The Effects of Age, Physical Inactivity and Fatigue on Handgrip Strength Related Upper Extremity Functionality in Patients With Breast Cancer: a Mediation Analysis

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Research Article

Keywords: Breast cancer, Cancer survivors, Handgrip strength, Upper extremity function, Fatigue, Mediation Analysis

Posted Date: April 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1401783/v1

Abstract

Purpose: This study was aimed to assess the effect of age, fatigue, self-reported function, and physical inactivity on handgrip strength related upper extremity function (HGSf) in breast cancer survivors (BCS). Secondarily, the potential mediator effects of fatigue and physical inactivity were also studied. This study was registered to Clinical Trials: NCT04245657.

Methods: 111 female BCS (Mean age and BMI: 51.20±9.33 year and 27.86±3.70 kg/m^2, respectively) were included in this study. Handgrip strength (HGS) was assessed with dynamometer while fatigue, self-reported upper extremity function and physical inactivity as sitting time were assessed with Fatigue Severity Scale (FSS), Disabilities of Arm, Shoulder and Hand Questionnaire (DASH), and 7th question of International Physical Activity Questionnaire Short Form, respectively.

Results: HGS was found significantly higher on the right side compared to the left side (22.63±3.50 kgF vs 21.30±3.65 kgF, t=5.083, p<0.001). The mean sitting time, DASH and FSS were found 5.7 hours, 22.67 and 39.55, respectively. The multivariate linear regression analysis showed a total of 28% of the cumulative variance in HGSf is explained by age, DASH and sitting time variables ($F (3,107) = 12.057$, $p<0.001$, $R^2=0.280$). Fatigue was not found as a mediator in the hypothesized structural equation model while sitting time had a significant mediator effect between the age and HGSf (β=-0.004 (95% CI-0.075/-0.004), p=0.019)

Conclusions: Increased physical inactivity and age play a major role in strength-related upper extremity function in BCS. Patient-specific physiotherapy programs should also consider this especially in older and physically BC patients in rehabilitation and long-term care.

Introduction

Breast cancer (BC) is a major and global health concern. American Cancer Society foresees nearly 300.000 new cases in 2021 while they reported the incidence of BC in every one out of eight women which nearly equals 13% (1). This rate is in parallel with the World Health Organization's report which was also reported as 12% (2). According to the Global cancer statistics 2020 report, female BC takes the first row among all other cancer types (3). However, five years survival rate is increased above 90% among breast cancer survivors (BCS) and a 40% decrease has been achieved in mortality from the '80s through 2020 thanks to early diagnosis and advancements in BC treatment (4).

The increased survival rate among BCS brings many consequences which should be thoroughly addressed to optimize the functionality of BCS. Upper body dysfunction among BCS is the most common complaint during and after BC treatment. Since BC treatment contains a multimodal approach such as surgery and adjuvant therapies, symptoms related to upper body dysfunction can be multifactorial (5, 6). Not only in patient perspective but also economic perspective of these problems can be devastating for both patients and third-party payers. Rashid et al. (7) reported that annual health expenses associated with secondary problems after BC treatment reached nearly six hundred million dollars in which musculoskeletal problems have a relatively huge share.

Age can be an important contributor and/or predictor regarding upper body function among BCS. However, contradicting results are still in debate for instance some researchers stated that (8, 9) older age is a significant contributor to the decreased upper extremity function while others reported the exact opposite (10, 11). Hopkins et al. (12) stated that treatment-related musculoskeletal problems are seen in more common in older age compared to younger ones. On the other hand, physical inactivity which can be induced by patient characteristics such as age or BMI as well as it can manifest itself only without any inductor. De Vrieze et al. (13) reported that 8% of the cumulative variance of functioning can be explained by age and physical inactivity. Many patients diagnosed with cancer are prone to decrease their physical activity levels even lower than pre-diagnosis level, even though the well-known deteriorating effects of physical inactivity during and/or after cancer treatment. Physical inactivity is reported as responsible for the functional decline (14, 15).

