Universiteit Leiden

Psychologie
Faculteit der Sociale Wetenschappen

“Detecting response shift and ‘true’ change with Structural Equation Modelling in Health-Related Quality of Life of Dutch bone metastasis patients undergoing radiotherapy.”

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Bachelorproject number: 238
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Abstract

Radiotherapy is a commonly applied treatment for cancer. Concurrently, assessments of its effect on Health-Related Quality of Life (HRQL) are being questioned. This article aims to measure a 'true' change in HRQL in 562 individuals from the population of Dutch bone metastasis patients undergoing radiotherapeutic treatment over a duration of 3 months, while accounting for the response shift. Response shift represents a change in an individual's self-evaluation. If unaccounted for, it can mask the 'true' change in HRQL. HRQL was operationalized as a combination of psychological and physical distress defined in the Rotterdam Symptom Checklist. The response shift and true change were calculated through the 4-step Structural Equation Modelling (SEM) procedure by Oort. The analysis revealed that response shift, especially uniform recalibration, was significantly altering the observed change, leading to underestimation of the true change. Both psychological and, to a larger extent, physical distress significantly decreased across the measurement occasions, indicating that the radiotherapy improved the HRQL of Dutch bone metastasis patients. In the discussion section, the limited external validity of the study and the suitability of the SEM method were discussed.

Key terms: health-related quality of life, HRQL, response shift, cancer, bone metastasis, radiotherapy, SEM, structural equation modelling

Introduction

Quality of Life (QoL) refers to well-being as measured from the individual's perspective (Cai et al., 2021). It is health-related when it refers to patients' experience of a medical condition or its treatment (Osoba, 2000). The construct should include two essential components: physical well-being and psychological well-being (De Haes et al., 1990; Ojelabi et al., 2017). Although additional components have been identified in the literature (Wilson, 1995; Olsen & Misajon, 2019), this paper focuses solely on physical and psychological well-being in order to maximise the generalizability of the findings to a wide range of research contexts. HRQL is measured to monitor patient wellbeing over time, or to assess treatment effectiveness (Chen et al., 2005). Such evaluations require longitudinal assessment of HRQL. That is, they require assessment of change in HRQL scores over time (Singer & Willet, 2003). In this study, patients' HRQL will be measured before and during the process of radiotherapy.

Response shift is a crucial concept in assessing longitudinal changes in health-related quality of life (HRQL). It represents the change in the meaning of an individual's self-evaluation (Testa et al., 2021b). More specifically, response shift refers to the changes in respondents' internal standards of measurement (recalibration), changes in importance of a target construct's components (reprioritization), and/or a redefinition of a target construct (reconceptualization) (Schwartz & Sprangers, 1999b). If response shift is not accounted for, it remains unknown whether the change that occurred in measures of HRQL is due to the HRQL being affected ('true' change) or due to alterations in the perception of HRQL (Chen et al., 2021; Sébille et al., 2021; Testa et al., 2021). As a consequence, the effectiveness of the treatment will remain either under- or over-estimated.

The current study uses measures of psychological and physical distress in relation to the effects of the radiotherapeutic treatment of bone metastasis. Bone metastasis occurs when the cancer has spread from the original (primary) tumor to the bone (*Comprehensive Cancer*

Information, n.d.). Its symptoms are extremely painful, affecting both physical and psychological well-being (Smith & Mohsin, 2013; Zajączkowska et al., 2019). Many studies argue for the effectiveness of radiotherapy in treating bone metastasis (Caissie et al., 2011; Chow et al., 2004; Gaze et al., 1997; Lam et al., 2013; McDonald et al., 2014; Zeng et al., 2012). However, according to some, questionable study design choices, such as a short measurement period or lack of randomization, might undermine the validity of the aforementioned studies (Westhoff et al., 2016). Bone metastasis affects the quality of life (Chow et al., 2008) and its common treatment, radiotherapy, has been questioned (Westhoff et al., 2016) Accounting for response shift while measuring the HRQL changes is of crucial importance, as it can clarify the influence of readiotherapy on HRQL of bone metastasis patients, and thus provide practitioners with knowledge to make substantiated treatment choices.

As such, this study aims to answer the following two research questions. Firstly, does response shift affect the change in HRQL scores of bone metastasis patients undergoing radiotherapy? It is hypothesized that response shift is present in the measurements of the Health-Related Quality of Life of bone metastasis patients undergoing radiotherapy (H_1). Secondly, is there a 'true' change in HRQL of bone metastasis patients undergoing radiotherapy? The hypothesis is that the radiotherapeutic treatment of bone metastasis patients significantly changed their HRQL after accounting for possible influences of the response shift (H_2). It is important to stress that the directionality of H_2 was not assumed intentionally. Although radiotherapy is utilized to treat the cancer (Washington et al., 2020), and thus can improve HRQL, it is also known to bear numerous severe side effects, affecting both psychological (depression, anxiety) and physical (fatigue, gastrointestinal issues) well-being (Dilalla et al., 2020). It is possible that they would, in turn, lead to a decrease in HRQL.

Response shift and 'true' change will be investigated through a 4-step procedure based on Oort (2005) and Oort et al. (2005). The procedure's primary function is to detect all of the instances of response shift and account for their influence in order to determine a 'true' effect of the intervention on the latent construct. For the purposes of this study, the procedure will be utilized to measure the 'true' effect of radiotherapy on HRQL.

Methods

Original data and design

The data used in the current study were originally obtained through the DBSM – Dutch Bone Metastasis Study (Van Der Linden et al., 2004). This study was a nationwide, randomized, controlled trial conducted on 1157 patients in the Netherlands between 1996 and 1998. The patients were randomised between the 2 groups – single fraction 8 Gy treatment or 6 fractions 24 Gy treatment. In the context of radiotherapy, Gy indicates the total radiation received by a patient, and the number of fractions corresponds to the number of times over which radiation was applied (Murphy & Chmiel, 2019). In other words, in one condition, 8 Gy was applied 1 time, and in the other, 24 Gy was applied 6 times (thus 4 Gy per application). The study was approved by the medical ethics committees of the participating institutions. Researchers chose a longitudinal study design. At randomisation and during follow-up, patients were asked to fill out 13 weekly questionnaires, followed by monthly questionnaires until 2 years or the participant's death. The questionnaires were mailed to participants.

Instrument

From all the questionnaires used in DBSM, the ongoing study will focus on the results of the RSCL (Rotterdam Question Checklist; De Haes, 1996). The RSCL is a self-report measure of proven validity and reliability (Pelayo-Alvarez et al., 2013) used to assess the

HRQL of cancer patients. It includes 23 items representing physical symptoms of distress (e.g., tiredness, shivering, headache), and 7 items representing psychological symptoms of distress (e.g., anxiety, tension, irritability), as well as several items representing activity level (e.g., climb stairs, go to work, go shopping) and an item representing overall valuation of life (Sanderman, 1996). Answers to the items are represented on a Likert scale ranging from 1 to 4, where 1 means 'not at all' and 4 means 'very much'. As the RSCL represents both physical and psychological well-being, it is suitable for assessing the HRQL.

Data preparation

The variables containing information on items representing physical and mental psychological distress at first and a second measurement occasion will be utilized. The baseline measurement was chosen for the first measurement occasion. As the second measurement, the data recorded in the 13th week of the study duration will be used. Substantiation for this decision is that 13 weeks is approximately 3 months, which is a commonly used period between measurements of HRQL for the detection of response shift (Chen et al., 2021; Testa et al., 2021). The analysis will be conducted solely on the patients in the treatment condition of 1 fraction and 8 Gy. The reason that I restrict my population to only one condition is to avoid any unaccounted-for differences between the participants. The reason I chose 8 Gy, 1 fraction condition is that it is a standard treatment option (Chow et al., 2017), which might in turn increase the external validity of the study.

With regard to the missing values, there is a possibility that needs to be acknowledged: if missing values appear only on the second measurement occasion of an observation, it might be due to the patient's death. Bone metastasis is, after all, lethal (De Salvo & Pucciarelli, 2005). Removing missing values that are caused by death will introduce a survivor bias (Hernán et al., 2004). In case non-randomness is found, Random Imputation (RI) will be used to impute the data. The method is considered reliable, especially in the case of missingness of

data due to death (Jolani et al., 2015; Van Buuren, 2018). The dedicated R package ‘mice’ is tailored to this purpose (Van Buuren & Groothuis-Oudshoorn, 2011) and thus will be utilized. In case no pattern of missingness will be found, data will be evaluated through Little’s MCAR test (Little, 1988) in the ‘naniar’ package (Tierney & Cook, 2023). If MCAR is implied, model parameters will be estimated directly from all the available data, without imputing or discarding missing values, through a dedicated full information maximum likelihood method in the lavaan package in R (Rosseel, 2012).

Structural Equation Modelling

The statistical tool utilized for the purposes of this study is Structural Equation Modelling (SEM). SEM enables modeling multiple constructs as latent variables at the same time - the relationships between them, and complex interdependencies between their observed variables. As such, it is suitable to measure HRQL, as it allows for analysis of both its two aspects (physical well-being and psychological well-being) on two measurement occasions, and for investigation of response shift associated with them. SEM will be fitted to the means, covariances, and variances of the observed data.

Response shift operationalizations

With SEM, response shift can be operationalized. The response shift parameters used for the purposes of response shift operationalization in SEM are factor loadings, intercepts, and residual variances.

Factor loadings are coefficients of the regression on the observed variables of a given factor. They measure the extent to which the observed variables are representative of a common factor (Oort, 2005). In other words, the higher the absolute factor loadings of a factor (e.g., psychological distress) on the observed variable (e.g., anxiety), the more this observed variable is representative of this factor. Both reprioritization and reconceptualisation

are operationalized through factor loadings. Reprioritization occurs when the relative importance between an item and a latent variable changes. It is operationalised as a shift in the value of a factor loading between the item and the latent variable across occasions. For instance, an observed variable ‘anxiousness’ has a factor loading of 0.1 at the first measurement occasion and 0.7 at the second measurement occasion. Reconceptualization occurs when the observed variable either stops or starts representing a latent variable due to a change in participants’ perception of the constructs, thus changing the structure of the model. It is operationalised as a difference in the pattern of common factor loadings (i.e., the pattern of zero versus non-zero factor loadings) across occasions. For example, at the first measurement occasion, ‘lack of appetite’ loads on physical distress, but its factor loading decreases to 0 on the second measurement occasion.

Intercepts are the expected values of observed variables when all latent variables and covariates are set to zero. They represent baseline levels of the observed variables, independently of the latent constructs they measure (Kaplan, 2009). Intercepts are utilized to operationalize uniform recalibration. Uniform recalibration is a change of the intercept of the observed variable across occasions (King-Kallimanis et al., 2011). It occurs when all (or most) of the items representing the observed variable change systematically in the same direction. For example, patients systematically score higher on questions regarding the observed variable ‘anxiety’ on the second measurement occasion, increasing the value of the intercept for this variable.

