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Obesity and Cognitive Dysfunction in Heart Failure: The Role of Hypertension, Type 2 Diabetes, and Physical Fitness

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Abstract

Background—Cognitive impairment is common in heart failure (HF). Obesity is a known risk factor for cognitive dysfunction in HF, though the mechanisms remain unclear. Obesity increases risk for conditions like hypertension and type 2 diabetes mellitus (T2DM), as well as poor fitness levels and this may serve as one possible pathway accounting for association between obesity and cognitive dysfunction.

Aims—We used structural equation modeling (SEM) to test whether the combination of hypertension, T2DM, and reduced fitness mediate the association between obesity and cognitive dysfunction.

Methods—200 HF patients completed neuropsychological testing and a physical fitness assessment. Hypertension and T2DM were ascertained via self-report and medical records. Body mass index (BMI) was calculated.

Results—43% of the sample was obese. Hypertension (70%) and T2DM (36%) were common, and fitness levels were reduced. The SEM model with these factors as mediators between BMI and cognitive function demonstrated excellent fit (CFI = 0.98; *RMSEA* = .03). Higher BMI correlated with hypertension, T2DM, and poorer fitness. Each of these factors predicted worse cognition. Models that isolated medical comorbidities and physical fitness as the mediator were weaker than the full model.

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Declaration of Conflicting Interests

None declared

Conclusions—Increased risk for medical comorbidities and reduced fitness levels helped to explain the negative effects of obesity on cognitive dysfunction in HF. Prospective studies should confirm this pattern and examine weight loss benefits cognitive function in HF. Keywords: Physical fitness; cognitive function; heart failure; obesity; hypertension; type 2 diabetes mellitus

Introduction

Patients with heart failure (HF) are at risk for accelerated cognitive decline, Alzheimer's disease, and vascular dementia.^{1,2} HF patients also exhibit more subtle impairments in cognitive function relative to healthy controls and medical patients, including in domains of memory, psychomotor speed, and executive function.³ The manifestation of cognitive impairment in HF is believed to stem from a combination of medical and clinical factors, most notably hypertension, type 2 diabetes mellitus (T2DM), and poor physical fitness. Hypertension and T2DM are among the most common comorbid conditions in HF^{4,5} and severe cardiac dysfunction and high rates of physical inactivity inevitably leads to reductions in physical fitness in this population.^{5–8} All of these factors are indeed well known predictors of poor neurocognitive outcomes in older adults with HF.^{9–11}

Although less well understood, obesity can be found in more than 40% of HF patients and suggested to be another important risk factor for cognitive dysfunction in this population.¹² Elevated BMI in HF is independently linked with brain abnormalities and reduced attention/executive function and language abilities.¹³ The adverse effect of obesity on cognitive function is also well documented in non-HF populations, including healthy adults.¹⁴ Despite these findings, the mechanisms by which obesity negatively impacts cognition in HF remain unclear and likely involves multiple physiological processes.

A combination of comorbid medical conditions and decreased physical fitness may provide a starting point to explain the adverse effects of obesity on cognitive function. Specifically, obesity is often comorbid to hypertension and T2DM, as >70% of obese individuals are hypertensive¹⁵ and nearly 90% have T2DM.¹⁶ Consistent with this notion, obese persons are also at risk for poor fitness given these individuals have been shown to exhibit >23 hours of sedentary behaviors per day.¹⁷ This pattern of findings raises the possibility that obese HF patients may be at greatest risk for poor neurocognitive function. Indeed, hypertension, T2DM, and decreased fitness levels are not only key contributors to obesity-related cognitive deficits in HF, but also represent well-established risk factors for dementia in non-cardiac populations.^{18–22}

Despite these findings, no study has used a multivariate model to empirically examine the role of hypertension, T2DM, and physical fitness in the obesity and cognitive dysfunction phenomenon, regardless of the population. The purpose of the current study was to use a model-based approach to determine whether the combination of comorbid medical conditions (i.e., hypertension and T2DM) and physical fitness mediate the association between obesity, as operationalized by body mass index (BMI), and cognitive function in a sample of older adults with HF.

