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Walking abnormalities are associated with COPD: An investigation of the NHANES III dataset

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1 **WALKING ABNORMALITIES ARE ASSOCIATED WITH COPD: AN**
2 **INVESTIGATION OF THE NHANES III DATASET**

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47 **Summary:**

48 Research on the peripheral effects of COPD has focused on physiological and structural changes.
49 However, different from muscular weakness or decreased physical activity, mechanical
50 abnormalities of the muscular system, e.g. walking, have yet to be investigated. Our purpose was
51 to utilize the National Health and Nutritional Examination Survey (NHANES) dataset to
52 determine whether walking abnormalities are associated with COPD severity. To determine if
53 walking abnormalities were independently associated with COPD severity, our analysis aimed to
54 investigate the association of physical activity levels with COPD severity and with walking
55 abnormalities. The NHANES III dataset that contains data for 31,000 persons that were collected
56 from 1988-1994, was used to explore the association of COPD severity on gross walking
57 abnormalities, i.e. limp, shuffle, etc. Logistic regression models were created using FEV₁/FVC
58 ratio, age, gender, BMI, and smoking status as predictors of walking abnormalities and physical
59 activity in persons aged 40 to 90 years old. Results demonstrated a significant correlation
60 between the presence of walking abnormalities and severe COPD (odds ratio: 1.97; 95% CI: 1.1
61 to 3.5). This suggests that disease severity can contribute to mechanical outcomes of patients
62 with COPD. In addition, decreased physical activity levels were significantly associated with all
63 COPD severity levels with the exception of mild COPD. The association between altered gait
64 and COPD status may be due to the presence of physical inactivity that is present in patients with
65 COPD. Future research directions should include investigating more closely the mechanical
66 outcomes of persons with COPD.

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68 **Keywords:**

69 Locomotion, Gait, Lung Disease, Physical Activity

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Conflict of Interest Statement:

SR has participated as a speaker in scientific meetings and courses under the sponsorship of AstraZeneca, GlaxoSmithKline and Pfizer. He has consulted with several pharmaceutical companies with relevance to the topics noted in the present manuscript (Almiral, Altana Amersham, Array Biopharma, AstraZeneca, Aventis, Boehringer Ingelheim, Critical Therapeutics, GlaxoSmithKline, Globomax, Intermune, Merck, Novartis, Ono, Otsuka, Roche, Sanofi, Scios, Wyeth). He serves on advisory boards for Altana and Pfizer. He has been sponsored by GlaxoSmithKline for several clinical trials and has received laboratory support. He has also conducted clinical trials for Roche, Pfizer, Sanofi and Novartis. He has conducted both clinical trials and basic studies under the sponsorship of Centocor. He has conducted basic studies under the sponsorship of AstraZeneca. A patent is pending on the use of miR-146a in lung disease; SR is a co-inventor of the patent owned by the University of Nebraska Medical Center.

The other authors have no conflicts of interest to disclose.

86 **Introduction:**

87 The effects of COPD are not limited to the lungs; rather the effects typically include “systemic
88 and complex abnormalities” affecting the peripheral systems ¹. At the forefront of these are the
89 effects of COPD on the cardiovascular and muscular systems. Much of the research into the
90 effects of COPD on the muscular system has focused on skeletal muscle changes, including
91 muscle atrophy, mitochondrial changes and shifting of muscle fiber types ²⁻⁵. It is possible then
92 that changes in muscular structure could affect mechanical outcomes, such as gait (walking).
93 However, this has not been explored in the COPD population.

94

95 COPD patients are less active than the average population ⁶⁻⁹. Using accelerometers to
96 objectively quantify physical activity ¹⁰⁻¹³, it is reported that one third of severe COPD patients
97 walk less than 15 min/day ⁸. Patients with the most severe levels of COPD spend less time
98 walking and when they do, they walk at slower speeds ¹⁴. The decreased physical activity seen in
99 COPD patients is not directly associated with disease severity. Mild COPD patients, that have
100 relatively normal lung function, walk approximately 50% less than healthy controls ⁷. Watz et al.
101 (2009) have further demonstrated that patients with moderate COPD have significantly
102 decreased physical activity levels and that these decremented physical activity levels are not
103 reflective of clinical tests of disease severity ¹⁵. Physical inactivity in COPD patients is the result
104 of many abnormalities, including the ventilatory, musculoskeletal, neurosensory, and
105 cardiovascular systems. Respiratory limits to physical activity are well established ¹⁶⁻¹⁸. Including
106 dynamic hyperinflation that worsens with activity, can impact activity levels by constraining
107 tidal volume, contributing to inspiratory muscle weakness, greater neuromechanical dissociation,
108 and increased perception of dyspnea regardless of the level of severity of COPD ¹⁶⁻¹⁸. In addition,

109 it has been noted that dynamic hyperinflation contributes to a circle of increased weakness and
110 fatigue of respiratory musculature; hence, causing a further impact physical activity levels ¹⁷.
111 Additional extrapulmonary effects of COPD include an association of physical inactivity with
112 systemic inflammation and impaired left cardiac function, as well as an increased prevalence of
113 peripheral arterial disease and depression ¹⁹.

