

Path Analysis Modeling of Impaired Well-being in Advanced Cancer Patients Undergoing Chemotherapy

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ABSTRACT

Background: Well-being is an overall indicator of an individual's health status. Psychological and somatic symptoms may negatively impact patients undergoing chemotherapy treatment for advanced cancer. Previous studies provided some understanding regarding cancer symptoms or psychosocial factors associated with impaired well-being but did not explore the factor structure of the whole spectrum of impaired well-being or assess the causal effects of those factors on impaired well-being.

Purpose: To develop and test the causal relationships between unpleasant symptoms and impaired well-being among patients undergoing chemotherapy for advanced cancer.

Methods: A cross-sectional study was conducted among 500 patients with advanced cancer who received treatments at the Chemotherapy Unit in a tertiary care hospital in the Lower Northern region of Thailand. Data was obtained using a questionnaire to collect personal and clinical data and the Edmonton Symptom Assessment System (ESAS). Path analysis was used to examine the relationships between symptoms and impaired well-being.

Results: The model explained 22.1% of the variance in impaired well-being. Loss of appetite had the strongest direct and total effect on impaired well-being, followed by depression and shortness of breath. Nausea, shortness of breath, pain, and anxiety indirectly affected impaired well-being through loss of appetite.

Conclusion: The study provides an explanatory model of the relationships between the eight symptoms measured by ESAS and impaired well-being in patients undergoing chemotherapy for advanced cancer. The model enables nurses to design interventions that consider the multi-dimensional interactions of symptoms causing impaired well-being, which ultimately leads to poor functional status.

Keywords: Advanced cancer; Chemotherapy; Path analysis; Impaired well-being

1. Introduction

Cancer is a major global health concern, accounting for 20 million new cases and nearly 10 million deaths annually (1 in 6 deaths) (World Health Organization International Agency for Research on Cancer (IARC), 2022; Sung et al., 202). In Thailand, the number of newly diagnosed cancer cases has continued to rise, as reported by the National Cancer Institute (2022).

Patients with advanced-stage cancer receiving chemotherapy commonly experience multiple physical and psychological symptoms, including pain, anxiety, nausea, shortness of breath, drowsiness, loss of appetite, fatigue, depression, and impaired well-being

(Lertpanit et al., 2021; Unsar et al., 2017). These unpleasant symptoms substantially compromise patients' functional status, psychological well-being, and overall quality of life (Khamboon & Pakanta, 2021; Yang et al., 2021).

Although previous studies have identified associations between cancer symptoms and impaired well-being, the full spectrum of factors contributing to impaired well-being and the causal interactions among these symptoms remain unclear. Causal pathways and comprehensive understanding of symptom interactions remain unexplored (Battat et al., 2023; Lewandowska et al., 2020; Nolan et al., 2018; Yang et al., 2021). Determining these causal relationships may guide the development of evidence-based interventions, allowing health professionals to focus on managing specific symptoms that influence impaired well-being and functional status, thereby improving patient outcomes. In a previous study conducted by the same authors, data from 500 patients with advanced cancer receiving chemotherapy at a tertiary care hospital in the lower northern region of Thailand were collected using the Edmonton Symptom Assessment System (ESAS). Prior findings highlighted the strong relationship between impaired well-being and functional status but did not clarify the causal structure or interrelations among symptoms (Khamboon et al., 2023). Other supporting evidence also showed that impaired well-being is most often found in patients with advanced-stage cancer, and the more the disease progresses, the more burden this symptom becomes (Torres et al., 2022; Unsar et al., 2017). Evidence supports the need for comprehensive symptom management targeting multiple symptoms concurrently.

This current study used ESAS to assess nine common symptoms in advanced cancer patients including pain, anxiety, nausea, shortness of breath, drowsiness, loss of appetite, fatigue, depression, and impaired well-being. A hypothesized model, grounded in a literature review and the Theory of Unpleasant Symptoms (TOUS), (Lenz & Pugh, 2018) was employed to examine both the direct and indirect relationships among these symptoms, thereby portraying the complexity of impaired well-being. This framework provides an understanding of symptom complexity and interactions, offering a comprehensive approach to improving interventions and patient care. This study incorporated direct and indirect relationships among variables in a hypothesized model based on a literature review and the TOUS to portray the complexity of impaired well-being (Figure 1). This study aimed to develop and test the causal relationships between pain, anxiety, nausea, shortness of breath, drowsiness, loss of appetite, tiredness or fatigue, depression, and impaired well-being among patients undergoing chemotherapy treatment for advanced cancer.