Residual variance is part of the variance of the observed variable that remains unexplained after accounting for covariates and the effect of the latent variable (Asparouhov & Muthén, 2022). It quantifies the baseline level of unexplained variability in the observed indicators, after accounting for the modeled relationships. Residual variance is utilized to operationalize nonuniform recalibration. Nonuniform recalibration refers to the nonuniform

changes in how participants interpret the items of the observed variable, resulting in different residual variances for given observed variables across the measurement occasions (Oort, 2005). For instance, on the first measurement occasions, answers to the item 'I often feel anxious' varied from 1 to 4, but on the second measurement occasions, all of the answers are within an interval of 2 and 3, affecting the 'anxiousness' observed variable's variance.

Procedure

The procedure to measure response shift and 'true' change is adapted from Oort (2005) and Oort et al. (2005) and consists of the following 4 steps:

Step 1: The first SEM model, the Reference Model, will be fitted to the data at both measurement occasions. The Reference Model will contain two latent variables - psychological and physical distress - at two measurement occasions – firstly, at the beginning of radiotherapeutic treatment, and secondly, 13 weeks later. The latent variables will be taken directly from RSCL's manual on the proposed structure of physical and psychological distress (Sanderman, 1996). Namely, 23 items will represent physical distress, and 7 items will represent psychological distress. The model will be estimated using the maximum likelihood estimation method. This method defines model parameters under which the observed data would be most probable (Casella & Berger, 2002). The response shift parameters (factor loadings, intercepts, and residual variances) will not be restricted across measurement occasions.

In the Reference Model, all covariances between latent factors will be allowed for. The reason for that is of an empirical nature. Firstly, one should expect that the same latent factor measured at different measurement occasions would correlate, as it is supposed to measure the same concept. Based on this logic, I will also allow for all the residual covariances between the same variable on two measurement occasions (eg, tension at first measurement

occasion correlates with tension at second measurement occasion). Secondly, even though physical and psychological distress are two distinct concepts, it has been established that they are closely interdependent (Segrin Badger, 2014) and influence each other heavily (Haug et al., 2004).

Following the estimation of the model, I will evaluate the model fit (see Section: Goodness of fit). If it proves less than close, I will further search for possible substantive changes guided by modification indices. Namely, I will search and account for the substantive crossloadings (load an observed variable on multiple latent factors) and residual covariances (establish correlations between residual variances of two observed variables). I will present the derived model in the results section.

Step 2: In the second model, the Constraint Model, the response shift parameters will be constrained to be equal across measurement occasions. Then, the difference between the Reference Model and the Constraint Model will be tested with a $\chi 2$ difference test. A significant result ($p<0.05$) would indicate that the equality restrictions across occasions are not tenable, which is taken to indicate the presence of response shift. If $p>0.05$, it is indicated that the response shift did not significantly alter the HRQL scores, and the process will be continued from Step 4.

Step 3: Detection Model - Model 3's purpose is to detect all the existing response shifts, i.e, which item is affected by which type of response shift. To achieve this goal, each response shift parameter constraint of the Constraint Model will be systematically removed, one at a time, while the other constraints remain unchanged. Each modification will be tested with a $\chi 2$ difference test between the original Constraint Model and the modified version. The constraint that removal proved to affect the model most significantly will be released permanently, and the process will be repeated iteratively until the removal of none of the remaining constraints improves the model fit significantly. Only parameters whose

substantive constraint modifications will result in $\chi 2$ p-value < 0.05 will be considered to contribute to the response shift.

Step 4: Guided by the Detection Model, in the Refined Model (Model 4), I will release constraints on the response shift parameters responsible for response shift but not the others. Next, I will test differences in common factor means between the two measurement occasions. As the changes caused by the response shift will be mitigated, the difference between common factor means in the Refined Model will represent true change. The effect sizes will be calculated using Standardized Response Mean (SRM) (Verdam et al., 2017).

Evaluation

For each variable affected by the response shift, the response shift's contribution will be represented as an effect size calculated in accordance with Oort (2005). Observed change - a total change in the variable's value - and true change will be calculated, and the subtraction of true change from observed change will yield in representative contribution of a response shift in the process. Contributions will then be classified as small (0.2), medium (0.5), or large (0.8) (Cohen, 1971).

Identification

Following the instructions of Oort et al. (2005), the model identification was achieved through fixing the mean of each latent variable to 0 and the variance of each latent variable to 1. In steps 2 to 4, I will fix the means and variances only at the first measurement occasion. On the second occasion, means and variances will be identified through constraining factor loading and intercepts to be equal across occasions.

Goodness of fit

In SEM, goodness of fit is primarily assessed with a $\chi 2$ test. It compares the observed covariance matrix with the model-implied expected covariance matrix (S & Mohanasundaram, 2024). The null hypothesis for the $\chi 2$ test is that the model fits the data perfectly – hence, a significant result suggests a poor fit. However, the $\chi 2$ test is known for its sensitivity to large sample sizes (Oort et al., 2005); thus alone is not enough to confirm the goodness-of-fit. As suggested by Oort et al. (2005), an additional fit index – Root Mean Square of Approximation (RMSEA; Steiger, 1980)– will be applied. RMSEA is a fit index used in SEM that measures the discrepancy between the sample covariance matrix and the model covariance matrix, adjusted for model complexity (Browne & Cudeck, 1992). As a commonly accepted rule of thumb, RMSEA < 0.08 indicates a 'reasonable fit', and RMSEA < 0.05 indicates a 'close fit'. In case of a 'reasonable fit', I will attempt further improvements guided by modification indices (see Procedure) before accepting the Reference Model. In case of a 'close fit', I will accept the Reference Model without alterations.

Software

Data preprocessing will be conducted using Python in Jupyter Notebook (Van Rossum & Drake, 2009). Imputation of missing values and analysis will be conducted in R in R Studio (R Core Team, 2014; RStudio Team, 2019), with the 'mice' package (Van Buuren & Groothuis-Oudshoorn, 2011) and the 'lavaan' package (Rosseel, 2012), respectively.

Results

Patients

The data consist of 562 Dutch patients with painful bone metastasis. The average age of the patients was 65 years, with a standard deviation of 11. 53% of the patients are female, and 47% of the patients are male.

Table 1: Overview of variables in the model with respect to their latent factor

General distress	
Psychological distress	Physical distress
Worrying	Lack of appetite
Depressed mood	Tiredness
Despairing about the future	Lack of energy*
Tension	Low back pain
Lack of energy*	Sore muscles
Irritability	Nausea
Nervousness	Difficulty sleeping
Hopelesness	Headaches
	Dizziness
	Decreased sexual interest
	Abdominal aches
	Constipation
	Acid indigestion
	Tingling hands or feet
	Difficulty concentrating
	Pain when swallowing
	Loss of hair
	Shortness of breath
	Dry mouth
	Vomiting
	Shivering
	Sore eyes
	Diaorrhea

Notes: * was placed next to 'Lack of energy', as this variable is originally representative of only physical distress, but proved to be representative of psychological distress simultaneously.

Reference Model

The Reference Model closely resembles the representation of psychological distress and physical distress in RSCL (Sanderman, 1996) (see Table 1) and is consistent across both measurement occasions. The model fit proved 'reasonable', thus in addition to modifications described in the method section, a minor adjustments were made. Lack of energy was added as a variable representing not only physical distress but also psychological distress at the same time. This was deemed a plausible modification as previous research has shown that energy level contributes to the representation of an individual's psychological well-being (R. M. Ryan & Deci, 2001). Moreover, residual covariances between nausea and vomiting on both measurement occasions were allowed for. Not only did the modification indices strongly

indicate the relationship, but also the definition of nausea states that it is the feeling that one is going to vomit (*Nausea*, 2025). The final Reference Model proved to be fitting acceptably well: $\chi^2(1670) = 5158.399$, $p < .001$; RMSEA = 0.061, CL 90% [0.059, 0.063].

Table 2: Overview of response shift parameters significantly affected by response shift.

	First measurement occasion			Second measurement occasion		
Variable name	Factor	Intercept	Residual	Factor	Intercept	Residual
Nervousness$_1$	0.641	**1.888**	0.317	0.641	**1.953**	0.317
Worrying$_1$	0.758	**2.220**	0.350	0.758	**2.358**	0.350
Depressed mood$_1$	0.667	**1.799**	0.306	0.667	**2.111**	0.306
Hopelesness$_1$	0.699	**1.955**	0.371	0.699	**2.151**	0.371
Tension$_1$	0.663	1.953	**0.351**	0.663	1.953	**0.473**
Lack of energy$_1$	**0.212**			**0.334**		
Irritability$_1$	**0.366**	1.661	0.473	**0.422**	1.661	0.473
Anxiety$_1$	**0.664**	**1.809**	**0.366**	**0.648**	**2.314**	**0.453**
Lack of apetite$_2$	**0.559**	**1.855**	0.642	**0.510**	**2.102**	0.642
Tiredness$_2$	**0.562**	**2.622**	0.556	**0.662**	**3.122**	0.556
Sore muscles$_2$	0.355	**2.213**	0.856	0.355	**2.477**	0.856
Lack of energy$_2$	**0.483**	2.189	**0.564**	**0.335**	2.188	**0.756**
Back pain$_2$	0.405	2.412	**1.160**	0.405	2.412	**0.877**
Nausea$_2$	**0.465**	**1.567**	0.464	**0.383**	**1.871**	0.464
Difficulty sleeping$_2$	0.299	**1.923**	**0.891**	0.299	**2.058**	**0.746**
Headaches$_2$	0.171	**1.313**	0.424	0.171	**1.409**	0.424
Vomiting$_2$	0.273	1.310	**0.359**	0.273	1.310	**0.490**
Dizziness$_2$	0.254	1.393	**0.339**	0.254	1.393	**0.424**
Swallowing pain$_2$	**0.111**	**1.178**	**0.242**	**0.223**	**1.656**	**0.299**
Decreases sex interest$_2$	**0.372**	2.759	1.555	**0.378**	2.759	1.555
Acid indigestion$_2$	**0.307**	**1.476**	**0.456**	**0.270**	**2.084**	**0.630**
Shivering$_2$	0.324	1.497	0.440	0.324	1.497	0.440
Tingling$_2$	**0.179**	**1.409**	**0.473**	**0.183**	**1.772**	**0.549**
Abdominal pain$_2$	**0.256**	**1.346**	**0.344**	**0.282**	**1.942**	**0.516**
Hair loss$_2$	**0.059**	**1.247**	**0.451**	**0.149**	**1.807**	**0.734**
Sore eyes$_2$	**0.102**	**1.244**	**0.301**	**0.212**	**1.645**	**0.416**
Difficulty concentrating$_2$	0.482	**1.833**	0.553	0.482	**2.171**	0.553
Shortness of breath$_2$	**0.396**	**1.802**	0.767	**0.444**	**2.338**	0.767
Dry mouth$_2$	0.471	**1.981**	0.754	0.471	**2.187**	0.754
Diaorrhea$_2$	**0.059**	**1.132**	**0.174**	**0.066**	**1.284**	**0.241**
Constipation$_2$	0.438	1.768	0.744	0.438	1.768	0.744

Notes: Parameters are presented across the measurement occasions. 'Factor' refers to factor loading, 'Residual' to residual variance, and 'Intercept' to intercept. $_1$ indicates belonging to the psychological distress latent variable, and $_2$ indicates belonging to the physical distress latent variable. Significantly changed response shift parameters are in **bold**.

Detecting Response Shift

The difference between the Constraint Model and Reference Model was tested with the $\chi 2$ difference test. Results did indicate that the models' fits are significantly different: $\chi^2(89) = 1305.4$, $p < .001$, implying that the response shift did take place.