Methods

Participants

The current study consisted of patients with HF recruited for participation in a larger NIH-funded study examining the effects of cardiac rehabilitation on neurocognitive outcomes in older adults with HF. Patients were recruited from known cardiac populations within cardiology practices at Summa Health System in Akron, Ohio, a mid-western city in Northeast, Ohio. Summa Health System is a network of teaching, and medical school affiliated hospitals. Participants reflect the HF population receiving treatment at this facility in terms of age, gender, race, ethnicity, and socioeconomic status.

The current sample included 200 consecutive HF patients that met the larger study's strict inclusion/exclusion criteria and completed a baseline assessment prior to cardiac rehabilitation. Inclusion criteria included between the ages of 50–85 years, English speaking, and a diagnosis of New York Heart Association (NYHA) HF class II, III, or IV at the time of enrollment. Potential participants were excluded for a history or current diagnosis of a significant neurological disorder (e.g. dementia, stroke), head injury >10 minutes loss of consciousness, severe psychiatric disorder (e.g. schizophrenia, bipolar disorder), substance abuse/dependence, and/or Stage 5 Chronic Kidney Disease. Participants averaged 68.19 (SD = 9.00) years of age, were 36.0% female, and 83.5% Caucasian. A medical record review indicated that the sample had an average left ventricular ejection fraction of 40.44 (SD = 14.41).

Measures

Physical Fitness—The 2-minute step test (2MST) assessed physical fitness.²³ The 2MST requires participants to step in place lifting his/her knees to a marked target set on the wall set at the midpoint between the kneecap and crest of the iliac for a 2-minute period. Greater step count reflects better fitness. Average step count for healthy males between the ages of 60–69 = 86 to 116; 70–79 = 73 to 110; 80–89: 59 to 103. Average step counts for healthy females according to age groups include: 60–69: 73 to 107; 70–79: 68 to 101; 80–89: 55 to 91.²³ The 2MST is a valid measure of fitness, as it has been linked with metabolic equivalents derived from stress testing and is also a sensitive predictor of neurocognitive outcomes in HF.^{11,23,24}

Cognitive Function—All participants were administered a brief neuropsychological test battery to assess cognitive function in multiple domains, including attention, executive function, and memory. All measures demonstrate strong psychometric properties, including validity and reliability. The domains and their respective measures include:

Attention/Executive Function: Trail Making Test A and B,²⁵ Digit Symbol Coding,²⁶ and Letter Number Sequencing.^{27,28}

Memory: California Verbal Learning Test-Second Edition (CVLT-II) short delay free recall.²⁹

Language: Animal fluency test³⁰ and Boston Naming Test.³¹

Demographic and Medical History—Demographic and medical characteristics were collected through participant self-report and supplemented and corroborated by medical record review. Through these methods, a diagnostic history of hypertension and T2DM were ascertained.

Procedures

The local Institutional Review Board (IRB) approved the study procedures and all participants provided written informed consent prior to study enrollment. During a baseline assessment, participants completed demographic and medical self-report measures, and a medical record review was performed. Height and weight were measured and used to compute BMI according to the standard formula. Participants completed the 2MST and were also administered a comprehensive cognitive test battery. Trained research assistants, under the supervision of a licensed neuropsychologist, performed all procedures.

Statistical Analyses

Structural equation modeling (SEM) was used to test the a priori derived model depicted in Figure 1. The model consists of one latent factor used to represent cognitive function. The seven neuropsychological measures served as the indicators of the endogenous latent variable cognitive function. Cognitive tests were transformed to T-scores (a distribution with a mean of 50 and a standard deviation of 10) using normative data (e.g., Halstead-Reitan) to account for the influence of demographic factors, including age and gender in the case of the CVLT-II. Higher scores represented better performance for all cognitive variables. The parameter of a single indicator was fixed at 1 in order to correct for scaling. Hypertension and T2DM (1 = positive history; 0 = negative history) and the 2MST served as manifest mediator variables. BMI represented the exogenous predictor.