2. Methods

2.1 Research design

A secondary data analysis of data from a previous study conducted by the same authors of this research (Khamboon et al., 2023). The original study used a cross-sectional descriptive design to determine the influence of unpleasant symptoms on the functional status of patients with advanced cancer. This present study adopted data to investigate further the causal relationships among the eight unpleasant symptoms and impaired well-being. The authors structured this article according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement, which provides guidelines for reporting observational studies.

2.2 Setting and samples

This study was conducted at the Chemotherapy Unit of a tertiary care hospital in the Lower Northern region of Thailand, between March 2020 and October 2021. The sample size was determined using G*Power software version 3.1.9.2 for multiple regression analysis (Kang, 2021), with a statistical power of 0.8, significance level of 0.05, and a small effect size. The R^2 value of 0.044 was obtained from a previous study on hematological malignancy patients undergoing chemotherapy, which examined the influence of symptom experiences on functional status (Suedee et al., 2015). To account for potential withdrawal or missing data, an additional 20% of the calculated sample size was included, resulting in a total sample of 500 patients. Eligible patients were adults with advanced cancer who had received at least one session of chemotherapy and were able to communicate effectively. Patients were excluded if they had undergone other combination treatments, such as radiotherapy or surgery, or if they had severe pre-existing comorbidities, complications, or diagnosed cognitive or psychological disorders. Eligible patients were invited to participate, and informed consent was obtained prior to data collection.

2.3 Measurement and data collection;

Two research instruments were used in this study. First, a structured questionnaire developed by the principal investigator was applied to collect demographic information (gender, age, marital status, level of education, occupation, and average monthly income) and clinical characteristics (type of cancer, stage, number of chemotherapy cycles received, and total duration since diagnosis). Second, the Edmonton Symptom Assessment System (ESAS), originally developed by Bruera and colleagues, was employed to measure the symptom burden in patients with advanced cancer (Hui & Bruera, 2017). The ESAS comprises nine symptoms assessed using a 0–10 numerical rating scale (NRS): pain, tiredness, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, and well-being. Scores are interpreted as 0 = no symptom, 1–3 = mild, 4–6 = moderate, and 7–10 = severe. The ESAS has been translated professionally into more than 20 languages, including Thai, and was validated in Thai patients with various types of cancer (Chinda et al., 2011). The Thai version demonstrated strong internal consistency, with a Cronbach's alpha of 0.89. For the present study, the authors tested reliability in a group of patients with characteristics similar to the study participants, yielding a Cronbach's alpha of 0.86. Data collection was conducted directly by the authors in the outpatient chemotherapy unit following the acquisition of informed consent.

2.4 Data analysis;

Data analysis was conducted using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY) and Mplus version 7.11. Descriptive statistics were applied to summarize demographic characteristics and key study variables. Pearson's correlation coefficients were computed to examine relationships among the study variables. Path analysis was performed in Mplus to assess the causal relationships. Statistical assumptions for path analysis, including linearity, homoscedasticity, and multicollinearity, were tested and satisfied. The model fit was evaluated using the following indices (Wang & Wang, 2019): Chi-square (χ^2) > 0.05, Chi-square to degrees of freedom ratio (χ^2/df) ≤ 2, Root Mean Square Error of Approximation (RMSEA) < 0.05, Comparative Fit Index (CFI) ≥ 0.95, Tucker–Lewis Index (TLI) ≥ 0.95, and Standardized Root Mean Square Residual (SRMR) < 0.008. A p-value of < .05 was considered statistically significant.

2.5 Ethical considerations.

This study adhered to recognized ethical standards for research involving human participants. Ethical approval was granted by two institutional review boards: the Naresuan University Institutional Review Board (COA No. 527/2019, IRB No. 0418/62) and the Ethics Committee of Buddhachinaraj Hospital Phitsanulok (IRB No. 020/63). All participants were approached in the chemotherapy unit, where the study objectives, procedures, potential benefits, and the voluntary nature of participation were clearly explained. Written informed consent was obtained from each participant prior to data collection. Participants were assured that confidentiality and anonymity would be maintained, and they retained the right to withdraw from the study at any point without affecting their ongoing treatment.