51 response shift parameters were deemed to be significantly affected by the response shift. An overview of these parameters can be found in Table 2. The result of the $\chi 2$ difference test between fits of the Refined Model and the Constraint Model was found significant and indicated substantial improvement: $\chi 2(51) = 1196.4$, $p < .001$.

Evaluation of the response shifts

No instance of reconceptualization was detected. However, reprioritisation was identified to affect multiple variables. In case of the psychological distress, 3 of the 8 factor loadings changed significantly (Table 2). Factor loadings grew larger for anxiety, and decreased for lack of energy, and irritability. Hence, the importance of these variables in representing psychological well-being has changed. As for the physical distress, 13 out of 23 possible cases of reprioritisation occurred. Namely, the value of factor loadings increased for tiredness, swallowing pain, acid indigestion, decreased sex interest, tingling, abdominal pain, hair loss, shortness of breath, diarrhea, and decreased for lack of appetite, lack of energy, and nausea. The size of the effects of reprioritization was small, with the largest effect size being $d = -0.195$ for swallowing pain.

Significant changes in intercepts were detected across observed variables of both latent factors. For psychological distress, 5 out of 7 intercepts' values shifted significantly (Table 2). Namely, the intercept decreased across measurement occasions for the nervousness, worrying, depressed mood, hopelessness, and anxiety variables. Hence, patients raised their internal standards for what it means to experience the above-mentioned phenomena.

Similarly, intercepts have uniformly increased for 16 out of 23 variables representing physical distress. Namely, they have increased for abdominal pain, swallowing pain, acid indigestion, hair loss, sore eyes, shortness of breath, tingling, nausea, tiredness, difficulty concentrating, diarrhea, lack of appetite, sore muscles, dry mouth, headaches, and difficulty sleeping. The sizes of the effect of uniform recalibration for psychological distress were mostly small, with the exception of anxiety (0.558) and depressed mood (0.418). For physical distress, effects of response shifts for 10 variables were medium to large in size, with acid indigestion (0.697), abdominal pain (0.744), shortness of breath (0.676) and swallowing pain (0.804) bearing the largest effect sizes.

Nonuniform recalibration was also found to be present. For psychological distress, nonuniform recalibration has occurred in 2 out of 7 cases (Table 2). Residual variance increased for both tension and anxiety. In other words, participants' answers to questions related to tension and anxiety became more inconsistent. As for physical distress, nonuniform recalibration significantly affected variables in 12 out of 23 instances. The following variables noted an increase in the residual variance: lack of energy, dizziness, vomiting, swallowing pain, acid indigestion, tingling, abdominal pain, hair loss, sore eyes, diarrhea. The only variables for which residual variance significantly decreased, hence participants' answers became more consistent, were difficulty sleeping and back pain.

Table 3 contains information on the contributions of 'true change' and response shift to the total (observed) change that affected the given variable. Overall, a change in the values of 25 out of 31 variables was partially caused by the response shift. The large majority of those contributions (22 out of 25) were positive, hence, response shift inflated the observed scores in physical and psychological distress variables, undermining the perception of the extent to which the intervention results in a 'true' change. The effect sizes of these variables range from small to large, with the largest being d=0.744 for the abdominal pain variable

representing physical distress. Only a few (3 out of 25) variable scores were negatively affected by the response shift, and their effect sizes were negligible: with the largest effect size being -0.072 for the lack of energy variable representing psychological distress. An overview of all of the contributions can be found in Table 3.

Table 3: Overview of the effect sizes of response shifts per variable.

	Effect sizes		
Variable name	Observed change	Response shift contribution	True change contribution
Nervousness$_1$	-0.473	0.093	-0.565
Worrying$_1$	-0.415	0.172	-0.587
Depressed mood$_1$	-0.138	0.418	-0.556
Hopelesness$_1$	-0.321	0.262	-0.583
Tension$_1$	-0.479		-0.479
Lack of energy$_1$	-0.196	-0.072	-0.124
Irritability$_1$	-0.292	-0.039	-0.253
Anxiety$_1$	0.112	0.569	-0.458
Lack of apetite$_2$	-0.296	0.314	-0.610
Tiredness$_2$	-0.210	0.447	-0.657
Sore muscles$_2$	-0.091	0.231	-0.322
Lack of energy$_2$	-0.328	0.144	-0.472
Back pain$_2$	-0.328		-0.328
Nausea$_2$	-0.103	0.429	-0.532
Difficulty sleeping$_2$	-0.169	0.130	-0.299
Headaches$_2$	-0.110	0.132	-0.242
Vomiting$_2$	-0.323		-0.323
Dizziness$_2$	-0.343		-0.343
Swallowing pain$_2$	0.415	0.609	-0.194
Decreases sex interest$_2$	-0.332	-0.005	-0.327
Acid indigestion$_2$	0.353	0.697	-0.344
Shivering$_2$	-0.379		-0.379
Tingling$_2$	0.210	0.436	-0.226
Abdominal pain$_2$	0.396	0.744	-0.348
Hair loss$_2$	0.448	0.516	-0.068
Sore eyes$_2$	0.270	0.429	-0.159
Difficulty concentrating$_2$	-0.186	0.387	-0.573
Shortness of breath$_2$	0.096	0.613	-0.517
Dry mouth$_2$	-0.261	0.190	-0.451
Diaorrhea$_2$	0.144	0.250	-0.106
Constipation$_2$	-0.452		-0.452

Notes: 'Observed change' refers to the total change in the variable, 'True change contribution' to the change solely attributed to the 'true change', and 'Response shift contribution' to the change caused specifically by the response shift. $_1$ indicates belonging to the psychological distress latent variable, and $_2$ indicate$_s$ belonging to the physical distress latent variable.

True Change

After accounting for the response shift, the true change was tested with Refined Model parameters. The comparison indicated that the level of psychological distress significantly decreased across the measurement occasions: ΔM = - 0.623, SE = 0.061, z = -10.178, p < .001, with a medium-sized effect of d=-0.653. Test of across-occasion difference between means of physical distress yielded stronger results: ΔM = - 1.038, SE = 0.075, z = - 13.877, p < .001; d = -1.291. Both of the latent factor mean differences exhibited a decrease with respect to their equivalents in the Constraint Model, where response shift was not accounted for. The latent factor means differences in Constraint Model were: ΔM = -0.378, SE = 0.041, z = - 9.297, p < .001; d = -0.469 and: : ΔM = - 0.482, SE = 0.050, z = - 9.594, p < .001; d = -0.487. for psychological and physical distress, respectively. While for psychological distress, the change in the effect size was substantial, the effect size did dramatically increase for physical distress, indicating that the response shift played a significant role in its assessment.

Discussion

Addressing research questions

This study aimed to clarify the effect of the radiotherapeutic treatment on HRQL of patients with bone metastasis, while accounting for the possible distortion in the observed results in the form of response shift. Hence, two research questions were formed.

Firstly, it was inquired whether response shift is present in the measurements of the Health-Related Quality of Life of bone metastasis patients undergoing radiotherapy. Indeed, many instances of the response shift were detected. Specifically, subcomponents of the response shifts that did affect the results are reprioritization, uniform recalibration, and nonuniform recalibration. The total effects of the detected response shifts were found to be

small for the majority of the selected variables (see Table 3). However, there are several variables for which the response shift had a more impactful effect on the scores.

Among these variables, the only ones representing psychological distress are depressed mood (0.418) anxiety (0.569). The overwhelming majority of this contribution is due to the uniform recalibration. Indeed, radiotherapy patients have reasons to reevaluate what the 'normal' anxiety and depressive mood score mean, as they are constantly prone to their causes. Patients have to face the constant awareness of the fragility of their lives, now revealed by cancer. Up to 49% of patients undergoing radiotherapy are experiencing continuous, intense anxiety (Elsner et al., 2017). Anxiety, on the other hand, can lead to depression (Long et al., 2022). It is thus possible that such exposure to anxiety, and depressed mood caused by it, influenced patients to increase the internal standards for what it means to be anxious and feel depressed. The findings are in line with the current evidence (Amiri, 2024).

Remaining impactful response shifts affected the variables representing physical distress (see Table 3). Similarly to response shifts affecting psychological distress, the contribution of the uniform recalibration is overwhelmingly dominant in all of the instances. Namely, the impactful response shifts in variables representing physical distress are caused by patients increasing their standard for what it means to experience them. The most notable response shifts relate to abdominal pain (0.744) and acid indigestion (0.697). It has been established in the body of research that radiotherapy can lead to severe injuries in the gastrointestinal tract, resulting in abdominal pain and acid indigestion (Chen et al., 2023; Shadad et al., 2013). Under constant exposure to gastrointestinal pain, the phenomenon of habituation is likely to occur - a decrease in pain and pain-related responses in reaction to the continuously occurring painful stimulus (Rennefeld et al., 2010). It is plausible that due to habituation, patients became partially desensitized toward pain caused by abdominal pain and

acid indigestion, and thus increased their internal standard, leading to the occurrence of uniform recalibration.

Regarding the second research question, radiotherapeutic treatment of bone metastasis did significantly change patients' HRQL. A 'true' change in the values of psychological and physical distress took place; the level of both psychological distress and physical distress lowered after the intervention, thus the overall HRQL was improved. Concurrently, the decrease in physical distress ($\Delta M = -1.038$; $d = -1.291$) was far more impactful than the decrease in psychological distress ($\Delta M = -0.623$; $d = -0.653$). Observed general tendency for radiotherapeutic palliative influences is in accordance with existing evidence (Lutz et al., 2016; McDonald et al., 2017). Furthermore, the physical distress exhibiting larger improvement than psychological distress under radiotherapeutic treatment is the common outcome in the scientific literature (Caissie et al., 2011; McDonald et al., 2017; Pielkenrood et al., 2022). Overall, this study contributes to the body of research by supporting the effectiveness of radiotherapy in increasing patients' quality of life, despite the treatment's side effects.

External validity

Firstly, all the patients were Dutch. There is no guarantee that the result would replicate if the study were conducted in a more economically challenged country. HRQL improvement could decrease due to the differences in the quality of medical staff and infrastructure. Dutch Human Development Index (HDI) is ranked as 'very high' in the global context (Organization, 2022), and HDI is positively correlated with the national quality of healthcare (Azadnajafabad et al., 2023). Lower quality of healthcare services could diminish the improvement in HRQL attributed to radiotherapy. Secondly, the results were collected 17 years ago. Since then, the quality of healthcare in the Netherlands has improved (OECD, 2025). As a result, the improvement in HRQL attributed to radiotherapy might have been

greater if the data were collected more recently. Therefore, the findings of this study may represent a conservative estimate of the actual influence of radiotherapy on HRQL today.

Throughout the analysis, I was required to make subjective decisions that could undermine the study's external validity. In the interest of transparency and scientific integrity, I documented them in this paper. However, it is important to acknowledge that they could have altered the results in a substantial way. One notable example is the operationalization of the physical and psychological distress. Guided by the modification indices and substantive evidence, I performed minor adjustments resulting in a deviation from the original structure of my instrument. Hence, even though similar, the psychological and physical distress examined in this study is not exactly the same as the structure suggested by the RSCL (Sanderman, 1996). Additionally, when performing SEM on a multifaceted and nuanced concept such as HRQL, the risk of overfitting is significant. To enhance the generalizability of the findings, they could be replicated while adapting another model of HRQL utilizing psychological and physical distress as latent variables.