A measurement model first examined model fit among the indicators with cognitive function. The strength of the relationship between BMI and the latent factor cognitive function was then tested. A full structural model was then performed to examine model fit with comorbid medical conditions and the 2MST as the mediators between obesity and cognitive function. EQS software using maximum likelihood approach tested the SEM. Model fit was evaluated by the chi-square value, and the comparative fit index (CFI), and the root mean-square error of approximations (RMSEA). A non-significant chi-square, and commonly accepted values of the CFI and RMSEA were used to determine goodness of fit (e.g., CFI .90; RMSEA .08).^{32,33} The model Akaike's Information Criteria (AIC) was used for non-nested model comparison; that is, to compare independent models that isolated medical comorbidities and physical fitness as mediators. A smaller AIC is suggestive of a better model.

Results

Obesity and Physical Fitness

The average BMI was 30.63 (SD = 7.07), placing the sample in the obese range. Within study participants, 43.0% exhibited a BMI consistent with obesity (i.e., ≥ 30), 38.5% fell in the overweight BMI classification (i.e., 25 to 30), and 18.5% were considered normal weight

(i.e., 18.5 to 25). Multivariate analysis of variance showed that overweight participants were significantly older than obese individuals ($F(2,197) = 4.98, p = 0.01$). No between BMI group differences emerged on other demographic variables (e.g., race, sex or education) or for left ventricular ejection fraction ($p > 0.05$ for all). Medical comorbidities were prevalent in this sample, with nearly 70% of HF patients having a diagnostic history of hypertension and 36.0% having T2DM. As expected, comorbid medical conditions were more prevalent in overweight and obese patients with HF than their normal weight counterparts. Refer to Table 1 for between BMI group differences on medical and demographic characteristics in the current sample.

In terms of physical fitness, the mean 2MST of the sample was 61.53 (SD = 23.47). Both males (mean (SD) = 64.93 (23.45) steps) and females (mean (SD) = 55.49 (22.41) steps) demonstrated decreased levels of fitness.

Cognitive Function

As a whole, participants performed in the average range on measures of attention, memory, and language. However, compared to normative data, this sample exhibited low average performance on the Trail Making Test B, a task of executive function. Nonetheless, many participants exhibited impairment on several cognitive tasks. Specifically, when using clinical convention to define impairment (i.e., a T-score 1.5 SD below the mean of normative standards), up to 11.0% of the sample demonstrated impairments in attention, >20% of the sample exhibited impairments in executive function, and 13.5% of the sample had impairments in language abilities. Memory deficits were less common. See Table 2.

Measurement Model

A measurement model was performed to examine fit of the neuropsychological indicators of the latent construct cognitive function. Digit symbol coding was fixed at 1.0. The measurement model demonstrated excellent fit: $\chi^2(14, 200) = 21.38, p = 0.09, CFI = 0.98, RMSEA = 0.05$ (90% CI = 0.00, 0.09). Factor loadings were significant for all neuropsychological measures ($\beta = 0.32$ to $0.76, p < .05$ for all).

A structural model then examined the strength of the relationship between BMI and the latent factor cognitive function. This model demonstrated excellent fit: $\chi^2(20, 200) = 24.88, p = 0.21, CFI = 0.99, RMSEA = 0.04$ (90% CI = 0.00, 0.07). BMI emerged as a significant predictor of cognitive function ($\beta = -0.22, p < 0.05$), with higher BMI predictive of worse cognitive function. Follow-up bivariate correlations showed specific effects between BMI with cognitive function in every domain: CVLT short delay free recall ($r(198) = -0.15, p = 0.03$), Trail Making Test A ($r(198) = -0.15, p = 0.04$), Trail Making Test B ($r(198) = -0.17, p = 0.02$), Animal fluency ($r(198) = -0.15, p = 0.03$), Boston Naming Test ($r(198) = -0.17, p = 0.02$), and Digit Symbol Coding ($r(198) = -0.15, p = 0.03$). No such pattern emerged for Letter Number Sequencing ($p > 0.05$).