Cancer-related fatigue negatively affects BCS in many aspects. One can be affected not only during adjuvant therapies but even also a few years later after the completion of primary treatment (16). National Comprehensive Cancer Network reported that almost 100% of cancer patients experience fatigue and it can last up to two years (17). However, as with age or other patient and clinical features, fatigue has also a multifactorial complex nature which can be affected drug use, physical inactivity, age as well as treatment-related procedures and duration, and so forth (18).

Handgrip strength (HGS) is accepted as an objective clinical outcome among the cancer population. Since its simple applicability, repeatability, and safe usage, HGS has been widely used in the BC population. HGS is also reported as a significant predictor for multiple cause morbidity (19, 20). Not only HGS but also patient-reported measures can be helpful to detect subjectively perceived functional limitations. Disabilities of Arm, Shoulder, and Hand (DASH) questionnaire was reported to be a useful patient-reported outcome measure in patients with BC (21, 22).

Since problems related to BC treatment are multifactorial and complex by affecting each other, we aimed to assess factors such as age, fatigue, self-reported function, and physical inactivity predicting HGS related upper extremity functionality. In the literature, many studies investigated the effects of parameters upon a dependent variable yet there is scarce evidence related to path analysis in which advanced methods are used. Research on this subject has been mostly restricted to limited comparisons. Therefore, we performed a mediation analysis within a structural equation model in which complex relationships can be observed.

Method

Study Design

This study was planned as a cross-sectional cohort study and registered to clinical trials with a unique identification number as follows: NCT04245657. All procedures and measurements in this study were performed according to the 1964 Helsinki declaration or comparable ethical standards. Ethical board approval was granted by Clinical Research Studies with the following protocol number 02/11092019. All patients were informed regarding the protocol of this study and written informed consent was taken for each patient.

Patients

Patients diagnosed with BC and applied to the Medical Oncology Unit for neoplastic adjuvant therapy were screened according to the following inclusion and exclusion criteria: Being a volunteer to participate, aged between 18- and 75-year-old, being woman, having unilateral breast surgery, being completed their adjuvant therapies, and having time spent six months or higher after surgery was set as inclusion criteria. Systemic infection, having active metastasis, having bilateral breast surgery, a mental or cognitive deficit, and having orthopedic and/or neurological deficit which might hamper the assessment parameters were set as exclusion criteria.

Study Sample

Sample size calculation for this study was performed according to the Cohen's d effect size formulation in a prediction model in which five different independent variables' effect on a single dependent variable. Low to moderate effect size for linear regression was calculated within 95% CI and 80% power as well as the alpha level was accepted as significant 0.05 or below. According to the output, a total of 101 patients were seen as adequate to perform this analysis. Power calculation was performed with G*Power 3.1.9 (23).

Demographic and Clinical Assessment

After informed consent was taken from each patient, a demographic data form was used to gather the patient's clinical and socio-demographic characteristics such as Type and date of surgery, type of axillary procedure as well as age, dominant and surgical side, BMI, drugs, etc.

Assessment of Handgrip Strength

The handgrip strength of patients was assessed with a dynamometer which has a measurement range of 0-100 kgF (*LaFayatte Handgrip Dynamometer, Model 5030L1, Lafayette, USA*). The operation of measuring handgrip strength was described in detail in previous studies (20, 24). Briefly, patients were requested to sit in an erect position in a chair without arm support. Then, they were informed that they are required to squeeze the dynamometer with the oral command as much as they can do while they keep their shoulder adducted, elbow flexed at 90°, and wrist positioned in mid-prone. Patients were also requested not to hold their breath while squeezing and keep their erect posture during the assessment. Three measurements were taken for each side and the mean value was recorded as kgF unit.

Disabilities of Arm, Shoulder, and Hand Function (DASH)

The upper extremity function was assessed with the Turkish version (25) of the DASH questionnaire. DASH has been widely used in musculoskeletal problems related to the upper extremity and it was reported that it is useful in patients with BC (21, 22). One is required to fill out each item which reflects different kinds of activities according to the Likert type scale from “No difficulty:1” through “Unable: 5” while one is requested to consider their last week. Higher scores indicate higher disability or vice versa (26, 27). The minimum and maximum scores are 0 and 100, respectively.