SEM alternatives

It is worth noting that utilizing SEM is not the only possible means for detecting response shift. There are several kinds of approaches that enable the detection of the response shift. Qualitative approaches analyse non-numeric data, such as interviews and open-ended questions, to detect response shift using methods such as thematic analysis. Design-based approaches are characterized by the use of additional measures to detect response shift. For instance, the 'then-test' – an additional measurement that is the same in content as the pre- and post-occasions measurement, but with an instruction to re-evaluate participants' level of pre-test functioning (Sébille et al., 2021c). Statistical approaches, on the other hand, use factor solutions and variance-covariance matrices to detect the response shift in numerical data (Visser et al., 2005c). As the data used in the study were numerical, and no additional

measurement was utilized, the statistical approach was deemed most suitable. SEM is a unique statistical approach in that it is designed to detect not only recalibration but also reconceptualization and reprioritization – mechanisms deepening the explanation of the process (Vanier et al., 2021). SEM, being a statistical approach encompassing this quality, appeared to be the most appropriate method given the context of this particular study.

Conclusion

Response shift, mainly uniform recalibration, was detected in the HRQL of Dutch bone metastasis patients undergoing radiotherapeutic treatment. Having accounted for it, both the psychological and, to a larger extent, physical distress levels of the patients decreased, indicating that radiotherapy improves the HRQL of bone metastasis patients.

Undergoing radiotherapy can be a daunting experience. The patient often experiences numerous side effects, including vomiting, fatigue, and inflammation. It can appear to some that radiotherapy would only damage someone's well-being. Therefore, it is of crucial importance that the doctor's decision to assign this kind of treatment is well-substantiated to improve the patient's life. With the help of the response shift, scientists can differentiate the effects of the hardships on perception from the actual improvement of the patient's well-being, and asses the true effects of the treatment. The confidence resulting from the clarity of this judgement is invaluable, since it will be heard in the doctor's words to the scared and disoriented patient: "I believe this treatment will help you".

Acknowledgements

I would like to acknowledge the help I received from my supervisor, Mathilde Verdam. She provided me with the data, instructions for conducting the 4-step procedure, and feedback throughout the whole process. I would also like to express my gratitude to my partner, Adriana Jurczyk, for her continuous and unwavering understanding and empathy, which supported me through the completion of this project. Special thanks to my colleagues, Ellis Van Oosterhout and Amelie J.C. Groß, whose sincerity and openness repeatedly reminded me that I was not struggling alone.

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Appendix A

First Step of the Analysis

```
#install.packages('lavaan')
#install.packages('mice')

#import metabone_ri_cleaned dataset

library('lavaan')

SEM_MODEL_1_new <- paste0('

#Latent factor: PSI1
  PSI1 =~ L1_PSI1*psi_nervousness_before +
    L2_PSI1*psi_worrying_before +
    L3_PSI1*psi_depressed_mood_before +
    L4_PSI1*psi_hopelesness_before +
    L5_PSI1*psi_tension_before +
    L6_PSI1*phy_lack_of_energy_before +
    L7_PSI1*psi_irritability_before +
    L8_PSI1*psi_anxiety_before

  # Constrain the variance of PSI1 to 1 (fixed)
  PSI1 ~~ 1*PSI1

  # Define unique variances for observed variables
  psi_nervousness_before ~~ E1_PSI1*psi_nervousness_before
  psi_worrying_before ~~ E2_PSI1*psi_worrying_before
  psi_depressed_mood_before ~~ E3_PSI1*psi_depressed_mood_before
  psi_hopelesness_before ~~ E4_PSI1*psi_hopelesness_before
  psi_tension_before ~~ E5_PSI1*psi_tension_before
  psi_irritability_before ~~ E7_PSI1*psi_irritability_before
  psi_anxiety_before ~~ E8_PSI1*psi_anxiety_before

  # Set latent factor mean to 0 (fixed)
```

```
  PSI1 ~ 0*1

  # Define intercepts for observed variables
  psi_nervousness_before ~ INT1_PSI1*1
  psi_worrying_before ~ INT2_PSI1*1
  psi_depressed_mood_before ~ INT3_PSI1*1
  psi_hopelesness_before ~ INT4_PSI1*1
  psi_tension_before ~ INT5_PSI1*1
  psi_irritability_before ~ INT7_PSI1*1
  psi_anxiety_before ~ INT8_PSI1*1


#Latent factor: PSI2
  PSI2 =~ L1_PSI2*psi_nervousness_after +
          L2_PSI2*psi_worrying_after +
          L3_PSI2*psi_depressed_mood_after +
          L4_PSI2*psi_hopelesness_after +
          L5_PSI2*psi_tension_after +
          L6_PSI2*phy_lack_of_energy_after +
          L7_PSI2*psi_irritability_after +
          L8_PSI2*psi_anxiety_after

  # Constrain the variance of PSI2 to 1 (fixed)
  PSI2 ~~ 1*PSI2

  # Define unique variances for observed variables (with "after" variables)
  psi_nervousness_after ~~ E1_PSI2*psi_nervousness_after
  psi_worrying_after ~~ E2_PSI2*psi_worrying_after
  psi_depressed_mood_after ~~ E3_PSI2*psi_depressed_mood_after
  psi_hopelesness_after ~~ E4_PSI2*psi_hopelesness_after
  psi_tension_after ~~ E5_PSI2*psi_tension_after
  psi_irritability_after ~~ E7_PSI2*psi_irritability_after
  psi_anxiety_after ~~ E8_PSI2*psi_anxiety_after

  # Set latent factor mean to 0 (fixed)
  PSI2 ~ 0*1
```

```
  # Define intercepts for observed variables (with "after" variables)
  psi_nervousness_after ~ INT1_PSI2*1
  psi_worrying_after ~ INT2_PSI2*1
  psi_depressed_mood_after ~ INT3_PSI2*1
  psi_hopelesness_after ~ INT4_PSI2*1
  psi_tension_after ~ INT5_PSI2*1
  psi_irritability_after ~ INT7_PSI2*1
  psi_anxiety_after ~ INT8_PSI2*1

#Latent factor: PHY1
  PHY1 =~ L1_PHY1*phy_lack_of_appetite_before +
          L2_PHY1*phy_tiredness_before +
          L3_PHY1*phy_sore_muscles_before +
          L4_PHY1*phy_lack_of_energy_before +
          L5_PHY1*phy_back_pain_before +
          L6_PHY1*phy_nausea_before +
          L7_PHY1*phy_difficulty_sleeping_before +
          L8_PHY1*phy_headaches_before +
          L9_PHY1*phy_vomiting_before +
          L10_PHY1*phy_dizziness_before +
          L11_PHY1*phy_swallowing_pain_before +
          L12_PHY1*phy_decreased_sex_interest_before +
          L13_PHY1*phy_acid_indigestion_before +
          L14_PHY1*phy_shivering_before +
          L15_PHY1*phy_tingling_before +
          L16_PHY1*phy_abdominal_pain_before +
          L17_PHY1*phy_hair_loss_before +
          L18_PHY1*phy_sore_eyes_before +
          L19_PHY1*phy_difficulty_concentrating_before +
          L20_PHY1*phy_short_breath_before +
          L21_PHY1*phy_dry_mouth_before +
          L22_PHY1*phy_diaorrhea_before +
          L23_PHY1*phy_constipation_before

  # Constrain the variance of PHY1 to 1
```

```
PHY1 ~~ 1*PHY1

# Defining unique variable variances for "before" variables
phy_lack_of_appetite_before ~~ E1_PHY1*phy_lack_of_appetite_before
phy_tiredness_before ~~ E2_PHY1*phy_tiredness_before
phy_sore_muscles_before ~~ E3_PHY1*phy_sore_muscles_before
phy_lack_of_energy_before ~~ E4_PHY1*phy_lack_of_energy_before
phy_back_pain_before ~~ E5_PHY1*phy_back_pain_before
phy_nausea_before ~~ E6_PHY1*phy_nausea_before
phy_difficulty_sleeping_before ~~ E7_PHY1*phy_difficulty_sleeping_before
phy_headaches_before ~~ E8_PHY1*phy_headaches_before
phy_vomiting_before ~~ E9_PHY1*phy_vomiting_before
phy_dizziness_before ~~ E10_PHY1*phy_dizziness_before
phy_swallowing_pain_before ~~ E11_PHY1*phy_swallowing_pain_before
phy_decreased_sex_interest_before ~~
    E12_PHY1*phy_decreased_sex_interest_before
phy_acid_indigestion_before ~~ E13_PHY1*phy_acid_indigestion_before
phy_shivering_before ~~ E14_PHY1*phy_shivering_before
phy_tingling_before ~~ E15_PHY1*phy_tingling_before
phy_abdominal_pain_before ~~ E16_PHY1*phy_abdominal_pain_before
phy_hair_loss_before ~~ E17_PHY1*phy_hair_loss_before
phy_sore_eyes_before ~~ E18_PHY1*phy_sore_eyes_before
phy_difficulty_concentrating_before ~~
    E19_PHY1*phy_difficulty_concentrating_before
phy_short_breath_before ~~ E20_PHY1*phy_short_breath_before
phy_dry_mouth_before ~~ E21_PHY1*phy_dry_mouth_before
phy_diaorrhea_before ~~ E22_PHY1*phy_diaorrhea_before
phy_constipation_before ~~ E23_PHY1*phy_constipation_before



# Setting latent factor mean to 0
PHY1 ~ 0*1

# Define intercepts for "before" variables (with unique names)
phy_lack_of_appetite_before ~ INT1_PHY1*1
phy_tiredness_before ~ INT2_PHY1*1
phy_sore_muscles_before ~ INT3_PHY1*1
```

```
  phy_lack_of_energy_before ~ INT4_PHY1*1
  phy_back_pain_before ~ INT5_PHY1*1
  phy_nausea_before ~ INT6_PHY1*1
  phy_difficulty_sleeping_before ~ INT7_PHY1*1
  phy_headaches_before ~ INT8_PHY1*1
  phy_vomiting_before ~ INT9_PHY1*1
  phy_dizziness_before ~ INT10_PHY1*1
  phy_swallowing_pain_before ~ INT11_PHY1*1
  phy_decreased_sex_interest_before ~ INT12_PHY1*1
  phy_acid_indigestion_before ~ INT13_PHY1*1
  phy_shivering_before ~ INT14_PHY1*1
  phy_tingling_before ~ INT15_PHY1*1
  phy_abdominal_pain_before ~ INT16_PHY1*1
  phy_hair_loss_before ~ INT17_PHY1*1
  phy_sore_eyes_before ~ INT18_PHY1*1
  phy_difficulty_concentrating_before ~ INT19_PHY1*1
  phy_short_breath_before ~ INT20_PHY1*1
  phy_dry_mouth_before ~ INT21_PHY1*1
  phy_diaorrhea_before ~ INT22_PHY1*1
  phy_constipation_before ~ INT23_PHY1*1

#Latent factor: PHY2
  PHY2 =~ L1_PHY2*phy_lack_of_appetite_after +
    L2_PHY2*phy_tiredness_after +
    L3_PHY2*phy_sore_muscles_after +
    L4_PHY2*phy_lack_of_energy_after +
    L5_PHY2*phy_back_pain_after +
    L6_PHY2*phy_nausea_after +
    L7_PHY2*phy_difficulty_sleeping_after +
    L8_PHY2*phy_headaches_after +
    L9_PHY2*phy_vomiting_after +
    L10_PHY2*phy_dizziness_after +
    L11_PHY2*phy_swallowing_pain_after +
    L12_PHY2*phy_decreased_sex_interest_after +
    L13_PHY2*phy_acid_indigestion_after +
    L14_PHY2*phy_shivering_after +
```

```
  L15_PHY2*phy_tingling_after +
  L16_PHY2*phy_abdominal_pain_after +
  L17_PHY2*phy_hair_loss_after +
  L18_PHY2*phy_sore_eyes_after +
  L19_PHY2*phy_difficulty_concentrating_after +
  L20_PHY2*phy_short_breath_after +
  L21_PHY2*phy_dry_mouth_after +
  L22_PHY2*phy_diaorrhea_after +
  L23_PHY2*phy_constipation_after

# Constrain the variance of PHY2 to 1
PHY2 ~~ 1*PHY2

# Defining unique variable variances for "after" variables
phy_lack_of_appetite_after ~~ E1_PHY2*phy_lack_of_appetite_after
phy_tiredness_after ~~ E2_PHY2*phy_tiredness_after
phy_sore_muscles_after ~~ E3_PHY2*phy_sore_muscles_after
phy_lack_of_energy_after ~~ E4_PHY2*phy_lack_of_energy_after
phy_back_pain_after ~~ E5_PHY2*phy_back_pain_after
phy_nausea_after ~~ E6_PHY2*phy_nausea_after
phy_difficulty_sleeping_after ~~ E7_PHY2*phy_difficulty_sleeping_after
phy_headaches_after ~~ E8_PHY2*phy_headaches_after
phy_vomiting_after ~~ E9_PHY2*phy_vomiting_after  # Added missing E9
phy_dizziness_after ~~ E10_PHY2*phy_dizziness_after
phy_swallowing_pain_after ~~ E11_PHY2*phy_swallowing_pain_after
phy_decreased_sex_interest_after ~~
    E12_PHY2*phy_decreased_sex_interest_after
phy_acid_indigestion_after ~~ E13_PHY2*phy_acid_indigestion_after
phy_shivering_after ~~ E14_PHY2*phy_shivering_after  # Added missing E14
phy_tingling_after ~~ E15_PHY2*phy_tingling_after
phy_abdominal_pain_after ~~ E16_PHY2*phy_abdominal_pain_after
phy_hair_loss_after ~~ E17_PHY2*phy_hair_loss_after
phy_sore_eyes_after ~~ E18_PHY2*phy_sore_eyes_after  # Adjusted name for
    this variable
phy_difficulty_concentrating_after ~~
    E19_PHY2*phy_difficulty_concentrating_after
phy_short_breath_after ~~ E20_PHY2*phy_short_breath_after
```

```
phy_dry_mouth_after ~~ E21_PHY2*phy_dry_mouth_after
phy_diaorrhea_after ~~ E22_PHY2*phy_diaorrhea_after  # Adjusted name for
    this variable
phy_constipation_after ~~ E23_PHY2*phy_constipation_after


# Setting latent factor mean to 0
PHY2 ~ 0*1


# Define intercepts for "after" variables (with unique names)
phy_lack_of_appetite_after ~ INT1_PHY2*1
phy_tiredness_after ~ INT2_PHY2*1
phy_sore_muscles_after ~ INT3_PHY2*1
phy_lack_of_energy_after ~ INT4_PHY2*1
phy_back_pain_after ~ INT5_PHY2*1
phy_nausea_after ~ INT6_PHY2*1
phy_difficulty_sleeping_after ~ INT7_PHY2*1
phy_headaches_after ~ INT8_PHY2*1
phy_vomiting_after ~ INT9_PHY2*1  # Added missing intercept for E9
phy_dizziness_after ~ INT10_PHY2*1
phy_swallowing_pain_after ~ INT11_PHY2*1
phy_decreased_sex_interest_after ~ INT12_PHY2*1
phy_acid_indigestion_after ~ INT13_PHY2*1
phy_shivering_after ~ INT14_PHY2*1  # Added missing intercept for E14
phy_tingling_after ~ INT15_PHY2*1
phy_abdominal_pain_after ~ INT16_PHY2*1
phy_hair_loss_after ~ INT17_PHY2*1
phy_sore_eyes_after ~ INT18_PHY2*1  # Adjusted name for this variable
phy_difficulty_concentrating_after ~ INT19_PHY2*1
phy_short_breath_after ~ INT20_PHY2*1
phy_dry_mouth_after ~ INT21_PHY2*1
phy_diaorrhea_after ~ INT22_PHY2*1  # Adjusted name for this variable
phy_constipation_after ~ INT23_PHY2*1
```

```
#defining relationships between latent variables
PHY2 ~~ PHY1
PSI2 ~~ PSI1
PSI2 ~~ PHY1
PHY2 ~~ PSI1
PSI1 ~~ PHY1
PSI2 ~~ PHY2


# defining residual correlations

            psi_nervousness_before ~~             psi_nervousness_after
               psi_worrying_before ~~                psi_worrying_after
         psi_depressed_mood_before ~~          psi_depressed_mood_after
            psi_hopelesness_before ~~             psi_hopelesness_after
                psi_tension_before ~~                 psi_tension_after
           psi_irritability_before ~~            psi_irritability_after
                psi_anxiety_before ~~                 psi_anxiety_after


       phy_lack_of_appetite_before ~~
   phy_lack_of_appetite_after
           phy_tiredness_before ~~
   phy_tiredness_after
        phy_sore_muscles_before ~~
   phy_sore_muscles_after
      phy_lack_of_energy_before ~~
   phy_lack_of_energy_after
          phy_back_pain_before ~~
   phy_back_pain_after
             phy_nausea_before ~~
   phy_nausea_after
    phy_difficulty_sleeping_before ~~
   phy_difficulty_sleeping_after
          phy_headaches_before ~~
   phy_headaches_after
           phy_vomiting_before ~~
   phy_vomiting_after
          phy_dizziness_before ~~
   phy_dizziness_after
     phy_swallowing_pain_before ~~
   phy_swallowing_pain_after
```

```
    phy_decreased_sex_interest_before ~~
      phy_decreased_sex_interest_after

          phy_acid_indigestion_before ~~
      phy_acid_indigestion_after

                 phy_shivering_before ~~
      phy_shivering_after

                  phy_tingling_before ~~
      phy_tingling_after

            phy_abdominal_pain_before ~~
      phy_abdominal_pain_after

                 phy_hair_loss_before ~~
      phy_hair_loss_after

                 phy_sore_eyes_before ~~
      phy_sore_eyes_after

  phy_difficulty_concentrating_before ~~
      phy_difficulty_concentrating_after

             phy_short_breath_before ~~
      phy_short_breath_after

                 phy_dry_mouth_before ~~
      phy_dry_mouth_after

                 phy_diaorrhea_before ~~
      phy_diaorrhea_after

             phy_constipation_before ~~
      phy_constipation_after


                    phy_nausea_after ~~ phy_vomiting_after
                   phy_nausea_before ~~  phy_vomiting_before


')



SEM_OUT_1_new <- sem(SEM_MODEL_1_new,
                 sample.cov = cov(metabone_ri_cleaned),
                 sample.mean = colMeans(metabone_ri_cleaned),
                 sample.nobs = nrow(metabone_ri_cleaned),
                 std.lv = TRUE)

#modindices(SEM_OUT_1_new, sort. = TRUE, maximum.number = 200)



summary(SEM_OUT_1_new, fit.measures = TRUE, standardized = TRUE)
```