3. Results

A total of 500 patients completed the study measures. Mean age was 53.08 years (SD 12.70), and 64.6% were female. Most of the participants were Buddhist (96.2%), married (77.4%), and had primary education (65.6%). Around 28.2% were farmers and 21.8% were unemployed. The average monthly income was less than 10,000 baths (51.4%). Gastrointestinal cancer accounted for 35.6% of the participants, followed by breast cancer (27.4%) and hematologic cancer (13.4%), respectively. More than half of the patients (56.0%) were in stage 3. The average time between diagnosis and current treatment was approximately 1-2 years (45.8%). Almost 90% of the participants had at least two cycles of chemotherapy treatment. While participants experienced mild pain, anxiety, nausea, shortness of breath, drowsiness, tiredness or fatigue, depression, and impaired well-being, loss of appetite was reported moderately. Table 1 shows the average rated scores for each symptom on the ESAS. The correlation matrix of the key variables included in the final analysis is presented in Table 2. The bivariate correlations among the study variables did not exceed 0.80 ($r = -0.96$ to 0.76), indicating no multicollinearity between the study variables (Shrestha, 2020). The initial result for the overall model indicated an inadequate model fit ($\chi^2 = 234.475$, $df = 13$, $\chi^2 / df = 18.04$, RMSEA = 0.000, CFI = 0.783, TLI = 0.499, SRMR = 0.066). Therefore, the model was modified while considering the conceptual and modification indices. After trimming the initial model, fit statistics for the final model demonstrated a good fit based on goodness-of-fit statistics (Wang & Wang, 2019) ($\chi^2 = 8.688$, $df = 9$, the ratio of ($\chi^2 / df = 0.97$, RMSEA = 0.000, CFI = 1.000, TLI = 1.001, SRMR = 0.018). Figure 2 shows the final model with standardized path estimates. The model of impaired well-being in advanced cancer undergoing chemotherapy explained 22.1 % of the total variance. The strongest total effect of impaired well-being was the loss of appetite ($\beta = 0.72$, $p < .001$). Loss of appetite ($\beta = 0.71$, $p < .001$), depression ($\beta = 0.31$, $p < .001$), and shortness of breath ($\beta = 0.21$, $p < .001$) directly affected impaired well-being. The final model indicated that anxiety, nausea, shortness of breath, pain, tiredness, and loss of appetite had indirect effects on impaired well-being. The effects of each symptom of impaired well-being are presented in Table 3.

4. Discussion

This study aimed to develop an impaired well-being model based on the TOUS and test the causal relationships between the nine symptoms measured by ESAS in patients with advanced stages of cancer receiving chemotherapy treatment. Findings from this study indicated that loss of appetite, depression, and shortness of breath directly affected impaired well-being. Besides, anxiety, nausea, shortness of breath, pain, tiredness, and loss of appetite indirectly affected impaired well-being experienced by this population. These

findings provide theory-based evidence supporting the constructs of the TOUS that symptoms can occur together as a single event or one symptom can precede another (Lenz & Pugh, 2018).

The findings from our study illustrated that loss of appetite had the most substantial effect on impaired well-being. It also influences impaired well-being directly and indirectly through tiredness and depression. Most patients with advanced cancer suffer from loss of appetite, affecting their ability to do usual activities and leading to poor quality of life (Ehret & Jatoi, 2021). The regulation of loss of appetite involves many factors and cytokines that modulate receptors and neurons in the Central nervous system (CNS) (Hariyanto & Kurniawan, 2021). The research found different cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor- α (TNF- α), and interferon γ (IFN- γ) elevating in cancer patients. These cytokines affect neuroendocrine control of appetite, leading to anorexia and hypermetabolism, resulting in muscle wasting and tiredness.