Fatigue Severity Scale (FSS)

Fatigue severity scale (FSS) was used to assess patients’ fatigue levels. FSS consists of a total of nine items each should be filled out according to the Likert type scale from “1: Completely Disagree” through “7: Completely Agree”. The total score is calculated as the sum of all items. Higher scores indicate more fatigue while lower scores indicate better (28). The minimum and maximum scores are 0 and 63, respectively.

Physical Inactivity

Physical inactivity was assessed with the Turkish version (29) of International Physical Activity Questionnaire Short Form’s 7th question which assesses daily sitting time. Sitting time was collected as an hour(s)/day.

Statistical Analysis

Clinical and socio-demographic characteristics of patients were shown as means and standard deviation or number and percent according to the type of data whether continuous or categorical. Normal distribution was analyzed with KS-SW normality tests. For the dependent variable, HGS was formulated for controlling the dominant side and BMI as follows: Bilateral means of HGS (*(Right HGS + Left HGS)/2)* was divided by BMI then multiplied by 100. Thereafter, this formulation was called as *HGSf*. Multivariate linear regression analysis was performed according to the assumptions. After regression analysis, a structural equation model was generated. Direct and indirect effects were analyzed according to the maximum likelihood procedure to analyze the mediator and moderator effects between parameters. The normed fit index (NFI), Tucker-Lewis index (TLI), Incremental fit index (IFI), (> .90 indicates good model fit for NFI, TLI and IFI), Comparative fit index (CFI) (for CFI > 0.90 acceptable and > 0.95 excellent), the Root Mean Square Error of Approximation (RMSEA: <0.08 acceptable and < 0.05 excellent) The ratio of the Chi-square test of model fit to the degrees of freedom (CMIN/DF) [values of five or less] (30). 15 cases are suggested to be adequate for path analysis per predictor in the hypothesized model (31). Statistical analyses were performed with IBM SPSS version 20.0 (IBM Corporation, Armonk, NY) and IBM AMOS Graphics version 23.0 (IBM SPSS, Chicago, USA) (32).

Results

A total of 162 patients (Mean age and BMI: 51.20 ± 9.33 year and 27.86 ± 3.70 kg/m^2, respectively) were included in this study. 51 patients were excluded according to the exclusion criteria. The final analysis was performed with a total of 111 patients. The detailed participation process is shown as a flow-chart supplementary Fig. 1.

All patients underwent BC surgery due to ductal carcinoma in situ. The great majority of patients underwent conservative breast surgery (74 out of 111 patients) while the rest of them underwent a modified radical mastectomy. 96 out of 111 patients underwent axillary lymph node dissection (ALND). Adjuvant chemotherapy and radiotherapy history were positive in 85.6% and 96.4% of patients, respectively. The right side was dominant in 96 out of 111 patients. For the vast majority of patients (72%), the time elapsed after surgery was within three years. Only 11 patients showed preclinical and clinical lymphedema. Patients' demographic and clinical characteristics are shown in Table 1.

Table 1
Clinical and demographic characteristics of patients

n = 111	**n (%) Right**	**n (%) Left**
Dominant side	107 (96.4%)	4 (3.6%)
Surgical side	56 (50.5%)	55 (49.5%)
	n (%)	**n (%)**
Lympedema	**No**	**Yes**
	100 (90.1%)	11 (9.9%)
Type of surgery	**Conservative**	**MRM**
	74 (66.7%)	37 (33.3%)
Axillary dissection type	**ALND**	**SLNB**
	93 (83.8%)	18 (16.2%)
	Yes	**No**
Adjuvant CT History	95 (85.6%)	16 (14.4%)
Adjuvan RT History	107 (96.4%)	4 (4.3%)
Tamoxifen	49 (44.1%)	62 (55.9%)
AI	49 (44.1%)	62 (55.9%)

