+)	Yes, mediation (+)	Yes, mediation ([a])
	Overall somatic symptom burden	Physical activity	Yes, mediation (-)	Yes, mediation (-)	Exploratory
	Overall symptom preoccupation	Physical activity	Yes, mediation (-)	Yes, mediation (-)	Exploratory

In this table "+" stands for a positive relationship, such that a reduction in the mean of the outcome variable is hypothesized to be associated with a reduction in the mean of the potential mediator. Analogously, "-" stands for a negative relationship, such that a reduction in the mean of the outcome variable is hypothesized to be associated with an increase in the mean of a potential mediator. Exposure, exposure therapy; HLP, healthy lifestyle promotion.
[a] As prespecified as part of the main study protocol.

Other indicators of treatment-specific factors
We also hypothesize that, in exposure therapy, there will be a Spearman correlation around 0.20-0.40 between the reduction in overall subjective somatic symptom burden (as derived from fitted regression lines) and the average number of reported exposure exercises per week. Moreover, we hypothesize that, in exposure therapy, there will be a Spearman correlation around 0.20-0.40 between the reduction in overall symptom preoccupation (as derived from fitted regression lines) and the average number of reported exposure exercises per week.

Other indicators of common factors
At week 3, participants reported how they perceived the strength of the relationship with the therapist (the working alliance) and to what degree they perceived the treatment as credible and expectancy-evoking. We hypothesize that credibility/expectancy will exhibit Pearson correlations around 0.10-0.50 with previous and subsequent improvement in somatic symptom burden and symptom preoccupation. We hypothesize that working alliance ratings will exhibit Pearson correlations around 0.10-0.40 with previous and subsequent improvement in somatic symptom burden and symptom preoccupation.

Methods

Design
This will be a secondary study of mediators of treatment effects in a randomized controlled trial of exposure therapy versus healthy lifestyle promotion (N=161).

Measurement
All questionnaires are administered online via a simple web interface, with black text on white background and radio buttons to indicate responses. Participants completed a 1-week focus version of the Patient Health Questionnaire 15 (PHQ-15) as a measure of somatic symptom burden on a weekly basis [13], a 1-week focus version of the Somatic Symptom Disorder B-criteria scale 12 (SSD-12) as a measure of symptom preoccupation on a weekly basis [14], and the Godin-Shepard Leisure-Time Exercise Questionnaire (GSLTPAQ) before and after treatment [15]. A study-specific item is administered to measure the number of exposure exercises conducted per week in the exposure treatment. A study-specific item is also administered to measure the development in stressors over the course of the study (Swedish: “Vissa saker kan få vem som helst att må dåligt. Hur stora påfrestningar har du haft i ditt liv under den senaste veckan, t.ex. när det gäller krav från andra, dödsfall, trauma, separation, ekonomi, förlust av arbete eller sjukdom?”, rated from ”Inte alls påfrestande vecka” to ”Extremt påfrestande vecka”).

Statistical analysis plan
For this secondary mechanistic study, scoring of the PHQ-15 and SSS-12 will be informed by preceding psychometric evaluation of these scales, focusing on factor structures [16]. From the PHQ-15, items 4 (menstrual problems), 5 (headaches), 8 (fainting spells), and 11 (sexual pain/problems) will not be used for the sum score. The remaining 11 items, unlike the full 15 items, appears to have a stable structure and an important advantage is also that the general somatic symptom burden factor appears to explain just above 50% of the variance in these items, thus supporting simple sum scoring which is not always as straightforward [17]. From the SSD-12, item 7 (reassured by others) will not be used for the sum score. The remaining 11 items, unlike the full 12 items, appears to have a relatively stable, replicated, structure [18].

Prior to the main analyses, key variable distributions and correlations will be evaluated, and change over time visually inspected. Tests of hypotheses pertaining to mediation (Table 1) will then be based on parallel process growth curve models. This main analysis will proceed in three stages: First, models with a random intercept and slope will be built to capture unconditional growth in each of the putative mediators and outcomes. Second, each putative mediator will be entered into the same model as the corresponding outcome, and tests for within-group mediation will concern the slope of the potential mediator (the a-path in the traditional Baron & Kenny mediation framework [19], assuming time to be the independent variable) multiplied by the effect of this slope on the slope of the outcome (equivalent to the b-path in the traditional Baron & Kenny mediation framework, assuming time to be the independent variable). Third, a variable for allocation (exposure therapy vs. healthy lifestyle promotion; 1/0) will be entered and tests for between-group mediation will concern the path from this variable, to the slope of the potential mediator, to the slope of the outcome. All tests of mediation will be bootstrapped (2000 samples) [20].

Mediation sensitivity analysis 1: general somatic symptom burden factor
A threat to the interpretation of the primary model is that the PHQ-15, and the 11 items used from this instrument, have a complex factor structure that is not fully reflected by a simple sum. An analogous secondary sensitivity analysis will therefore evaluate the effect on the general somatic symptom burden factor specifically.

Mediation sensitivity analyses 2: stressors experienced over the period (competing process)
Another threat to valid conclusions is potential confounding over the a- and b-paths of tests of within-group mediation, and the b-path of tests of between-group mediation. Thus, whenever significant mediating effects are seen, sensitivity analyses will also be conducted to evaluate whether, potentially, the correlation between the mediator and outcome slopes could be explained merely by a corresponding change in stressors over the course of the treatment. In this analysis, assuming that change in stressors can be modelled in a convincing manner, this variable will be entered into the model alongside the mediator and outcome, and paths will be specified from the slope of stressors to both the slope of the mediator and the slope of the outcome before tests for mediation are repeated.

Conditional indirect effects
We will test for conditional indirect effects such that the mediated effect (i.e., the influence of a particular change process) depends on the baseline level of the corresponding mediator. For this test, the intercept will be centered at the pre-treatment assessment, and we will test the path from this intercept, to the slope in the mediator (a-path), to the slope in the outcome (b-path) within each treatment.

Week-by-week temporal precedence
For outcomes and mediators both measured on a weekly basis, secondary analyses will explore week-by-week temporal precedence of each potential mediator variable relative to the corresponding outcome. This will be modelled using random-intercepts cross-lagged panel models [21], with sensitivity analyses detrended by the inclusion of correlated random slopes which implies that cross-lagged paths are indicative of relationships between deviations from the random intercept and slope, rather than deviations from the random intercept only.

Evaluation of exposure exercises, working alliance, and credibility/expectancy
Secondary analyses will also concern the Spearman correlation between the number of conducted exposure exercises and the outcome of exposure therapy in terms of change

derived from fitted slopes. Prior to the analysis of credibility/expectancy, the factor structure for this instrument will be evaluated to determine if is best conceived of as one score or two separate scores for credibility and expectancy respectively. Pearson correlations will then be calculated to evaluate the relationship between working alliance and credibility/expectancy and change in somatic symptom burden (fitted slopes) and symptom preoccupation (fitted slopes) over time. Within each treatment, working alliance and credibility/expectancy will be tested as a predictor of treatment completion status. In order to assess the relevance of the process variables as contributing to treatment effects, credibility/expectancy and working alliance will also be added to the primary models used to estimate within- and between-group effects on somatic symptom burden and symptom preoccupation for the primary publication.

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