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IMPACT OF COGNITIVE STATUS ON EXERCISE PERFORMANCE AND QUALITY OF LIFE IN PATIENTS WITH SYMPTOMATIC PERIPHERAL ARTERY DISEASE

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Abstract

Purpose—We determined whether scores on a cognitive screening measure were associated with the primary outcome measure of peak walking time (PWT) and with secondary outcome measures related to mobility, community-based ambulation, health-related quality of life (QoL), and vascular function in patients with claudication and PAD.

Methods—Gross cognitive status of 246 PAD patients was assessed with the Mini-Mental State Examination (MMSE) questionnaire. Patients were grouped according to whether they had a perfect MMSE score of 30 points (n=123) or whether they missed one or more points (n=123). Patients were characterized on numerous outcomes, including PWT during a treadmill test and QoL.

Results—Compared to the Higher MMSE group, there was a trend for lower PWT in the Lower MMSE group (p=.06) after adjusting for age, sex, race, and education level (model 1), which became significant (380±250 s vs. 460±270 s, p<.05) after adjusting for model 1 plus coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and arthritis (model 2). Multiple domains of QoL were lower (p<.05) in the Lower MMSE group after adjusting for model 1, but only mental health remained lower (75±20% vs. 80±5%, p=.02) after further adjustment with model 2.

Conclusions—In symptomatic patients with PAD, lower cognitive screening scores were associated with greater ambulatory impairment than in patients with higher MMSE scores. Furthermore, worse cognitive status was associated with lower scores in multiple dimensions of health-related QoL, all of which except mental health were explained by the comorbid conditions of CAD, COPD, and arthritis. The clinical significance is that there is a need for enhanced

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cognitive and mental health screening as potential indicators of poor outcome among symptomatic patients with PAD. Furthermore, patients identified as having worse cognitive status may be in greatest need of intervention to improve ambulation and quality of life related to mental health.

INTRODUCTION

Peripheral artery disease (PAD) is a significant medical concern, as it is a highly prevalent,[1] costly,[2] disabling,[3, 4] and deadly condition[5]. A less appreciated concern of PAD is that it is a marker of cognitive impairment and dementia[6] and is associated with a 2-fold greater risk for vascular dementia[7]. We have shown that patients with claudication and PAD have worse performance on cognitive tests of nonverbal memory, concentration, executive function, perceptuo-motor speed, and manual dexterity than healthy controls and carefully screened older adults with hypertension[8].

Patients with PAD are at high risk for impaired cognitive function, at least in part, because PAD is a marker of overt atherosclerosis in the cerebral vasculature, which may disrupt the finely tuned regulation between the brain and vascular perfusion, thereby leading to cognitive dysfunction[9]. The high burden of cardiovascular risk factors in patients with PAD[10] may lead to further cognitive dysfunction, as hypertension,[11] diabetes,[12, 13] dyslipidemia,[12, 14] obesity,[15] cigarette smoking,[16] and inflammation[17] all negatively impact cognitive function.

Serious cardiovascular consequences are associated with cognitive dysfunction, as even subtle deficits in cognitive performance increase the risk of stroke, hospitalization for congestive heart failure, and cardiovascular death[18]. Furthermore, poorer cognitive function, particularly executive function, is associated with impaired gait velocity and stability in older adults[19]. However, little is known about the impact of cognitive dysfunction on physical function and disability in patients with PAD who already have some degree of ambulatory impairment due to claudication. Therefore, the aim of this study was to determine whether a commonly used cognitive screening measure was associated with the primary outcome measure of peak walking time (PWT) and with secondary outcome measures related to mobility, community-based ambulation, health-related quality of life, and vascular function in patients with claudication and PAD. Compared to those with better cognitive status, we hypothesized that patients with lower cognitive screening scores would have shorter PWT, worse mobility, lower community-based ambulation, worse health-related quality of life, and greater impairment in vascular function.

METHODS

Patients

Approval and Informed Consent—The institutional review board at the University of Oklahoma Health Sciences Center (HSC), and the Research and Development committee at the Oklahoma City VA Medical Center approved the procedures of this study. Written informed consent was obtained from each patient at the beginning of investigation.