Cancer treatments, including chemotherapy, may also lower the appetite or change how food tastes or smells. Some side effects from chemotherapy, such as mouth and throat problems, nausea, vomiting, or fatigue, can also lower a patient's appetite (Childs & Jatoi, 2018). Decreasing the desire to eat also relates to tiredness and depression, which are some of the most common causes of impaired well-being in cancer patients. Consistent with previous studies, loss of appetite and tiredness often occur together, and they are frequently observed as related clusters of symptoms.

Other symptoms related to loss of appetite found in the participants of this study were nausea, shortness of breath, pain, and anxiety; these symptoms worsened the participants' well-being by enhancing or causing loss of appetite. However, from our analysis, nausea affected the loss of appetite the most. Nausea is an unpleasant feeling in the back of the throat or stomach that may come and go in waves (Gupta et al., 2021). Vomiting is throwing up the contents of the stomach through the mouth. Retching is the movement of the stomach and esophagus without vomiting, also called dry heaves. These symptoms can significantly reduce quality of life and may potentially deter patients from continuing treatment. Chemotherapy-induced nausea and vomiting (CINV) involves the coordination of several gastrointestinal tract organs and the peripheral and central nervous systems. Many neurotransmitters are involved in this process, and the predominant receptors are serotonin, neurokinin-1, and dopamine receptors. Despite the development of new antiemetic agents, nausea and vomiting remain the most feared, affecting up to 50% of patients undergoing chemotherapy (Gupta et al., 2021). Nausea is one of the most distressing symptoms that interfere with patients' quality of life. It decreases the desire to eat, leading to malnutrition and tiredness.

Depression emerged as the second most influential symptom directly affecting well-being in this study. Cancer is widely recognized as a life-threatening and highly feared diagnosis, which often causes substantial psychological distress for patients. Prolonged experiences of intense mental anguish in individuals with cancer may lead to anxiety, depression, or both. The prevalence of depression among cancer patients has been reported to be up to three times higher than that in the general population, with approximately two-thirds of those experiencing depression also presenting clinically significant anxiety symptoms (Pitman et al., 2018). These findings highlight the critical role of mood and overall mental well-being in the cancer experience, emphasizing that emotional health should be considered an integral part of patient care and management.

Depression and anxiety are expected long-term consequences of cancer, with detrimental effects on the quality of life, treatment adherence, and potentially mortality

(Götze et al., 2020). A cross-sectional cohort study of 1,002 cancer survivors across a large variety of tumor entities five and ten years after diagnosis revealed moderate to severe depression and anxiety occurring concomitantly among this group of patients, and these symptoms also affected global quality of life (Götze et al., 2020). The results are consistent with our findings that depression mediates between anxiety and impaired well-being. Thus, appropriate prevention and treatment of depression and anxiety in long-term cancer survivors are necessary to improve an individual's well-being.

The last symptom directly affected impaired well-being was shortness of breath. Shortness of breath, also referred to as breathlessness or dyspnea, is a common symptom in patients with advanced cancer. It is defined as an individual experience of breathing discomfort, and many factors can modulate the severity and intensity of the symptoms (Hui et al., 2020). A shortness of breath can become a frightening experience for both patient and carer. Thus, the symptoms can affect them physically, emotionally, and socially. Shortness of breath can be related to cancer progression, its therapies, and acute complications such as infections or pulmonary embolism. Pre-existing comorbidities such as COPD and heart failure may also contribute to breathlessness (Crombeen & Lilly, 2020).

A prospective observational study in India recruited 500 patients registered with a palliative medicine outpatient department to determine factors influencing dyspnea and its impact on the overall quality of life (Damani et al., 2018). The study found approximately 44% of the participants experienced symptoms. It increased with worsening anxiety, depression, fatigue, appetite, well-being, pain, lung involvement by primary or metastatic cancer, performance status, and deteriorating overall quality of life and emotional well-being. These findings are partially in line with our findings. We found loss of appetite acts as a mediator for shortness of breath and impaired well-being. As the symptoms occur, breathing takes extra energy, and it can be challenging to coordinate breathing and eating simultaneously. A shortness of breath also makes getting groceries and preparing food more challenging. This, in turn, results in impaired well-being and overall quality of life (Crombeen & Lilly, 2020; Hui et al., 2020). One finding from this study that should be noted is that drowsiness did not directly or indirectly affect impaired well-being, which contradicts the findings from Olson (2014) (Olson et al., 2014). In patients with cancer, sleep problems may cause drowsiness, or it could be a side effect of opioids used to alleviate the pain among this group of patients. However, this study did not record the participants' sleep problems and medications used to control pain. This inconsistency highlights the need for nurses to carefully assess drowsiness in relation to pain management and sleep disturbance, as its role in impaired well-being remains inconclusive. Further investigation on this issue should be conducted in a future study.