MRM: Modified radical mastectomy, **ALND**: Axillary lymph node dissection, **SLNB**: Sentinel lymph node dissection, **CT**: Chemotherapy, **RT**: Radiotherapy, **AI**: Aromatase inhibitor

Handgrip strengths for the right and left sides were 22.63 kgF and 21.30 kgF, respectively. Handgrip strength was also found significantly higher on the right side compared to the left side (22.63 ± 3.50 kgF vs 21.30 ± 3.65 kgF, $t = 5.083$, $p < 0.001$). The mean sitting time of patients was found 5.7 hours. Mean patient-reported upper extremity function assessed with DASH and fatigue level which was assessed with FSS were found 22.67 and 39.55, respectively.

Handgrip strength, BMI, DASH, and fatigue was not different in patients with or without lymphedema ($p > 0.05$). The same parameters were also not found different between patients who underwent ALND or SLNB as well as between patients who underwent breast-conserving surgery or modified radical mastectomy ($p > 0.05$, data not shown). Comparative analyses according to the history of drugs used were not found significant except for age. Patients who use Aromatase inhibitors (AI) showed significantly higher age compared to non-users ($t=-4.198$, $p < 0.001$), while patients who use Tamoxifen showed significantly lower age compared to non-users ($t = 6.564$, $p < 0.001$). However, the interaction effect of using AI and using Tamoxifen was found significant regarding the effect on HGSf in the two-way analysis of variance ($F_{(1,107)} = 4.015$, $p = 0.048$, $\eta^2 = 0.036$).

Significant negative correlations among HGSf, DASH, age, and sitting time were obtained whereas positive significant correlations were seen between age and sitting time as well as between fatigue and patient reported function scores. Correlations among variables are shown in supplementary Table 1.

The multivariate linear regression analysis for the cumulative predictive effects of age, DASH score, and sitting time on HGSf showed a total of 28% of the cumulative variance can be explained by these variables ($F_{(3,107)} = 12.057$, $p < 0.001$, $R^2 = 0.280$). Details of Regression analysis are shown in Table 2.

Table 2
The predictive effects of age, patient reported function score and sitting time on HGSf in multivariate linear regression analysis

n = 111	β	β S. E	95%CI	t	p
(Constant)	119.081	7.548	104.091, 134.070		**< 0.001**
Age (year)	-0.492	0.143	-0.776, -0.207	-3.435	**0.001**
DASH	-0.316	0.092	-2.056, -0.228	-2.482	**0.001**
Sitting time (hours/day)	-1.142	0.460	-0.498, -0.133	-3.427	**0.015**
DASH: Disabilities of Arm, Shoulder and Hand, $\mathbf{R^2}$ = 0.280, **F** = 12.057, Regression formula: **HGSf** = 119.081+ -0.492*Age + -0.316*DASH+ -1.142*Sitting time					
S.E: Standard eror, **CI**: Confidence interval					

The path analysis was performed and interpreted according to the path coefficients, direct and indirect effects, lower and upper bounds of 95% CI, and p values. Following fit indexes were used to assess the mediation model: NFI, TLI, IFI, CFI, RMSEA, and CMIN/DF. The first model was created to analyze the mediator effect of fatigue between age, DASH and sitting time, and HGSf. Within 95% CI and bootstrap sampling, total, direct and indirect effects were analyzed. The results showed that fatigue was not found as a mediator in this hypothesized model. The model diagram is shown in Fig. 1 and direct, indirect, total effects, as well as path coefficients and p values, are shown in Table 3. Fit indexes are shown in supplementary Table 2.

Table 3
Standardized path coefficients, direct, indirect and total effects of age, DASH and sitting time on HGSf

Paths	Direct effect	p	Indirect effect	p	Total effect	p
DASH→HGSf	-0.313	0.004	-0.004	0.872	-0.309	**0.003**
DASH→FSS	0.447	**0.002**	0.000	-	0.447	**0.003**
Sitting Time→ HGSf	-0.201	**0.011**	-0.001	0.780	-0.202	**0.010**
Sitting Time→ FSS	0.069	0.360	0.000	-	0.069	0.360
Age→HGSf	-0.305	**0.004**	0.001	0.774	-0.304	**0.003**
Age→FSS	-0.070	0.530	0.000	-	-0.070	0.530
FSS→HGSf	-0.009	0.864	0.000	-	-0.009	0.864
Total effect is calculated by summing indirect and direct effect.						