Recruitment—Vascular labs and vascular clinics from the University of Oklahoma HSC referred patients for possible enrollment into an exercise rehabilitation program to treat leg pain secondary to PAD[20].

Medical and Cognitive Screening

Patients were evaluated in the morning at the Clinical Research Center (CRC), at the University of Oklahoma HSC. Patients arrived fasted, but were permitted to take their usual medications. To begin the study visit, patients completed the Mini-Mental State Examination (MMSE) questionnaire[21] and were grouped according to whether they had a perfect MMSE score of 30 points (n=123) or whether they missed one or more points (n=123). Patients were evaluated with a medical history and physical examination in which demographic information, height, weight, waist circumference,[22] cardiovascular risk factors, co-morbid conditions, claudication history, ankle-brachial index (ABI), blood samples, and a list of current medications were obtained.

Inclusion and Exclusion Criteria—Patients with PAD were included in this study if they met the following criteria for vascular claudication: (a) a history of ambulatory leg pain, (b) ambulatory leg pain confirmed by treadmill exercise,[3] and (c) an ABI ≤ 0.90 at rest[23] or ≤ 0.73 after exercise[24]. Patients were excluded for the following conditions: (a) absence of PAD (ABI > 0.90 at rest and ABI > 0.73 after exercise), (b) non-compressible vessels (ABI > 1.40), (c) asymptomatic PAD, (d) use of medications indicated for the treatment of claudication (cilostazol or pentoxifylline) initiated within 3 months prior to investigation, (e) exercise limited by other diseases or conditions, (f) active cancer, (g) end stage renal disease defined as stage 5 chronic kidney disease, and, (h) abnormal liver function. A consecutive series of 339 individuals were evaluated for eligibility, and 246 patients were deemed eligible for inclusion into the study and 93 patients were ineligible.

Measurements

MMSE—The MMSE is a 30-item measure of cognitive status originally designed for use in hospitalized patients[21]. It is the most commonly used screening measure for cognitive impairment and dementia, and includes items that examine orientation, registration, attention, calculation, memory, language, and ability to follow simple commands. Thus, it is considered a very gross cognitive screening measure, rather than a test of the major domains of cognitive function.

Maximal Treadmill Test: Patients performed a graded treadmill test to determine study eligibility and then repeated the test on a following visit within one week to obtain the outcome measures of claudication onset time (COT) and peak walking time (PWT) as previously described. The measurements of COT and PWT during our graded treadmill test are highly stable and reliable with repeat testing[3]. Ankle systolic blood pressure was obtained from the more severely diseased lower extremity before and after the maximal treadmill test[3] to determine the ischemic window[25]. Calf muscle hemoglobin oxygen saturation was measured using a continuous-wave, NIRS unit (InSpectra model 325; Hutchinson Technology, Inc, Hutchinson, MN), an optical cable attached to a 25-mm probe, InSpectra software (version 2.0), and a dedicated laptop computer[26].

6-Minute Walk Test: Patients performed a 6-minute walk test and the total walking distances was recorded, as previously described[27].

Gait Speed Obtained from a 4-Meter Walk Test: Gait speed was measured from a 4-meter walk test in a hallway[28]. Patients performed this test twice at their usual walking pace, and the faster of the two walks was used in the analyses. The test-retest intraclass reliability coefficient is R = 0.96 for the velocity to walk four meters[29]. No gait testing was performed prior to the 4-meter walk trials in this investigation.

Ambulatory Activity Monitoring: Daily ambulatory activity was assessed during seven consecutive days using a step activity monitor (StepWatch3™, Orthoinnovations, Inc., Oklahoma City, OK) as previously described[30]. The step activity monitor is accurate and reliable[30].

Walking Impairment Questionnaire (WIQ): Self-reported ambulatory ability was obtained using a validated questionnaire for PAD patients that assesses ability to walk at various speeds and distances, and to climb stairs[31].

Health-Related Quality of Life: Self-reported mental and physical function was assessed with the Medical Outcomes Study Short-Form 36 (MOS SF-36) General Health Survey[32].

Diastolic Pulse Contour Analysis: Large artery elasticity index (LAEI) and small artery elasticity index (SAEI) were obtained by an HDI/Pulsewave™ CR-2000 Cardiovascular Profiling System (Hypertension Diagnostic, Inc., Eagan, Minnesota, USA) following 5 to 10 minutes of rest in the supine position[33]. Measurements were averaged over three continuous 30-second trials. LAEI and SAEI are reliable in patients with PAD[33].