Structural Model

Table 3 shows the covariance matrix between variables tested in the model. The effect of BMI on cognitive function was attenuated to nearly zero ($\beta = -0.02, p > 0.05$) when the

mediators hypertension, T2DM, and 2MST were introduced. The model demonstrated excellent fit: $\chi^2(41, 200) = 49.43, p = 0.17, CFI = 0.98; RMSEA = .03$ (90% CI = 0.00, 0.06). Examination of the structural pathways showed that higher BMI was associated with a greater likelihood of having a diagnostic history of hypertension ($\beta = 0.25, p < 0.05$) and T2DM ($\beta = 0.38, p < 0.05$) as well as worse 2MST performance ($\beta = -0.26, p < 0.05$). In turn, the pathways connecting hypertension ($\beta = -0.15, p < 0.05$), T2DM ($\beta = -0.20, p < 0.05$), and 2MST ($\beta = 0.37, p < 0.05$) with cognitive function were all significant. A diagnostic history of hypertension and T2DM and worse 2MST performance were all associated with decreased cognitive function. Sobel test revealed significant indirect effects of BMI on cognitive function through hypertension, T2DM, and 2MST ($p < 0.05$). See Figure 1 for standardized parameter estimates.

Non-Nested Model Comparisons

Two models were conducted that isolated medical comorbidities (i.e., hypertension and T2DM) and then the 2MST as the mediators. As expected, both models demonstrated excellent fit: Hypertension and T2DM Model ($\chi^2(33, 200) = 37.37, p = 0.28, CFI = 0.99; RMSEA = .03$ (90% CI = 0.00, 0.06); 2MST Model ($\chi^2(26, 200) = 29.82, p = 0.28, CFI = 0.99; RMSEA = .03$ (90% CI = 0.00, 0.06). The AIC value was slightly smaller for the medical covariate model (AIC = -28.63) relative to the physical fitness model (AIC = -22.18), suggesting hypertension and T2DM possibly represent stronger mediators. Nevertheless, the full model (i.e., Figure 1) still exhibited the smallest AIC (AIC = -32.57) and indicates that the negative effects of obesity on cognitive function is likely a combination of medical factors and poor physical fitness.

Discussion

Obesity was prevalent and increased BMI was linked with cognitive dysfunction in this sample of older adults with HF. Obesity is a well-recognized risk factor for poor neurocognitive outcomes,³⁴ though the mechanisms for this relationship remain poorly understood. The current study extends the literature by showing that the combination of common comorbid medical conditions and decreased fitness may provide an initial model for explaining the obesity and cognitive dysfunction phenomenon in persons with HF. Several aspects of these findings warrant further review.

The current findings suggest that obesity may lead to cognitive dysfunction in persons with HF through its association with increased risk for hypertension and T2DM. HF stems from medical conditions (e.g., hypertension, T2DM) that damage the cardiac muscle³⁵ possibly due to a longstanding history of being overweight or obese. Indeed, the prevalence of hypertension and T2DM rapidly increases with rising BMI.^{15,16,36} These medical factors are well-established risk factors for cognitive impairment in older adults with and without HF.^{9,10,37,38} There are several cerebrovascular-related mechanisms to explain the neurocognitive impairments that accompany hypertension and T2DM. Hypertension leads to brain abnormalities (e.g., white matter hyperintensities) perhaps via endothelial dysfunction, atherosclerosis of the cerebral arteries, and/or altered cerebral hemodynamics.^{39–42} Similar microvascular disease (e.g., endothelial dysfunction) processes may also account for reduced

brain integrity in T2DM, but more unique factors to T2DM such as hyperinsulinemia and poor glycemic control are also suggested to impact neurocognitive outcomes.^{43,44} Indeed, the physiological abnormalities of hypertension and T2DM likely interact to further exacerbate cognitive impairment. Prospective studies that employ advanced neuroimaging and direct assessments of hypertension and T2DM are much needed to confirm their role as mediators between obesity and cognitive dysfunction in HF and elucidate underlying mechanisms.