The second model was primarily aimed to be constructed on basic mediation procedure to assess the mediator effect of sitting time between age and HGSf. All procedures and interpretation of results were the same as the previous model. It was found that sitting time has a significant mediator effect between the age and HGSf (standardized indirect effect β=-0.004 (95% CI -0.075/-0.004), p = 0.019). Path coefficients as well as direct, indirect, and total effects along with p values are shown in Table 4. Figure 2 shows the basic mediation model diagram.

Table 4
The mediator effect of sitting time between age and HGSf

Paths	Direct effect	p	Indirect effect	p	Total effect	p
Age→ Sitting Time	0.150	0.032	-	-	0.150	**0.032**
Sitting Time→ HGSf	-0.190	0.017	-	-	-0.190	0.017
Age→HGSf	-0.340	**0.004**	-0.004	0.774	-0.344	**0.019**
Total effect is calculated by summing indirect and direct effect.						

Discussion

This study showed the significant predictive effects of age, sitting time, and patient reported upper extremity function score upon handgrip strength-related upper extremity functionality in patients after BC surgery. In addition, fatigue did not mediate or moderate the effects of age, sitting time, and DASH upon handgrip strength-related upper extremity function. However, sitting time was a significant mediator of the effect of age upon handgrip strength-related upper extremity function.

Since the HGS test is practical, safe, and repeatable; it is not only commonly used to assess upper extremity gross muscle strength but also to assess functional disability level because it is based on performance (19, 33). It is also stated that HGS has been used in the cancer population as a multifactorial morbidity predictor or to predict survival and/or treatment outcomes due to its safely applicability and objectivity (20, 34). Bilateral participation of the upper extremities is a prerequisite for optimal function. Studies reported that the mean HGS value must be considered in statistical analysis (35, 36). Hayes et al. (37) also pointed out that surgical and dominant side should also be considered when assessing upper extremity function. Thus, we chose to use a formulated mean HGS to control the dominant/non-dominant side and BMI. Owusu et al (38). reported that one unit decrease in HGS caused a 18% increase in functional limitation in older BC patients. In our study, we also found that one unit increase in age caused a 0.49-unit decrease in functionality. This was an expected result due to patients with older age show more vulnerability and functional limitation compared to the younger ones. Besides, patients may be affected more due to the multifactorial nature of cancer treatment. However, literature also supports that younger age might be a risk factor for functional limitation in patients with BC since younger patients might experience more mental affliction. (13).

A broad spectrum of complaints may be experienced with patients after BC surgery. Due to the affected upper extremity function, the DASH questionnaire is reported to be the optimal choice to assess function in BCS (21, 22). In our study, the DASH score was found relatively lower which indicates roughly 20% disability of upper extremity function. This might result from features of our cohort such as being the first three years after primary treatment and relatively younger age of our sample. However, a somewhat wide range of deviation of our study’s DASH score indicates patients may experience a broader range of symptoms. Yet, other researchers also reported nearly the same and heterogenous DASH scores in BC patients in parallel with our findings (24, 39, 40).

General upper extremity strength can be thought of as one of the key factors for optimal function. In 1 out of 4 women is shown that decreased shoulder girdle muscle strength in the surgical side in BCS. It is shown that ALND plays a role in decreased upper extremity strength in grade 1 evidence level (41). In parallel with these, DASH score and HGSf were found significantly correlated in a moderate level in our study. In addition, this result can also be originated from the that the great majority of our sample (83.8%) underwent ALND. On the other hand, Smoot et al (22). showed the significant predictive effect of HGS on the DASH score. We chose to predict HGSf with a DASH score and we found it also significant in our study. Each unit increase in DASH score results in a 0.31 unit decrease in HGSf. Studies reported that objective assessments show better results compared to subjective assessments in BC population (37). Smoot et al. (22) reported lower DASH scores which mean good functionality in patients who underwent

BC surgery even though they had somewhat upper extremity dysfunction. Therefore, we chose to use both DASH and HGS to predict upper extremity function.