High Sensitivity C-Reative Protein (HsCRP): Concentration of HsCRP was quantified from 300 μl of sera using a high-sensitivity Near Infrared Particles Immunoassay. The SYNCHRON LX-20 (Beckman-Coulter; California, USA), a commercially available device, was used to perform the assay. Prior to performing each assay, the SYNCHRON system was calibrated, and a calibration curve was established[34].

Statistical Analyses

The MMSE score was dichotomized into a binary group variable (<30 vs =30) and used in all statistical analyses. Initially we examined the relationships between response variables and the MMSE score as a continuous variable, however, the relationships did not appear to be linear. We then decided to discretize the MMSE score, but it had a narrow range from 25 to 30, and the distribution was not favorable to analyze with quartiles. We decided to use the MMSE score as a binary variable because using a cut-off score of 29 provided an even split of patients into the two groups,

Patient demographics and baseline characteristics were summarized and compared between the two MMSE groups. Continuous variables were presented as means (SDs) and compared between MMSE groups using the two-sample t-test, and categorical variables were presented as proportions and compared between MMSE groups using the chi square test.

Baseline variables that significantly differed between two MMSE groups ($p < .05$) were further considered in the multi-variable analyses.

Outcome variables included exercise performance measures, daily ambulatory activity measures, walking impairment questionnaire, MOS SF-36 questionnaire, and vascular and StO_2 measures. The association between all these outcome variables with MMSE groups was assessed using two multiple linear regression models: model 1 and model 2. Model 1 included MMSE group, age, sex, race, and education level as covariates; while model 2 included those covariates in model 1 and additional coronary artery disease, chronic obstructive pulmonary disease, and arthritis which were found to be significantly different between the two MMSE groups.

All statistical analyses were performed using SAS 9.3. P-values less than .05 were considered to be statistically significant.

RESULTS

The clinical characteristics of the patients are shown in Table I. The mean ABI was typical of patients with claudication in those with an MMSE score of 30 points and in those with an MMSE score below 30. Dyslipidemia, hypertension, and metabolic syndrome were highly prevalent conditions in both groups. The group with lower MMSE scores had a lower education level ($p < .01$), a greater prevalence of coronary artery disease (CAD) ($p = .02$), chronic obstructive pulmonary disease (COPD) ($p = .01$), and arthritis ($p < .01$), and took more medications for diabetes ($p < .01$). All other variables were not significantly different between the two groups. Very few patients reported back problems, and most patients with diabetes had mild neuropathy on their toes and metatarsal heads of their feet.

Table II displays the exercise performance measures and community-based daily ambulatory activity measures of both groups. In unadjusted analyses, the mean PWT was 81 seconds shorter in the group with lower MMSE scores than in the higher MMSE group ($p = .02$). After adjusting for the demographic variables of age, sex, race, and education level (model 1), there was a trend for PWT to remain lower in the group with lower MMSE scores ($p = .06$), and this trend was significant in model 2 ($p < .05$) after adjusting for variables in model 1 plus CAD, COPD, and arthritis. All other variables were not significantly different between the groups.

Walking impairment and health-related quality of life measurements in the patients are shown in Table III. After adjusting for age, sex, race, and education (model 1), the group with lower MMSE scores had a lower mean WIQ stair climbing score ($p = .03$), and lower MOS SF-36 domains consisting of physical role limitations ($p = .04$), general health ($p = .04$), social function ($p = .03$), emotional role limitations ($p = .03$), mental health ($p < .01$), as well as the physical component score ($p = .01$) and the mental component score ($p < .01$). After further adjustment for CAD, COPD, and arthritis (model 2), only the mental health domain of the MOS SF-36 questionnaire remained significantly lower ($p = .02$) in the group with lower MMSE scores.

The vascular and calf muscle StO_2 measurements in the patients are depicted in Table IV. None of the variables were significantly different between the two groups after model 1 or model 2 adjustments. However, there was a modest trend for Hs-CRP to be higher in the group with lower MMSE scores.