5. Implication and limitations

The present study has several notable strengths. All participants were recruited through a chemotherapy unit in a tertiary care hospital, ensuring accurate diagnosis and reliable clinical information. Additionally, the diverse characteristics of the sample, including a wide range of age, duration since diagnosis, and tumor types, provide a reasonable representation of patients receiving treatment in the study hospital. However, several limitations must be acknowledged. The data were obtained from a single-site study, which may restrict the generalizability of findings to the broader cancer population. Laboratory assessments and information regarding medications used to alleviate pain and sleep disorders were not included, and the study relied primarily on patient self-reports. These factors may have influenced the results and should be considered in future research.

From a nursing perspective, the study underscores the importance of comprehensive symptom assessment and management in patients with advanced cancer. Nurses should prioritize interventions that target symptoms directly impacting impaired well-being, such as loss of appetite, depression, and shortness of breath. Furthermore, indirect contributors to impaired well-being, including nausea, pain, and anxiety, should also be addressed. Incorporating these findings into nursing practice can improve patient care outcomes, functional status, and overall quality of life. Multidisciplinary collaboration is recommended to develop evidence-based guidelines and interventions tailored to the complex symptom interactions in this population.

6. Conclusion

This study successfully developed an explanatory model of impaired well-being based on the relationships between eight symptoms measured by the ESAS in patients with advanced cancer undergoing chemotherapy. The findings provide advanced knowledge regarding the direct and indirect pathways through which specific symptoms affect well-being, thereby extending our understanding beyond previous research (Khamboon et al., 2023). The study offers clear scientific justification for its clinical relevance. The model allows nurses and multidisciplinary healthcare teams to design interventions that consider the multi-dimensional interactions of symptoms, particularly those directly affecting impaired well-being, including loss of appetite, depression, and shortness of breath. Indirect contributors such as nausea, pain, and anxiety should also be integrated into intervention planning. Future research is recommended to include multi-site studies, laboratory assessments, and medication effects to validate and extend these findings. These results have practical implications for nursing practice, emphasizing comprehensive symptom management as a strategy to improve patient well-being and functional outcomes.

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Author contribution

Khamboon Thidarat: Conceptualized and designed the study, supervised data collection, analyzed and interpreted the data, and critically revised the manuscript.

Pakanta Intira: Served as the corresponding author, coordinated manuscript submission, contributed to data interpretation, and reviewed the manuscript.

Both authors: Read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Figure 1. Hypothesized causal relationships of impaired well-being in advanced cancer undergoing chemotherapy

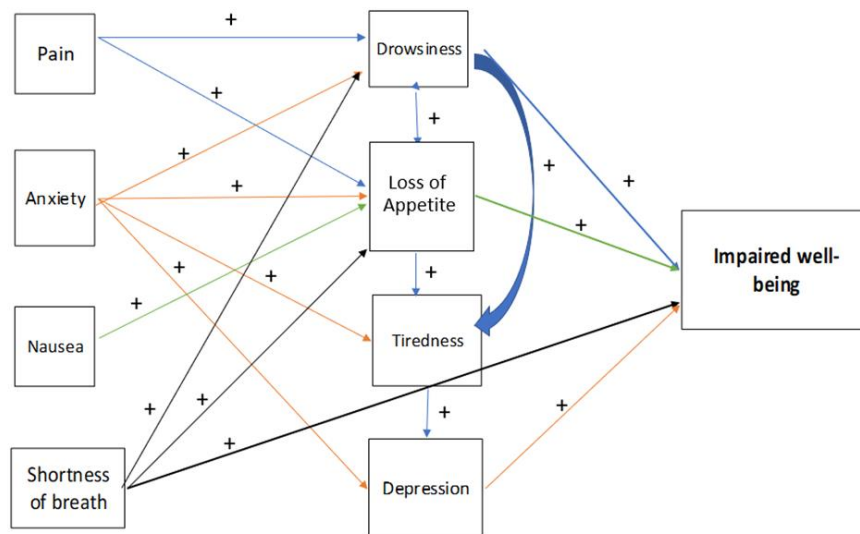


Figure 1. Hypothesized causal relationships of impaired well-being in advanced cancer undergoing chemotherapy