Cancer-related fatigue is a common symptom that can be experienced with nearly 70% through 100% of patients and can persist a relatively long time even after completion of primary treatment in cancer patients. Since fatigue has a multifactorial nature, assessment of fatigue with a single perspective such as a visual analog scale has been debated as being inadequate (42). In our study, we used FSS to assess self-reported fatigue. A relatively moderate mean fatigue score was obtained due to relatively middle-aged BCS participated in our study. It was the same as in Gerber et al (43). ‘s study, in which the mean fatigue score was reported nearly 25% and they also concluded that younger age might have played a role in this. Yet these researchers used a numeric scale instead of a questionnaire. FSS was also found significantly correlated in a moderate level with the DASH questionnaire. It is important to show close relationship between fatigue and function. However, in path analysis, fatigue did not play a role as a moderator or mediator between sitting time, age, DASH and HGSf. Even increased age is known as a risk factor for increased perception of fatigue, we did not find any significant correlation between age and fatigue. This result might be originated from the cross-sectional nature of fatigue assessment of this study since FSS items should be scored according to the previous seven days. In addition, questions of FSS related to family and/or other responsibilities might have underscored since mothership or wifeship duties are sometimes can be overestimated in family life especially in eastern countries.

Physical inactivity is widely seen in BC patients not only during the cancer treatment but also during the survivorship period even though the vast majority of evidence of deleterious effects of physical inactivity are known. Irwin et al. (15) reported a significant decrease in physical activity in patients with BC within one year following the diagnosis while Ottenbacher et al. (44) reported a 37% decrease in physical activity compared to the previous year before diagnosis in BCS. In our study, we found a mean sitting time of nearly six hours a day. Though physical activity and fatigue are shown as closely related in the literature (43, 45), we did not find a significant correlation between physical inactivity and FSS. We think that patients might not have reflected their real physical inactivity level due to family and mothership responsibilities. In addition, the pandemic period might have also affected this rate. This result can also explain the relatively lower level of fatigue. However, we found that each unit increase in sitting time as hour caused a 1.14 unit decrease in HGSf. In addition, physical inactivity mediated the effect of age on HGSf. This relatively substantial result is valuable to affirm that irrespective of age, increased physical inactivity reduces the strength-related function.

This study has some limitations. First, due to the cross-sectional nature of this study and scale-based assessments, fluctuations about perceived symptoms and recall bias might have inadequately affected the results or overestimated. However, using together objective and relatively subjective outcomes such as HGS and DASH might be thought as strengths. Secondly, performing a path analysis within a structural equation modeling might be thought of as a strength since this method has been tried to be recently known in health science literature.

Conclusion

Since overall survival is increased in BC, management of secondary problems which are frequently experienced with patients is gaining much more importance. However, detecting problems might be cumbersome due to its multifactorial nature; true determination can be the first step to improve clinical outcomes in the long-term period. It is shown that increased physical inactivity and age play a major role in strength-related upper extremity function. Patient-specific physiotherapy programs should consider this especially in older and physically inactive BC patients. Thus, using advanced methods such as path analysis can enlighten our view of cancer populations whose experienced symptoms can affect one another. We believe that extending this method with more complex models in health science literature especially in the cancer population might contribute substantial understanding in the biopsychosocial frame in the context of BCS.

Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material: Not applicable

Code availability: Not applicable

Author Contributions: All authors contributed to the study conception and design. Material preparation and data collection were performed by Alper Tuğral, Yeşim Bakar and Murat Akyol. Statistical analysis was performed by Alper Tuğral. The first draft of the manuscript was written by Alper Tuğral and Yeşim Bakar. All authors commented on previous versions of the manuscript and all authors read and approved the final manuscript.