Appendix B

Second Step of the Analysis

```
SEM_MODEL_2_new <- paste0('

#Latent factor: PSI1
  PSI1 =~ L1_PSI1*psi_nervousness_before +
    L2_PSI1*psi_worrying_before +
    L3_PSI1*psi_depressed_mood_before +
    L4_PSI1*psi_hopelesness_before +
    L5_PSI1*psi_tension_before +
    L6_PSI1*phy_lack_of_energy_before +
    L7_PSI1*psi_irritability_before +
    L8_PSI1*psi_anxiety_before

  # Constrain the variance of PSI1 to 1 (fixed)
  PSI1 ~~ 1*PSI1

  # Define unique variances for observed variables
  psi_nervousness_before ~~ E1_PSI1*psi_nervousness_before
  psi_worrying_before ~~ E2_PSI1*psi_worrying_before
  psi_depressed_mood_before ~~ E3_PSI1*psi_depressed_mood_before
  psi_hopelesness_before ~~ E4_PSI1*psi_hopelesness_before
  psi_tension_before ~~ E5_PSI1*psi_tension_before
  psi_irritability_before ~~ E7_PSI1*psi_irritability_before
  psi_anxiety_before ~~ E8_PSI1*psi_anxiety_before

  # Set latent factor mean to 0 (fixed)
  PSI1 ~ 0*1

  # Define intercepts for observed variables
  psi_nervousness_before ~ INT1_PSI1*1
  psi_worrying_before ~ INT2_PSI1*1
  psi_depressed_mood_before ~ INT3_PSI1*1
```

```
  psi_hopelesness_before ~ INT4_PSI1*1
  psi_tension_before ~ INT5_PSI1*1
  psi_irritability_before ~ INT7_PSI1*1
  psi_anxiety_before ~ INT8_PSI1*1


#Latent factor: PSI2
  PSI2 =~ L1_PSI1*psi_nervousness_after +
          L2_PSI1*psi_worrying_after +
          L3_PSI1*psi_depressed_mood_after +
          L4_PSI1*psi_hopelesness_after +
          L5_PSI1*psi_tension_after +
          L6_PSI1*phy_lack_of_energy_after +
          L7_PSI1*psi_irritability_after +
          L8_PSI1*psi_anxiety_after

  PSI2 ~~ PSI2

  psi_nervousness_after ~~ E1_PSI1*psi_nervousness_after
  psi_worrying_after ~~ E2_PSI1*psi_worrying_after
  psi_depressed_mood_after ~~ E3_PSI1*psi_depressed_mood_after
  psi_hopelesness_after ~~ E4_PSI1*psi_hopelesness_after
  psi_tension_after ~~ E5_PSI1*psi_tension_after
  psi_irritability_after ~~ E7_PSI1*psi_irritability_after
  psi_anxiety_after ~~ E8_PSI1*psi_anxiety_after

  PSI2 ~ m_psi*1

  psi_nervousness_after ~ INT1_PSI1*1
  psi_worrying_after ~ INT2_PSI1*1
  psi_depressed_mood_after ~ INT3_PSI1*1
  psi_hopelesness_after ~ INT4_PSI1*1
  psi_tension_after ~ INT5_PSI1*1
  psi_irritability_after ~ INT7_PSI1*1
  psi_anxiety_after ~ INT8_PSI1*1
```

```
#Latent factor: PHY1
  PHY1 =~ L1_PHY1*phy_lack_of_appetite_before +
          L2_PHY1*phy_tiredness_before +
          L3_PHY1*phy_sore_muscles_before +
          L4_PHY1*phy_lack_of_energy_before +
          L5_PHY1*phy_back_pain_before +
          L6_PHY1*phy_nausea_before +
          L7_PHY1*phy_difficulty_sleeping_before +
          L8_PHY1*phy_headaches_before +
          L9_PHY1*phy_vomiting_before +
          L10_PHY1*phy_dizziness_before +
          L11_PHY1*phy_swallowing_pain_before +
          L12_PHY1*phy_decreased_sex_interest_before +
          L13_PHY1*phy_acid_indigestion_before +
          L14_PHY1*phy_shivering_before +
          L15_PHY1*phy_tingling_before +
          L16_PHY1*phy_abdominal_pain_before +
          L17_PHY1*phy_hair_loss_before +
          L18_PHY1*phy_sore_eyes_before +
          L19_PHY1*phy_difficulty_concentrating_before +
          L20_PHY1*phy_short_breath_before +
          L21_PHY1*phy_dry_mouth_before +
          L22_PHY1*phy_diaorrhea_before +
          L23_PHY1*phy_constipation_before

  PHY1 ~~ 1*PHY1

  phy_lack_of_appetite_before ~~ E1_PHY1*phy_lack_of_appetite_before
  phy_tiredness_before ~~ E2_PHY1*phy_tiredness_before
  phy_sore_muscles_before ~~ E3_PHY1*phy_sore_muscles_before
  phy_lack_of_energy_before ~~ E4_PHY1*phy_lack_of_energy_before
  phy_back_pain_before ~~ E5_PHY1*phy_back_pain_before
  phy_nausea_before ~~ E6_PHY1*phy_nausea_before
  phy_difficulty_sleeping_before ~~ E7_PHY1*phy_difficulty_sleeping_before
  phy_headaches_before ~~ E8_PHY1*phy_headaches_before
  phy_vomiting_before ~~ E9_PHY1*phy_vomiting_before
```

```
  phy_dizziness_before ~~ E10_PHY1*phy_dizziness_before

  phy_swallowing_pain_before ~~ E11_PHY1*phy_swallowing_pain_before

  phy_decreased_sex_interest_before ~~
E12_PHY1*phy_decreased_sex_interest_before

  phy_acid_indigestion_before ~~ E13_PHY1*phy_acid_indigestion_before

  phy_shivering_before ~~ E14_PHY1*phy_shivering_before

  phy_tingling_before ~~ E15_PHY1*phy_tingling_before

  phy_abdominal_pain_before ~~ E16_PHY1*phy_abdominal_pain_before

  phy_hair_loss_before ~~ E17_PHY1*phy_hair_loss_before

  phy_sore_eyes_before ~~ E18_PHY1*phy_sore_eyes_before

  phy_difficulty_concentrating_before ~~
E19_PHY1*phy_difficulty_concentrating_before

  phy_short_breath_before ~~ E20_PHY1*phy_short_breath_before

  phy_dry_mouth_before ~~ E21_PHY1*phy_dry_mouth_before

  phy_diaorrhea_before ~~ E22_PHY1*phy_diaorrhea_before

  phy_constipation_before ~~ E23_PHY1*phy_constipation_before



  PHY1 ~ 0*1


  phy_lack_of_appetite_before ~ INT1_PHY1*1

  phy_tiredness_before ~ INT2_PHY1*1

  phy_sore_muscles_before ~ INT3_PHY1*1

  phy_lack_of_energy_before ~ INT4_PHY1*1

  phy_back_pain_before ~ INT5_PHY1*1

  phy_nausea_before ~ INT6_PHY1*1

  phy_difficulty_sleeping_before ~ INT7_PHY1*1

  phy_headaches_before ~ INT8_PHY1*1

  phy_vomiting_before ~ INT9_PHY1*1

  phy_dizziness_before ~ INT10_PHY1*1

  phy_swallowing_pain_before ~ INT11_PHY1*1

  phy_decreased_sex_interest_before ~ INT12_PHY1*1

  phy_acid_indigestion_before ~ INT13_PHY1*1

  phy_shivering_before ~ INT14_PHY1*1

  phy_tingling_before ~ INT15_PHY1*1

  phy_abdominal_pain_before ~ INT16_PHY1*1

  phy_hair_loss_before ~ INT17_PHY1*1
```

```
  phy_sore_eyes_before ~ INT18_PHY1*1
  phy_difficulty_concentrating_before ~ INT19_PHY1*1
  phy_short_breath_before ~ INT20_PHY1*1
  phy_dry_mouth_before ~ INT21_PHY1*1
  phy_diaorrhea_before ~ INT22_PHY1*1
  phy_constipation_before ~ INT23_PHY1*1

#Latent factor: PHY2
  PHY2 =~ L1_PHY1*phy_lack_of_appetite_after +
    L2_PHY1*phy_tiredness_after +
    L3_PHY1*phy_sore_muscles_after +
    L4_PHY1*phy_lack_of_energy_after +
    L5_PHY1*phy_back_pain_after +
    L6_PHY1*phy_nausea_after +
    L7_PHY1*phy_difficulty_sleeping_after +
    L8_PHY1*phy_headaches_after +
    L9_PHY1*phy_vomiting_after +
    L10_PHY1*phy_dizziness_after +
    L11_PHY1*phy_swallowing_pain_after +
    L12_PHY1*phy_decreased_sex_interest_after +
    L13_PHY1*phy_acid_indigestion_after +
    L14_PHY1*phy_shivering_after +
    L15_PHY1*phy_tingling_after +
    L16_PHY1*phy_abdominal_pain_after +
    L17_PHY1*phy_hair_loss_after +
    L18_PHY1*phy_sore_eyes_after +
    L19_PHY1*phy_difficulty_concentrating_after +
    L20_PHY1*phy_short_breath_after +
    L21_PHY1*phy_dry_mouth_after +
    L22_PHY1*phy_diaorrhea_after +
    L23_PHY1*phy_constipation_after

  PHY2 ~~ PHY2

  phy_lack_of_appetite_after ~~ E1_PHY1*phy_lack_of_appetite_after
  phy_tiredness_after ~~ E2_PHY1*phy_tiredness_after
```

```
  phy_sore_muscles_after ~~ E3_PHY1*phy_sore_muscles_after

  phy_lack_of_energy_after ~~ E4_PHY1*phy_lack_of_energy_after

  phy_back_pain_after ~~ E5_PHY1*phy_back_pain_after

  phy_nausea_after ~~ E6_PHY1*phy_nausea_after

  phy_difficulty_sleeping_after ~~ E7_PHY1*phy_difficulty_sleeping_after

  phy_headaches_after ~~ E8_PHY1*phy_headaches_after

  phy_vomiting_after ~~ E9_PHY1*phy_vomiting_after

  phy_dizziness_after ~~ E10_PHY1*phy_dizziness_after

  phy_swallowing_pain_after ~~ E11_PHY1*phy_swallowing_pain_after

  phy_decreased_sex_interest_after ~~
E12_PHY1*phy_decreased_sex_interest_after

  phy_acid_indigestion_after ~~ E13_PHY1*phy_acid_indigestion_after

  phy_shivering_after ~~ E14_PHY1*phy_shivering_after

  phy_tingling_after ~~ E15_PHY1*phy_tingling_after

  phy_abdominal_pain_after ~~ E16_PHY1*phy_abdominal_pain_after

  phy_hair_loss_after ~~ E17_PHY1*phy_hair_loss_after

  phy_sore_eyes_after ~~ E18_PHY1*phy_sore_eyes_after

  phy_difficulty_concentrating_after ~~
E19_PHY1*phy_difficulty_concentrating_after

  phy_short_breath_after ~~ E20_PHY1*phy_short_breath_after

  phy_dry_mouth_after ~~ E21_PHY1*phy_dry_mouth_after

  phy_diaorrhea_after ~~ E22_PHY1*phy_diaorrhea_after

  phy_constipation_after ~~ E23_PHY1*phy_constipation_after


  PHY2 ~ m_phy*1


  phy_lack_of_appetite_after ~ INT1_PHY1*1

  phy_tiredness_after ~ INT2_PHY1*1

  phy_sore_muscles_after ~ INT3_PHY1*1

  phy_lack_of_energy_after ~ INT4_PHY1*1

  phy_back_pain_after ~ INT5_PHY1*1

  phy_nausea_after ~ INT6_PHY1*1

  phy_difficulty_sleeping_after ~ INT7_PHY1*1

  phy_headaches_after ~ INT8_PHY1*1

  phy_vomiting_after ~ INT9_PHY1*1

  phy_dizziness_after ~ INT10_PHY1*1

  phy_swallowing_pain_after ~ INT11_PHY1*1
```

```
  phy_decreased_sex_interest_after ~ INT12_PHY1*1
  phy_acid_indigestion_after ~ INT13_PHY1*1
  phy_shivering_after ~ INT14_PHY1*1
  phy_tingling_after ~ INT15_PHY1*1
  phy_abdominal_pain_after ~ INT16_PHY1*1
  phy_hair_loss_after ~ INT17_PHY1*1
  phy_sore_eyes_after ~ INT18_PHY1*1
  phy_difficulty_concentrating_after ~ INT19_PHY1*1
  phy_short_breath_after ~ INT20_PHY1*1
  phy_dry_mouth_after ~ INT21_PHY1*1
  phy_diaorrhea_after ~ INT22_PHY1*1
  phy_constipation_after ~ INT23_PHY1*1

# Latent factor correlations
  PHY1 ~~ PHY2
  PSI1 ~~ PSI2
  PSI2 ~~ PHY1
  PHY2 ~~ PSI1
  PSI1 ~~ PHY1
  PSI2 ~~ PHY2

# defining residual correlations

               psi_nervousness_before ~~             psi_nervousness_after
                  psi_worrying_before ~~                psi_worrying_after
            psi_depressed_mood_before ~~          psi_depressed_mood_after
               psi_hopelesness_before ~~             psi_hopelesness_after
                   psi_tension_before ~~                 psi_tension_after
              psi_irritability_before ~~            psi_irritability_after
                   psi_anxiety_before ~~                 psi_anxiety_after


          phy_lack_of_appetite_before ~~
phy_lack_of_appetite_after
                 phy_tiredness_before ~~
phy_tiredness_after
              phy_sore_muscles_before ~~
phy_sore_muscles_after
```

```
            phy_lack_of_energy_before ~~
phy_lack_of_energy_after

                 phy_back_pain_before ~~
phy_back_pain_after

                    phy_nausea_before ~~
phy_nausea_after

       phy_difficulty_sleeping_before ~~
phy_difficulty_sleeping_after

                 phy_headaches_before ~~
phy_headaches_after

                  phy_vomiting_before ~~
phy_vomiting_after

                 phy_dizziness_before ~~
phy_dizziness_after

           phy_swallowing_pain_before ~~
phy_swallowing_pain_after

    phy_decreased_sex_interest_before ~~
phy_decreased_sex_interest_after

          phy_acid_indigestion_before ~~
phy_acid_indigestion_after

                 phy_shivering_before ~~
phy_shivering_after

                  phy_tingling_before ~~
phy_tingling_after

             phy_abdominal_pain_before ~~
phy_abdominal_pain_after

                 phy_hair_loss_before ~~
phy_hair_loss_after

                 phy_sore_eyes_before ~~
phy_sore_eyes_after

  phy_difficulty_concentrating_before ~~
phy_difficulty_concentrating_after

               phy_short_breath_before ~~
phy_short_breath_after

                 phy_dry_mouth_before ~~
phy_dry_mouth_after

                 phy_diaorrhea_before ~~
phy_diaorrhea_after

              phy_constipation_before ~~
phy_constipation_after


                    phy_nausea_after ~~ phy_vomiting_after

                   phy_nausea_before ~~  phy_vomiting_before

')
```

```
SEM_OUT_2_new <- sem(SEM_MODEL_2_new,
                     sample.cov = cov(metabone_ri_cleaned),
                     sample.mean = colMeans(metabone_ri_cleaned),
                     sample.nobs = nrow(metabone_ri_cleaned),
                     std.lv = TRUE)

#modindices(SEM_OUT_1_new, sort. = TRUE, maximum.number = 200)


summary(SEM_OUT_2_new, fit.measures = TRUE, standardized = TRUE)

anova(SEM_OUT_1_new, SEM_OUT_2_new)
```