Figure 2. The causal model of impaired well-being in advanced cancer undergoing chemotherapy

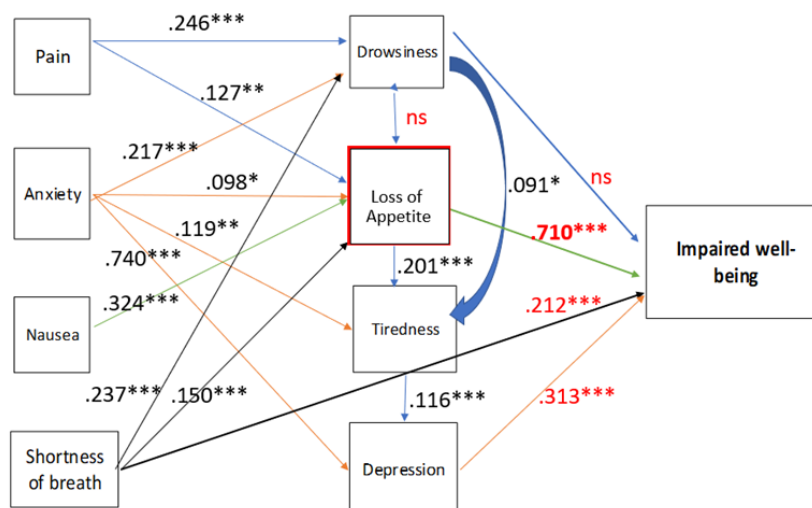


Figure 2. The causal model of impaired well-being in advanced cancer undergoing chemotherapy

Table 1. The summary of average rated scores for each symptom on the ESAS (n = 500)

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Variables	Possible Range	Actual Range	Mean	SD	Level of score
Pain	0-10	0-9	2.72	2.52	Mild
Anxiety	0-10	0-8	1.84	2.37	Mild
Nausea	0-10	0-9	1.08	1.94	Mild
Shortness of breath	0-10	0-8	0.75	1.82	Mild
Drowsiness	0-10	0-7	1.20	2.04	Mild
Loss of appetite	0-10	0-9	3.26	2.69	Moderate
Tiredness	0-10	0-8	2.88	2.19	Mild
Depression	0-10	0-6	1.14	1.92	Mild
Impaired Well-being	0-10	0-10	1.71	2.44	Mild

Table 2 Correlation matrix of study variables (n = 500)

Variables	1	2	3	4	5	6	7	8
1. Impaired well-being	1.00							
2.Pain	.26**	1.00						
3.Anxiety	.32**	-.02	1.00					
4.Nausea	.16**	-.11*	-.03	1.00				
5.Shortness of breath	.34**	.07	.04	-.09	1.00			
6.Drowsiness	.32**	.26**	.22**	.01	.25**	1.00		
7.Loss of appetite	.24**	.11*	.10*	.29**	.14**	.13**	1.00	
8.Tiredness	.26**	-.02	.17**	.11*	.38**	.22**	.28**	1.00
9.Depression	.22**	-.16**	.76**	-.10*	.05	.31**	.07	.25**

Note: * $p < .05$, ** $p < .01$

Table 3 Parameter estimates of direct, indirect, and total effects of study variables in the model (n = 500)

Variables	Impaired Well-being		
	DE	IE	TE
1. Pain		0.11**	0.11**
2. Anxiety		0.32***	0.32***
3. Nausea		0.23***	0.23***
4. Shortness of breath	0.21***	0.12**	0.33***
5. Drowsiness	0.03	0.03	0.06
6. Loss of appetite	0.71***	0.01**	0.72***
7. Tiredness		0.04**	0.04**
8. Depression	0.31***		0.31***

Note: * $p < .05$, ** $p < .01$, *** $p < .001$

DE = direct effect, IE = indirect effect, TE = total effect