Ethics approval: Ethical approval was granted by Izmir Bozyaka Research and Teaching Hospital Ethical Board of Clinical Studies 02/11092019.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Patients signed informed consent regarding publishing their data.

Acknowledgements: The Authors would like to thank patients who voluntarily participated to this study.

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Figures

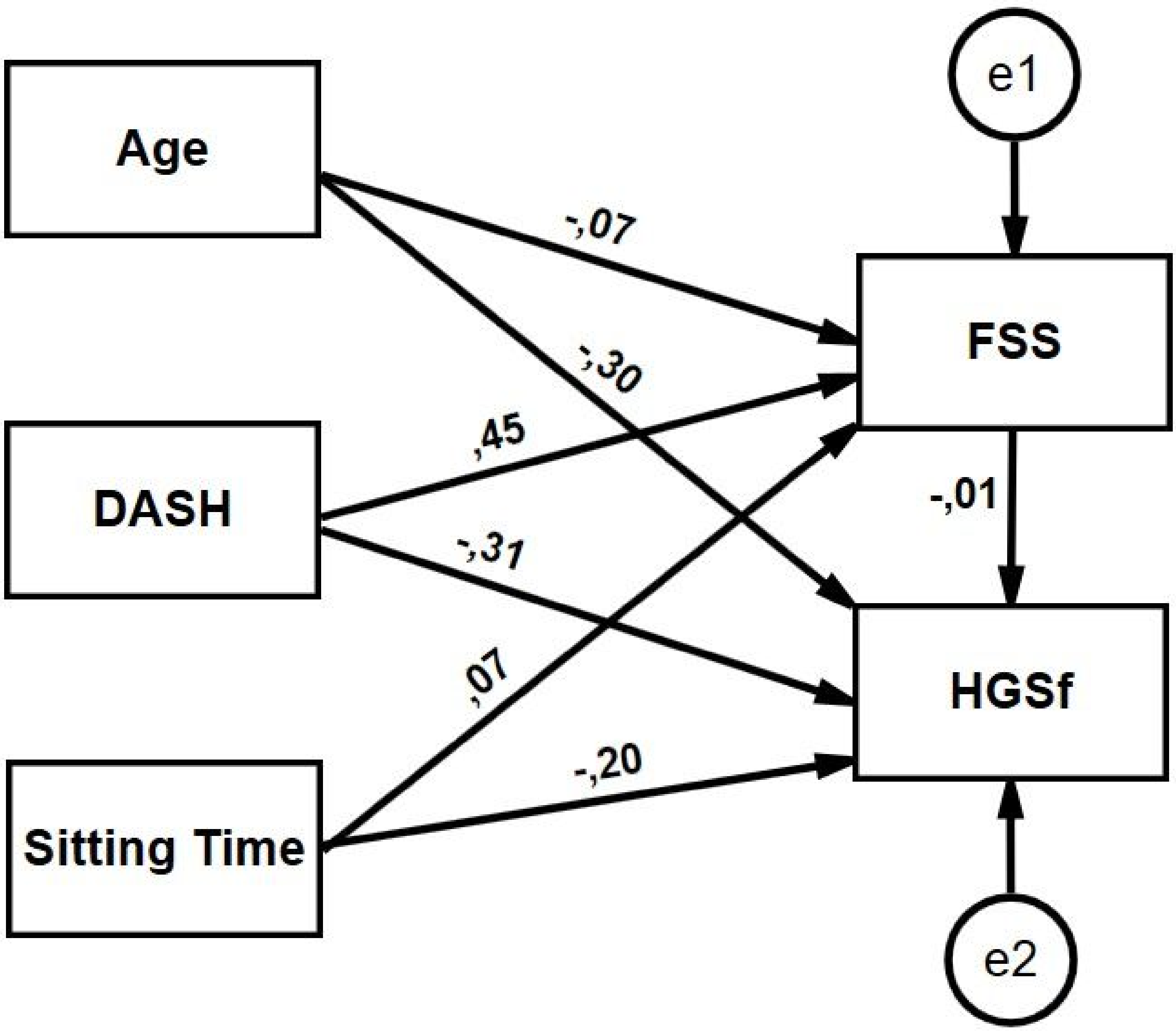

Figure 1

The hypothesized structural equation modeling depicting the mediator effect of fatigue between age, patient reported upper extremity function, sitting time and formulated handgrip strength. Values show regression coefficients.