Appendix C

Third Step of the Analysis

```
iterative_response_shift_detector <- function(first_line, last_line,
switched_from, switched_to, restricted_model = SEM_MODEL_2_new,
restricted_output = SEM_OUT_2_new, dataset = metabone_ri_cleaned) {


  model_lines <- strsplit(restricted_model, '\n')[[1]]

  key_parameters <- character(0)

  old_model_out <- restricted_output


  for (j in first_line:last_line) {


    cat('\n' ,"Iteration", j, '\n')


    results <- numeric(0)


    for (i in first_line:last_line) {


      target_index <- i

      model_lines[target_index] <- gsub(switched_from, '_test',
model_lines[target_index])

      model_test <- paste(model_lines, collapse = '\n')

      model_test_out <- sem(model_test,

                            sample.cov = cov(dataset),

                            sample.mean = colMeans(dataset),

                            sample.nobs = nrow(dataset),

                            std.lv = TRUE)


      anova_results <- anova(old_model_out, model_test_out)

      model_lines[target_index] <- gsub('_test', switched_from,
model_lines[target_index])

      p_value <- anova_results[2, "Pr(>Chisq)"]

      cat("  Tried index:", i, "| p-value =", p_value, "\n")

      results <- c(results, setNames(p_value, target_index))


    }
```

```
    results[is.na(results)] <- 1


    if(min(results) < 0.05){
      key_index <- as.numeric(names(results)[which.min(results)])
      key_parameter <- gsub(switched_from, switched_to,
model_lines[key_index])
      key_parameters <- c(key_parameters, key_parameter)
      model_lines[key_index] <- key_parameter
      updated_model <- paste(model_lines, collapse = '\n')
      old_model_out <- sem(updated_model,
                           sample.cov = cov(dataset),
                           sample.mean = colMeans(dataset),
                           sample.nobs = nrow(dataset),
                           std.lv = TRUE)


    }else{
      return(key_parameters)
    }
  }
}


#iterative_response_shift_detector()
```