DISCUSSION

A novel finding of this study was that the PAD group with lower MMSE scores had greater ambulatory impairment, measured by lower PWT, than the group with higher MMSE scores. Furthermore, the group with lower MMSE scores perceived less ability to perform the high-intensity exercise of climbing stairs, and they had lower levels of quality of life related to multiple physical and mental domains. A final novel result was that after adjusting for co-morbid conditions of CAD, COPD, and arthritis, the only quality of life variable that remained significantly lower in the group with lesser MMSE scores was the mental health domain.

Cognitive Status and Ambulation

On average, the PAD group with lower MMSE scores walked 81 fewer seconds on the progressive treadmill test than the PAD group with higher MMSE scores, and this difference was significant even after adjusting for demographic variables in model 1 and for comorbid conditions in model 2. Due to the nature of the graded treadmill test, the average PWT occurred 15 seconds into the work stage consisting of walking at a 6% grade for the lower MMSE group, whereas PWT occurred near the end of this grade for the higher MMSE group. Consequently, the more rapid occurrence of exercise-limiting, maximal claudication pain not only resulted in a shorter PWT, but it indicates that the lower MMSE group is not capable of sustaining ambulation at an intensity of approximately 4 metabolic equivalents (MET's). The shorter PWT of the lower MMSE group is clinically relevant given that exercise capacity of patients with PAD, as measured by MET's calculated from the duration of walking on a graded treadmill test, is the strongest predictor of mortality[35]. Furthermore, we have previously found that sedentary symptomatic patients with PAD who do not perform ambulatory activity above light intensities have a higher rate of mortality[36]. Thus, lower exercise capacity of patients with worse cognitive status may partially explain, and possibly contribute towards their heightened risk of cardiovascular mortality[18].

In addition to the lower MMSE group having lower PWT, they also perceived their ability to perform higher-intensity exercise to be impaired, as measured by a lower stair climbing score. However, after adjusting for CAD, COPD, and arthritis (model 2), group differences in the stair climbing score no longer remained. This finding indicates that the lower perceived ability to perform stair climbing in the lower MMSE group is largely explained by their higher prevalence of CAD, COPD, and arthritis, common comorbidities that also impact cognitive and functional status. Interestingly, no differences were found between the groups on performing exercise of lower intensities, such as 4-meter gait speed, 6-minute walk distance, and daily ambulatory activities. Thus, a lower cognitive screening score, measured by at least one or more mistakes obtained during the MMSE questionnaire, may be an early marker of impaired exercise ability that is only detected by a maximal exercise

test. It is not clear whether this predisposes patients with lower MMSE scores to have faster declines in ambulatory function over time once their PWT is shortened.

Cognitive Status and Health-Related Quality of Life

For the secondary outcome measures of health-related quality of life, after adjustment for model 1 the PAD group with lower MMSE scores had significantly lower scores in multiple dimensions of quality of life than the PAD group with higher MMSE scores. The lower MMSE group scored lower on both physical and mental domains and component scores of quality of life, but only the mental health domain remained lower after further adjusting for CAD, COPD, and arthritis (model 2). These results indicate that cardiovascular, pulmonary, and arthritis comorbid conditions largely explained the group differences in the quality of life measures except for the domain of mental health. Patients with lower cognitive screening scores had lower self-reported quality of life related to mental health independent of demographic and comorbid variables. The consequences of having lower scores in the mental health domain of quality of life is not clear in symptomatic patients with PAD, and it is not known whether this can be improved with intervention. However, it is notable that the mental health subscale of the MOS-SF-36 assesses symptoms of depression and anxiety. Depression is a particularly well-established predictor of poor outcomes, including mortality, in patient with coronary heart disease[37]. Depression is prevalent in PAD[38] and may similarly bode poorly for various patient outcomes. Future work should address these issues in symptomatic patients with PAD.

Exercise as a Potential Treatment for Cognitive Function

We speculate that exercise rehabilitation of patients with PAD and intermittent claudication, which is well established to improve ambulation,[23] may also be used as an intervention to improve cognitive function[39, 40]. A recent review suggests that aerobic exercise intervention positively impacts both cognitive and physical function in older adults[39]. Additionally, exercise intervention studies in patients with other forms of cardiovascular disease and other medical conditions, such as COPD have positively changed cognitive function[40]. Exercise may improve cognitive function through two different mechanisms which include favorably altering cardiovascular risk factors, and increasing cerebrovascular perfusion[40]. Thus, exercise rehabilitation, primarily in the form of aerobic exercise, may be a likely treatment to improve cognitive function and reduce its' decline over time in patients with PAD.