DASH: Disabilities of Arm, Shoulder and Hand Questionnaire, FSS: Fatigue Severity Scale, HGSf: Formulated Handgrip Strength, e1: Error term 1 and e2: Error term 2 show the measurement error of endogenous variables.

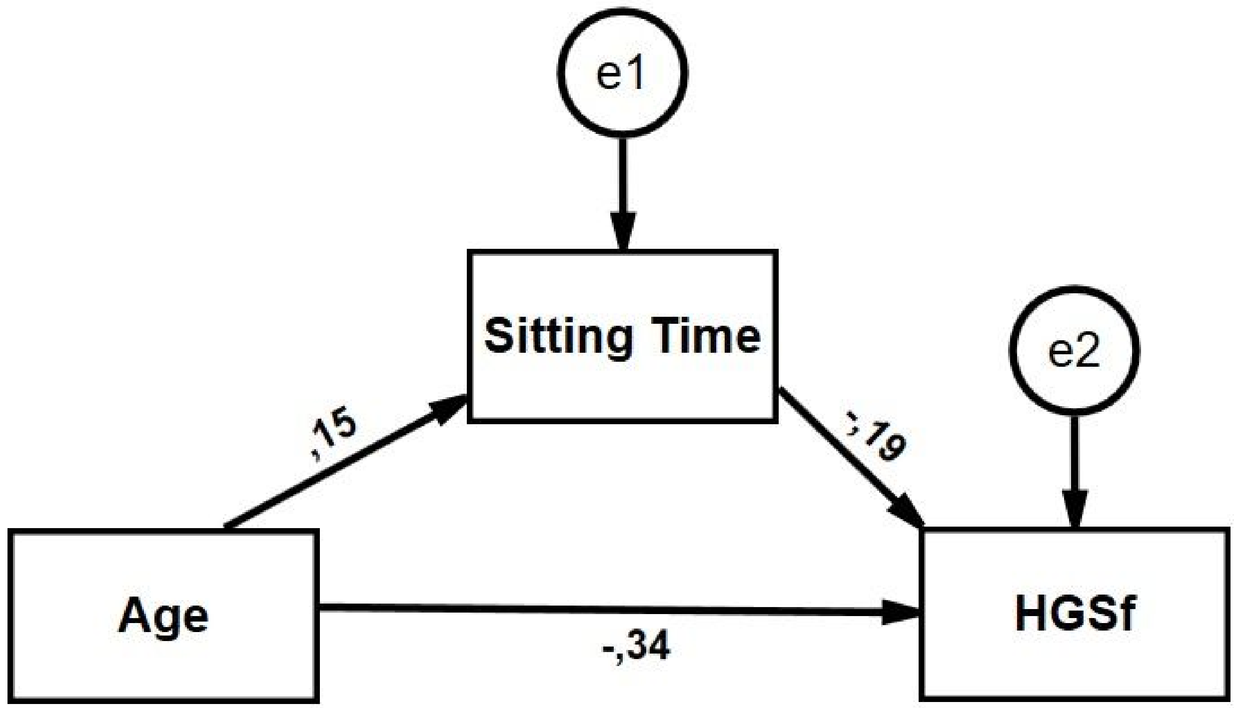

Figure 2

The hypothesized model of the basic mediation modeling of the mediation effect of sitting time between age and formulated handgrip strength. Values show regression coefficients. The mediating effect of sitting was found significant between age and HGSf (95% CI -0.075/-0.004, p=0.019).

HGSf: Formulated Handgrip Strength, e1: Error term 1 and e2: Error term 2 show the measurement error of endogenous variables

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