Appendix D

Fourth Step of the Analysis

```
SEM_MODEL_4_new <- paste0('

#Latent factor: PSI1


  PSI1 =~ L1_PSI1*psi_nervousness_before +
    L2_PSI1*psi_worrying_before +
    L3_PSI1*psi_depressed_mood_before +
    L4_PSI1*psi_hopelesness_before +
    L5_PSI1*psi_tension_before +
    L6_PSI1*phy_lack_of_energy_before +
    L7_PSI1*psi_irritability_before +
    L8_PSI1*psi_anxiety_before


  # Constrain the variance of PSI1 to 1 (fixed)
  PSI1 ~~ 1*PSI1

  # Define unique variances for observed variables
  psi_nervousness_before ~~ E1_PSI1*psi_nervousness_before
  psi_worrying_before ~~ E2_PSI1*psi_worrying_before
  psi_depressed_mood_before ~~ E3_PSI1*psi_depressed_mood_before
  psi_hopelesness_before ~~ E4_PSI1*psi_hopelesness_before
  psi_tension_before ~~ E5_PSI1*psi_tension_before
  psi_irritability_before ~~ E7_PSI1*psi_irritability_before
  psi_anxiety_before ~~ E8_PSI1*psi_anxiety_before

  # Set latent factor mean to 0 (fixed)
  PSI1 ~ 0*1

  # Define intercepts for observed variables
  psi_nervousness_before ~ INT1_PSI1*1
  psi_worrying_before ~ INT2_PSI1*1
```

```
  psi_depressed_mood_before ~ INT3_PSI1*1
  psi_hopelesness_before ~ INT4_PSI1*1
  psi_tension_before ~ INT5_PSI1*1
  psi_irritability_before ~ INT7_PSI1*1
  psi_anxiety_before ~ INT8_PSI1*1


#Latent factor: PSI2
  PSI2 =~ L1_PSI1*psi_nervousness_after +
          L2_PSI1*psi_worrying_after +
          L3_PSI1*psi_depressed_mood_after +
          L4_PSI1*psi_hopelesness_after +
          L5_PSI1*psi_tension_after +
          L6_PSI2*phy_lack_of_energy_after +
          L7_PSI2*psi_irritability_after +
          L8_PSI2*psi_anxiety_after

  PSI2 ~~ var_psi2*PSI2



  psi_nervousness_after ~~ E1_PSI1*psi_nervousness_after
  psi_worrying_after ~~ E2_PSI1*psi_worrying_after
  psi_depressed_mood_after ~~ E3_PSI1*psi_depressed_mood_after
  psi_hopelesness_after ~~ E4_PSI1*psi_hopelesness_after
  psi_tension_after ~~ E5_PSI2*psi_tension_after
  psi_irritability_after ~~ E7_PSI1*psi_irritability_after
  psi_anxiety_after ~~ E8_PSI2*psi_anxiety_after

  PSI2 ~ m_psi*1

  psi_nervousness_after ~ INT1_PSI2*1
  psi_worrying_after ~ INT2_PSI2*1
  psi_depressed_mood_after ~ INT3_PSI2*1
  psi_hopelesness_after ~ INT4_PSI2*1
  psi_tension_after ~ INT5_PSI1*1
```

```
  psi_irritability_after ~ INT7_PSI1*1
  psi_anxiety_after ~ INT8_PSI2*1

#Latent factor: PHY1
  PHY1 =~ L1_PHY1*phy_lack_of_appetite_before +
          L2_PHY1*phy_tiredness_before +
          L3_PHY1*phy_sore_muscles_before +
          L4_PHY1*phy_lack_of_energy_before +
          L5_PHY1*phy_back_pain_before +
          L6_PHY1*phy_nausea_before +
          L7_PHY1*phy_difficulty_sleeping_before +
          L8_PHY1*phy_headaches_before +
          L9_PHY1*phy_vomiting_before +
          L10_PHY1*phy_dizziness_before +
          L11_PHY1*phy_swallowing_pain_before +
          L12_PHY1*phy_decreased_sex_interest_before +
          L13_PHY1*phy_acid_indigestion_before +
          L14_PHY1*phy_shivering_before +
          L15_PHY1*phy_tingling_before +
          L16_PHY1*phy_abdominal_pain_before +
          L17_PHY1*phy_hair_loss_before +
          L18_PHY1*phy_sore_eyes_before +
          L19_PHY1*phy_difficulty_concentrating_before +
          L20_PHY1*phy_short_breath_before +
          L21_PHY1*phy_dry_mouth_before +
          L22_PHY1*phy_diaorrhea_before +
          L23_PHY1*phy_constipation_before

  PHY1 ~~ 1*PHY1

  phy_lack_of_appetite_before ~~ E1_PHY1*phy_lack_of_appetite_before
  phy_tiredness_before ~~ E2_PHY1*phy_tiredness_before
  phy_sore_muscles_before ~~ E3_PHY1*phy_sore_muscles_before
  phy_lack_of_energy_before ~~ E4_PHY1*phy_lack_of_energy_before
  phy_back_pain_before ~~ E5_PHY1*phy_back_pain_before
  phy_nausea_before ~~ E6_PHY1*phy_nausea_before
```

```
  phy_difficulty_sleeping_before ~~ E7_PHY1*phy_difficulty_sleeping_before
  phy_headaches_before ~~ E8_PHY1*phy_headaches_before
  phy_vomiting_before ~~ E9_PHY1*phy_vomiting_before
  phy_dizziness_before ~~ E10_PHY1*phy_dizziness_before
  phy_swallowing_pain_before ~~ E11_PHY1*phy_swallowing_pain_before
  phy_decreased_sex_interest_before ~~
E12_PHY1*phy_decreased_sex_interest_before
  phy_acid_indigestion_before ~~ E13_PHY1*phy_acid_indigestion_before
  phy_shivering_before ~~ E14_PHY1*phy_shivering_before
  phy_tingling_before ~~ E15_PHY1*phy_tingling_before
  phy_abdominal_pain_before ~~ E16_PHY1*phy_abdominal_pain_before
  phy_hair_loss_before ~~ E17_PHY1*phy_hair_loss_before
  phy_sore_eyes_before ~~ E18_PHY1*phy_sore_eyes_before
  phy_difficulty_concentrating_before ~~
E19_PHY1*phy_difficulty_concentrating_before
  phy_short_breath_before ~~ E20_PHY1*phy_short_breath_before
  phy_dry_mouth_before ~~ E21_PHY1*phy_dry_mouth_before
  phy_diaorrhea_before ~~ E22_PHY1*phy_diaorrhea_before
  phy_constipation_before ~~ E23_PHY1*phy_constipation_before



  PHY1 ~ 0*1


  phy_lack_of_appetite_before ~ INT1_PHY1*1
  phy_tiredness_before ~ INT2_PHY1*1
  phy_sore_muscles_before ~ INT3_PHY1*1
  phy_lack_of_energy_before ~ INT4_PHY1*1
  phy_back_pain_before ~ INT5_PHY1*1
  phy_nausea_before ~ INT6_PHY1*1
  phy_difficulty_sleeping_before ~ INT7_PHY1*1
  phy_headaches_before ~ INT8_PHY1*1
  phy_vomiting_before ~ INT9_PHY1*1
  phy_dizziness_before ~ INT10_PHY1*1
  phy_swallowing_pain_before ~ INT11_PHY1*1
  phy_decreased_sex_interest_before ~ INT12_PHY1*1
  phy_acid_indigestion_before ~ INT13_PHY1*1
  phy_shivering_before ~ INT14_PHY1*1
```

```
  phy_tingling_before ~ INT15_PHY1*1
  phy_abdominal_pain_before ~ INT16_PHY1*1
  phy_hair_loss_before ~ INT17_PHY1*1
  phy_sore_eyes_before ~ INT18_PHY1*1
  phy_difficulty_concentrating_before ~ INT19_PHY1*1
  phy_short_breath_before ~ INT20_PHY1*1
  phy_dry_mouth_before ~ INT21_PHY1*1
  phy_diaorrhea_before ~ INT22_PHY1*1
  phy_constipation_before ~ INT23_PHY1*1

#Latent factor: PHY2
  PHY2 =~ L1_PHY2*phy_lack_of_appetite_after +
    L2_PHY2*phy_tiredness_after +
    L3_PHY1*phy_sore_muscles_after +
    L4_PHY2*phy_lack_of_energy_after +
    L5_PHY1*phy_back_pain_after +
    L6_PHY2*phy_nausea_after +
    L7_PHY1*phy_difficulty_sleeping_after +
    L8_PHY1*phy_headaches_after +
    L9_PHY1*phy_vomiting_after +
    L10_PHY1*phy_dizziness_after +
    L11_PHY2*phy_swallowing_pain_after +
    L12_PHY2*phy_decreased_sex_interest_after +
    L13_PHY2*phy_acid_indigestion_after +
    L14_PHY1*phy_shivering_after +
    L15_PHY2*phy_tingling_after +
    L16_PHY2*phy_abdominal_pain_after +
    L17_PHY2*phy_hair_loss_after +
    L18_PHY2*phy_sore_eyes_after +
    L19_PHY1*phy_difficulty_concentrating_after +
    L20_PHY2*phy_short_breath_after +
    L21_PHY1*phy_dry_mouth_after +
    L22_PHY2*phy_diaorrhea_after +
    L23_PHY1*phy_constipation_after

  PHY2 ~~ var_phy2*PHY2
```

```
  phy_lack_of_appetite_after ~~ E1_PHY1*phy_lack_of_appetite_after
  phy_tiredness_after ~~ E2_PHY1*phy_tiredness_after
  phy_sore_muscles_after ~~ E3_PHY1*phy_sore_muscles_after
  phy_lack_of_energy_after ~~ E4_PHY2*phy_lack_of_energy_after
  phy_back_pain_after ~~ E5_PHY2*phy_back_pain_after
  phy_nausea_after ~~ E6_PHY1*phy_nausea_after
  phy_difficulty_sleeping_after ~~ E7_PHY2*phy_difficulty_sleeping_after
  phy_headaches_after ~~ E8_PHY1*phy_headaches_after
  phy_vomiting_after ~~ E9_PHY2*phy_vomiting_after
  phy_dizziness_after ~~ E10_PHY2*phy_dizziness_after