Limitations

There are limitations to this study. A self-selection bias may exist regarding study participation, as patients who participated in this trial were volunteers. Therefore, they may represent those who were more interested in participation, who had better access to transportation to the research center, and who had relatively better health than patients who did not volunteer. Furthermore, the results of this study are only applicable to symptomatic patients with PAD, and may not be generalized to asymptomatic patients and patients with more severe forms of PAD, such as critical limb ischemia. Another limitation is that the MMSE questionnaire only provides a crude assessment of cognitive status and therefore likely underestimates the magnitude of association between specific cognitive functions and physical performance or HRQoL .In that regard, the MMSE does not assess executive

functions, which may be a particularly potent predictor of functional outcomes. Future studies should include more comprehensive assessment of major domains of cognitive function. An additional limitation is that we did not measure hemoglobin A1c levels, and thus do not have an estimate of long-term control of diabetes. However, we believe the patients with diabetes were well-controlled prior to entering the study because most were taking medications, and no patient had glucose values indicating that they were metabolically out of control. Finally, there are limitations associated with the design of the study. Significant differences found in the variables between the two groups of MMSE patients do not provide evidence of causality. Although these limitations exist, we believe that the findings of the present study are generalizable to the large number of symptomatic patients with PAD because women and African-Americans are well represented, and typical risk factors for PAD such as dyslipidemia, hypertension, obesity, diabetes, and smoking are highly prevalent.

Conclusion and clinical significance

In symptomatic patients with PAD, lower scores on a commonly used cognitive screening measure were associated with greater ambulatory impairment than in patients with better cognitive status. Furthermore, lower cognitive status was associated with worse perceived ability to climb stairs, and with lower scores in multiple dimensions of health-related quality of life, all of which except for mental health were explained by the comorbid conditions of CAD, COPD, and arthritis. The clinical significance is that there is a need for enhanced cognitive and mental health screening as potential indicators of poor outcome among symptomatic patients with PAD. Furthermore, patients identified as having worse cognitive status may be in greatest need of intervention to improve ambulation and quality of life related to mental health. These interventions should initially consist of more aggressive conservative treatment which includes exercise training, pharmacotherapy, and risk factor modification.

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Table I

Clinical characteristics of patients with claudication and peripheral artery disease. Values are means (standard deviation) or percentage of patients.

Variables	MMSE Score = 30 (n = 123)	MMSE Score < 30 (n = 123)	P Value
Age (yrs)	64 (10)	65 (11)	.34
Weight (kg)	84 (18)	83 (19)	.61
Body Mass Index (kg/m^2)	29.4 (5.9)	29.6 (6.4)	.81
HOMA-IR (mg/dL)	4.0 (6.3)	2.7 (3.9)	.07
Ankle/Brachial Index	0.71 (0.23)	0.72 (0.24)	.85
Sex (% Men)	47	50	.61
Race (% Caucasian)	56	48	.20
Education (% beyond high school)	74	44	<.01
Current Smoking (% yes)	35	41	.39
Hypertension (% yes)	83	88	.26
Medication Use (% yes)	79	85	.19
Number of Medications	2.3 (1.1)	2.4 (1.0)	.41
Dyslipidemia (% yes)	90	89	.85
Medication Use (% yes)	66	72	.27
Number of Medications	1.2 (0.6)	1.2 (0.4)	.39
Diabetes (% yes)	41	44	.61
Medication Use (% yes)	37	38	.79
Number of Medications	1.5 (0.8)	2.0 (0.9)	< .01
Abdominal Obesity (% yes)	61	49	.06
Metabolic Syndrome (% yes)	79	80	.75
Metabolic Syndrome Components	3.5 (1.2)	3.5 (1.3)	.88
Obesity (% yes)	45	45	.91
Lower Extremity Revascularization (% yes)	31	41	.08
Coronary Artery Disease (% yes)	25	39	.02
Myocardial Infarction (% yes)	15	21	.19
Cerebrovascular Disease (% yes)	12	20	.10
Cerebrovascular Accident (% yes)	17	14	.56
Chronic Kidney Disease (% yes)	21	28	.20
Chronic Obstructive Pulmonary Disease (% yes)	17	32	< .01
Dyspnea (% yes)	54	64	.10
Arthritis (% yes)	49	69	< .01

HOMA-IR = homeostatic model assessment – insulin resistance.