We also found that obesity adversely affects cognitive function in HF through its negative impact on physical fitness levels. Poor fitness is considered a hallmark of HF due to cardiac dysfunction and resulting exercise intolerance.⁶ Obesity is known to promote cardiac dysfunction⁴⁵ and can exacerbate poor fitness in this population through increased sedentary behavior.^{17,46,47} Regardless of the population, decreased fitness often co-exists with obesity and predicts poor neurocognitive outcomes in HF and non-HF samples.^{11,21,22} Poor fitness in non-cardiac older adults and in persons with HF is associated with decreased brain volume,^{23,48} suggested to stem from reduced vascular health. For instance, poorer fitness is linked with an array of vascular abnormalities that influence cognitive function such as endothelial dysfunction and additive reductions in systemic and cerebral perfusion.^{6,10,49–53} Prospective studies are needed to determine whether poor fitness is one mechanism by which obesity may accelerate risk for cognitive decline in older adults with HF.

Taken together, interventions that target improved medical status and physical fitness in obese HF patients may help to attenuate cognitive deficits in this population. Specifically, participation in recommended medication and exercise regimens may benefit cognitive outcomes in HF. Although the current study did not directly assess adherence or ascertain whether medical comorbidities were controlled versus uncontrolled, past work shows that medication therapy for hypertension and T2DM attenuates risk for cognitive impairment.^{54,55} Participation in structured exercise regimens (e.g., cardiac rehabilitation) may also improve cognitive function in HF through increased fitness levels and better vascular function (e.g., cerebral perfusion).⁵⁶ Indeed, exercise interventions have been linked with improved cognitive function in both HF and obese older adults.^{56,57} Even daily physical activity levels have been suggested to have possible neuroprotective effects in HF patients.⁷ Future work should examine the neuroprotective effects of medication treatment and exercise interventions (e.g., cardiac rehabilitation) in obese HF patients.

The generalizability of the current findings is limited in several ways. Although the literature strongly supports the directionality of our findings, prospective studies are needed to confirm the role of medical comorbidities and physical fitness in the relationship between obesity and cognitive dysfunction. Studies with extended follow-ups will also help to clarify the role of BMI in the actual development of medical and clinical comorbidities, including the onset of cardiac failure. Longitudinal studies that employ healthy controls and medical comparison groups are also needed to elucidate the role of adiposity in cognitive outcomes in older adults with HF. We also assessed hypertension and T2DM via diagnostic status. This method is valid and may be sensitive to the long-term effects of these conditions on the brain; however, future research should investigate the impact of these conditions on neurocognitive outcomes using direct measurements (e.g., HbA1C, blood pressure readings).

Likewise, future work that employs more sensitive measures of physical fitness (e.g., stress testing) is also needed to clarify the relationships among obesity, fitness, and cognition in older adults with HF. Lastly, obesity may negatively impact cognitive function through many other novel mechanisms that were not examined in this study, including genetic polymorphisms (e.g., Fat Mass and Obesity gene) and/or altered appetitive hormones such as leptin and ghrelin.^{58–60}

In brief summary, the current study suggests that the combination of common comorbid medical conditions and reduced physical fitness help to explain the negative effects of obesity on cognitive dysfunction in HF. Prospective studies should examine whether exercise programs in HF can attenuate elevated risk for cognitive decline via improve medical comorbidity status and better physical fitness levels.

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Figure 1. Possible Mechanisms for the Effects of BMI on Cognitive Function in Patients with Heart Failure (N = 200)

Notes. The pathway between cognitive function and Digits was fixed. Standardized parameters estimates are presented in the model; significance levels for these paths are based on the unstandardized estimates.