  phy_swallowing_pain_after ~~ E11_PHY2*phy_swallowing_pain_after
  phy_decreased_sex_interest_after ~~
E12_PHY1*phy_decreased_sex_interest_after
  phy_acid_indigestion_after ~~ E13_PHY2*phy_acid_indigestion_after
  phy_shivering_after ~~ E14_PHY1*phy_shivering_after
  phy_tingling_after ~~ E15_PHY2*phy_tingling_after
  phy_abdominal_pain_after ~~ E16_PHY2*phy_abdominal_pain_after
  phy_hair_loss_after ~~ E17_PHY2*phy_hair_loss_after
  phy_sore_eyes_after ~~ E18_PHY2*phy_sore_eyes_after
  phy_difficulty_concentrating_after ~~
E19_PHY1*phy_difficulty_concentrating_after
  phy_short_breath_after ~~ E20_PHY1*phy_short_breath_after
  phy_dry_mouth_after ~~ E21_PHY1*phy_dry_mouth_after
  phy_diaorrhea_after ~~ E22_PHY2*phy_diaorrhea_after
  phy_constipation_after ~~ E23_PHY1*phy_constipation_after


  PHY2 ~ m_phy*1


  phy_lack_of_appetite_after ~ INT1_PHY2*1
  phy_tiredness_after ~ INT2_PHY2*1
  phy_sore_muscles_after ~ INT3_PHY2*1
  phy_lack_of_energy_after ~ INT4_PHY1*1
  phy_back_pain_after ~ INT5_PHY1*1
  phy_nausea_after ~ INT6_PHY2*1
  phy_difficulty_sleeping_after ~ INT7_PHY2*1
  phy_headaches_after ~ INT8_PHY2*1
```

```
  phy_vomiting_after ~ INT9_PHY1*1
  phy_dizziness_after ~ INT10_PHY1*1
  phy_swallowing_pain_after ~ INT11_PHY2*1
  phy_decreased_sex_interest_after ~ INT12_PHY1*1
  phy_acid_indigestion_after ~ INT13_PHY2*1
  phy_shivering_after ~ INT14_PHY1*1
  phy_tingling_after ~ INT15_PHY2*1
  phy_abdominal_pain_after ~ INT16_PHY2*1
  phy_hair_loss_after ~ INT17_PHY2*1
  phy_sore_eyes_after ~ INT18_PHY2*1
  phy_difficulty_concentrating_after ~ INT19_PHY2*1
  phy_short_breath_after ~ INT20_PHY2*1
  phy_dry_mouth_after ~ INT21_PHY2*1
  phy_diaorrhea_after ~ INT22_PHY2*1
  phy_constipation_after ~ INT23_PHY1*1

# Latent factor correlations
  PHY1 ~~ PHY2
  PSI1 ~~ PSI2
  PSI2 ~~ PHY1
  PHY2 ~~ PSI1
  PSI1 ~~ PHY1
  PSI2 ~~ PHY2

# Residual correlations
               psi_nervousness_before ~~             psi_nervousness_after
                  psi_worrying_before ~~                psi_worrying_after
            psi_depressed_mood_before ~~          psi_depressed_mood_after
               psi_hopelesness_before ~~             psi_hopelesness_after
                   psi_tension_before ~~                 psi_tension_after
              psi_irritability_before ~~            psi_irritability_after
                   psi_anxiety_before ~~                 psi_anxiety_after

          phy_lack_of_appetite_before ~~
phy_lack_of_appetite_after
                 phy_tiredness_before ~~
phy_tiredness_after
```

```
              phy_sore_muscles_before ~~
phy_sore_muscles_after

             phy_lack_of_energy_before ~~
phy_lack_of_energy_after

                  phy_back_pain_before ~~
phy_back_pain_after

                     phy_nausea_before ~~
phy_nausea_after

       phy_difficulty_sleeping_before ~~
phy_difficulty_sleeping_after

                  phy_headaches_before ~~
phy_headaches_after

                   phy_vomiting_before ~~
phy_vomiting_after

                  phy_dizziness_before ~~
phy_dizziness_after

            phy_swallowing_pain_before ~~
phy_swallowing_pain_after

    phy_decreased_sex_interest_before ~~
phy_decreased_sex_interest_after

          phy_acid_indigestion_before ~~
phy_acid_indigestion_after

                  phy_shivering_before ~~
phy_shivering_after

                   phy_tingling_before ~~
phy_tingling_after

             phy_abdominal_pain_before ~~
phy_abdominal_pain_after

                  phy_hair_loss_before ~~
phy_hair_loss_after

                  phy_sore_eyes_before ~~
phy_sore_eyes_after

  phy_difficulty_concentrating_before ~~
phy_difficulty_concentrating_after

               phy_short_breath_before ~~
phy_short_breath_after

                  phy_dry_mouth_before ~~
phy_dry_mouth_after

                  phy_diaorrhea_before ~~
phy_diaorrhea_after

               phy_constipation_before ~~
phy_constipation_after


                     phy_nausea_after ~~ phy_vomiting_after

                    phy_nausea_before ~~  phy_vomiting_before
```

```
')

SEM_OUT_4_new <- sem(SEM_MODEL_4_new,
                     sample.cov = cov(metabone_ri_cleaned),
                     sample.mean = colMeans(metabone_ri_cleaned),
                     sample.nobs = nrow(metabone_ri_cleaned),
                     std.lv = TRUE)

#modindices(SEM_OUT_1_new, sort. = TRUE, maximum.number = 200)

#RESPONSE SHIFT EFFECT SIZE

params <- parameterEstimates(SEM_OUT_4_new)

var_psi_before <- params[10:16, 'est']
var_psi_after <- params[34:40, 'est']
cov_var_psi <- params[197:203, 'est']
nom_var_psi <- sqrt(var_psi_before + var_psi_after - 2*cov_var_psi)

var_phy_before <- params[73:95, 'est']
var_phy_after <- params[144:166, 'est']
cov_var_phy <- params[204:226, 'est']
nom_var_phy <- sqrt(var_phy_before + var_phy_after - 2*cov_var_phy)


var_PHY1 <- params[params$rhs == 'PHY1' & params$lhs == 'PHY1', 'est']
var_PHY2 <- params[params$label == 'var_phy2', 'est']
var_PSI1 <- params[params$rhs == 'PSI1', 'est']
var_PSI2 <- params[params$label == 'var_psi2', 'est']

cov_PSI <- params[params$lhs == 'PSI1' & params$rhs == 'PSI2', 'est']
cov_PHY <- params[params$lhs == 'PHY1' & params$rhs == 'PHY2', 'est']

nom_PSI <- sqrt(var_PHY1 + var_PHY2 - 2*cov_PHY)
nom_PHY <- sqrt(var_PSI1 + var_PSI2 - 2*cov_PSI)
```

```
rnom_var_psi <- append(nom_var_psi, nom_var_phy[4], 5)

#true change PSI calculation
C1_PSI <- params[params$lhs == "PSI1" & params$op == "=~", "est"]
alpha2_PSI <- params[params$lhs == "PSI2" & params$op == "~1", "est"]
true_change_PSI <- (C1_PSI * alpha2_PSI)/rnom_var_psi

#true change PHY calculation
C1_PHY <- params[params$lhs == "PHY1" & params$op == "=~", "est"]
alpha2_PHY <- params[params$lhs == "PHY2" & params$op == "~1", "est"]
true_change_PHY <- (C1_PHY * alpha2_PHY)/nom_var_phy

#recalibration PSI
s1 <- params[params$op == "~1" & grepl("psi.*before", params$lhs), "est"]
s2 <- params[params$op == "~1" & grepl("psi.*after", params$lhs), "est"]
recalibration_PSI <- (s2 - s1)/nom_var_psi

#recalibration PHY
s1 <- params[params$op == "~1" & grepl("phy.*before", params$lhs), "est"]
s2 <- params[params$op == "~1" & grepl("phy.*after", params$lhs), "est"]
recalibration_PHY <- round((s2 - s1)/nom_var_phy, 3)



#repriotization PSI
C2_PSI <- params[params$lhs == "PSI2" & params$op == "=~", "est"]
reprioritization_PSI <- round(((C2_PSI - C1_PSI) *
alpha2_PSI)/rnom_var_psi, 3)

#repriotization PHY
C2_PHY <- params[params$lhs == "PHY2" & params$op == "=~", "est"]
reprioritization_PHY <- round(((C2_PHY - C1_PHY) * alpha2_PHY/nom_var_phy),
3)



recalibration_PSI[[8]] <- recalibration_PSI[[7]]
recalibration_PSI[[7]] <- recalibration_PSI[[6]]
```

```
recalibration_PSI[[6]] <- 0
```

```
observed_change_PSI <- recalibration_PSI + reprioritization_PSI +
true_change_PSI

observed_change_PHY <- recalibration_PHY + reprioritization_PHY +
true_change_PHY
```

```
response_shift_contribution_PSI <- observed_change_PSI - true_change_PSI

response_shift_contribution_PHY <- observed_change_PHY - true_change_PHY
```

```
standarised_response_mean_PSI <- alpha2_PSI/nom_PSI

standarised_response_mean_PHY <- alpha2_PHY/nom_PHY
```

```
summary(SEM_OUT_4_new, fit.measures = TRUE, standardized = TRUE)
```

```
anova(SEM_OUT_4_new, SEM_OUT_2_new)
```