Table II

Exercise performance measures in patients with claudication and peripheral artery disease. Values are means (SD).

Variables	MMSE Score = 30 (n = 123)	MMSE Score < 30 (n = 123)	Model 1 P Value	Model 2 P Value
Exercise Performance Measures				
Peak Walking Time (s)	460 (270)	380 (250)	.06	< .05
Claudicaton Onset Time (s)	220 (160)	190 (170)	.31	.29
Gait Speed (m/s)	1.08 (0.24)	1.07 (0.20)	.50	.40
6-Minute Walk Distance (m)	350 (100)	340 (90)	.87	.86
Daily Ambulatory Activity Measures				
Maximum 30-Minute Activity Rate (strides/min)	15.0 (6.8)	14.4 (5.2)	.47	.52
Peak Activity Index (strides/min)	29.2 (7.9)	28.2 (6.7)	.33	.41
Average Activity Rate (strides/min)	12.0 (2.9)	11.4 (2.4)	.10	.20

Values adjusted for age, sex, race, and education level (model 1), and for variables in model 1 plus coronary artery disease, chronic obstructive pulmonary disease, and arthritis (model 2).

Table III

Self-perceived ambulatory function and health-related quality of life in patients with claudication and peripheral artery disease. Values are means (SD).

Variables	MMSE Score = 30 (n = 123)	MMSE Score < 30 (n = 123)	Model 1 P Value	Model 2 P Value
Walking Impairment Questionnaire				
Distance Score (%)	38 (33)	35 (32)	.68	.88
Speed Score (%)	37 (24)	30 (22)	.09	.12
Stair Climbing Score (%)	43 (29)	35 (29)	.03	.18
MOS SF-36 Questionnaire				
Physical Function (%)	48 (22)	42 (20)	.08	.26
Role Limitations – Physical (%)	53 (42)	42 (41)	.04	.34
Bodily Pain (%)	62 (23)	59 (26)	.07	.51
General Health (%)	60 (22)	53 (22)	.04	.29
Social Function (%)	81 (24)	76 (26)	.03	.20
Role Limitations – Emotional (%)	79 (39)	67 (41)	.03	.14
Mental Health (%)	80 (15)	75 (20)	< .01	.02
Vitality (%)	57 (22)	54 (23)	.18	.79
Physical Component Score (%)	56 (23)	49 (21)	.01	.22
Mental Component Score (%)	74 (20)	68 (22)	.01	.09

MOS SF-36 = medical outcomes survey study short-form 36 item general health survey. Values adjusted for age, sex, race, and education level (model 1), and for variables in model 1 plus coronary artery disease, chronic obstructive pulmonary disease, and arthritis (model 2).

Table IV

Vascular and calf muscle hemoglobin oxygen saturation (StO_2) measures in patients with claudication and peripheral artery disease. Values are means (SD).

Variables	MMSE Score = 30 (n = 123)	MMSE Score < 30 (n = 123)	Model 1 P Value	Model 2 P Value
Ischemic Window after Exercise (AUC/m)	−0.3 (0.6)	−0.5 (1.3)	.35	.54
Large Artery Elasticity Index (ml × $mmHg^{-1}$) × 10	13.6 (6.1)	13.3 (5.0)	.70	.89
Time to Minimum Calf StO_2 during exercise (s)	230 (260)	220 (260)	.82	.86
Recovery Half-Time of Calf StO_2 (s)	140 (160)	180 (180)	.28	.41
C-Reactive Protein (mg/L)	4.8 (5.6)	7.4 (5.2)	.12	.10

StO_2 = hemoglobin oxygen saturation. Values adjusted for age, sex, race, and education level (model 1), and for variables in model 1 plus coronary artery disease, chronic obstructive pulmonary disease, and arthritis (model 2).