Abbreviations—2MST = 2 minute step test; TMTA = Trail Making Test A; TMTB = Trail Making Test B; Digits = Digit Symbol Coding; LNS = Letter Number Sequencing; CVLT= California Verbal Learning Test Short Delay Recall; BNT = Boston Naming Test; BMI = Body Mass Index

* $p < .05$

Table 1

Between BMI Group Differences among Older Adults with Heart Failure

Demographic Characteristics	Overall Sample	Normal Weight	Overweight	Obese	χ^2/F statistic
<i>N</i>	200	37	77	86	--
Age, mean (SD)	68.19 (9.00)	67.35 (9.63)	70.64 (9.06)	66.36 (8.23)	4.98**
Sex (% Women)	36.0	43.2	27.3	40.7	4.21
Years of Education, mean (SD)	13.59 (2.64)	13.70 (2.62)	13.68 (2.83)	13.45 (2.49)	0.19
Race (% Caucasian)	83.5	86.5	83.1	82.6	8.28
Medical Characteristics					
LVEF, mean (SD)	40.44 (14.41)	38.49 (14.58)	38.92 (15.08)	42.67 (13.57)	1.74
Hypertension (%)	69.5	48.6	64.9	82.6	15.26**
Diabetes (%)	36.0	16.2	29.9	50.0	14.86**
Overall 2MST, mean (SD)	61.53 (23.47)	67.14 (22.28)	63.84 (22.33)	57.05 (24.38)	3.06*

Note.

** $p < 0.01$;

* $p < 0.05$;

LVEF = Left Ventricular Ejection Fraction; 2MST = two minute step test; Sample size for LVEF is 192 due to missing data.

Table 2

Cognitive Test Performance (N = 200)

	Mean (SD)	% < 35*
Trail Making Test A	49.31 (11.64)	11.0
Trail Making Test B	43.52 (18.12)	20.5
Digit Symbol Coding	47.42 (9.27)	10.0
Letter Number Sequence	50.51 (8.99)	4.0
CVLT-II SDFR	47.38 (10.51)	6.0
Animals	54.52 (11.21)	3.0
Boston Naming Test	49.21 (15.00)	13.5

Note. Values are T-scores;

* % < 35 = impaired test performance;

CVLT-II SDFR = California Verbal Learning Test Short Delay Free Recall

Table 3

Bivariate Covariance Matrix

	2MST	HTN	T2DM	CVLT-II	TMT A	TMT B	Animals	BNT	Digits	LNS	BMI
2MST	550.67	--	--	--	--	--	--	--	--	--	--
HTN	-2.43	0.21	--	--	--	--	--	--	--	--	--
T2DM	-2.07	0.04	0.23	--	--	--	--	--	--	--	--
CVLT-II	21.65	-0.33	-0.03	110.54	--	--	--	--	--	--	--
TMT A	85.10	-1.15	-1.28	27.92	135.41	--	--	--	--	--	--
TMT B	141.46	-1.95	-1.92	40.03	123.03	328.33	--	--	--	--	--
Animals	58.07	-0.29	-0.54	23.90	34.96	66.36	125.57	--	--	--	--
BNT	103.22	-1.19	-0.77	38.71	71.40	109.61	60.55	224.88	--	--	--
Digits	77.14	-0.73	-1.28	18.91	62.92	93.36	39.58	55.48	85.86	--	--
LNS	34.80	-0.59	-0.48	23.04	37.84	78.25	28.75	53.70	35.66	80.90	--
BMI	-43.39	0.82	1.29	-11.61	-11.94	-21.27	-12.08	-17.81	-10.12	-5.27	50.01

Note. 2MST = 2-minute step test; HTN = hypertension; T2DM = type 2 diabetes mellitus; TMT A = Trail Making Test A; TMT B = Trail Making Test B; Digits = Digit Symbol Coding; LNS = Letter Number Sequencing; CVLT-II = California Verbal Learning Test-II Long Delay Recall; ADL = Activities of Daily Living