114
115 There is evidence that lack of physical activity contributes to peripheral muscle abnormalities
116 and dysfunction. Disuse of the muscular system can result in muscular atrophy, decreased
117 muscle strength, increased muscle fatigability, reduced oxidative capacity, and capillary loss ²⁰⁻²³.
118 It has also been reported that activity may be limited in COPD patients due to leg fatigue ²⁴.
119 Muscle fatigue is present in mild to moderate COPD patients irrespective to lung function,
120 anthropometric data, or quadriceps strength ²⁵. A contributing factor to leg fatigue could be
121 abnormal skeletal muscle structure, including abnormal body cell mass alterations, muscular
122 protein degradation leading to muscle wasting/atrophy, impaired energy production and
123 metabolic performance, and increased susceptibility to muscle weakness ^{2, 26-33}. These muscular
124 impairments may also lead to abnormal walking patterns; however this has not previously been
125 tested in COPD patients. In support of such a concept, however, Butcher et al. (2004)
126 investigated balance, coordination and mobility in COPD patients and determined that
127 decrements in these measures were found when compared to controls ³⁴. These differences were
128 attributed to severity of disease and lower levels of physical activity ³⁴. Whatever the cause,
129 mechanical abnormalities are present in COPD patients. Using biomechanical measures to
130 quantify static balance control in COPD, it has been found that COPD patients demonstrate
131 greater medio-lateral center of pressure displacement and increased hip angular displacement of

132 the hip ³⁵. Whether these are reflected in walking abnormalities remains to be determined.
133 Interestingly, patients with COPD also demonstrate an increase risk of falls as compared to
134 healthy controls, with a reported odds ratio of 4 to 5 times higher ^{36,37}. Roig et al. (2009) propose
135 a theoretical framework to identify fall risk factors in COPD patients which includes walking
136 abnormalities leading to poor mobility ³⁸. Hence, there is a demonstrated need to investigate
137 mechanical outcomes in COPD, including but not limited to, walking abnormalities and balance
138 measures.

139
140 The purpose of this study was to investigate whether or not walking abnormalities are associated
141 with the presence of COPD using data from the NHANES III dataset. The National Health and
142 Nutritional Examination Survey (NHANES) III dataset is a public use data set that provides
143 interview and physical examination information on over 31,000 American patients from 1988 to
144 1994. NHANES is a major program of the United States National Center for Health Statistics
145 that is regulated by Centers for Disease Control and Prevention. This dataset provides
146 information regarding mechanical outcomes of patients as well as history, physical examination
147 and laboratory measures, including information on the prevalence of chronic diseases.

148 Using this dataset, we hypothesized that walking abnormalities would be significantly associated
149 with COPD severity, due to the prevalence of peripheral muscle abnormalities and dysfunction
150 noted in COPD. It is thought that these peripheral muscle changes are due to the severe physical
151 inactivity commonly present in patients with COPD. Therefore, a secondary analysis conducted
152 investigating the association of subjective physical activity levels with COPD severity. It was
153 hypothesized that all levels of COPD severity would be significantly associated with decreased
154 physical activity levels, providing further support that physical inactivity associated with COPD

155 is related to walking abnormalities. The relationship between COPD severity and activity level is
156 neither novel nor unexpected; however the goal was to determine if activity level was related to
157 walking abnormality and which variables are independently associated with abnormal walking
158 patterns.

159

160 **Methods and Materials:**

161 Data from the NHANES III dataset were used for analysis. Extensive details of the sampling and
162 data collection methodologies are available at
163 www.cdc.gov/nchs/about/major/nhanes/nh3data.htm. In order to account for the sampling design
164 that produced the NHANES dataset, all modeling analyses and descriptive analyses where
165 weights are taken into account were performed using SAS SURVEY procedures with appropriate
166 stratification, clustering, and weighting variables (SAS Institute Inc., Cary, NC). These analyses
167 utilized data from the full six year sample as recommended by the study documentation. These
168 analyses were approved as exempt by the University's Institutional Review Board.

169

170 Selection Criteria: The original NHANES III dataset contains data on 31,311 Americans
171 examined and surveyed from 1988-1994. Patients that had completed the adult examination and
172 were 40 to 90 years old were selected for analysis (n = 10,049). From this selected group,
173 subjects were eliminated from analyses if they reported being unable to walk without help (n =
174 240). This variable is included in the physical function evaluation given to anyone over the age
175 of 60 years. Persons who were coded as "no" they could not walk without help were removed
176 from the analyses. Finally, potential subjects were removed if they were missing data from one
177 of the key variables for analyses (FEV₁, FVC, walking abnormalities, age, gender, body mass

178 index (BMI) (n = 1,404)). In total, 8,405 patient records were utilized as a sample for this
179 analysis.

180

181 Selection of Variables: The independent variable chosen for this analysis was classification of
182 COPD status. Spirometric function was used for the definition of COPD. The key parameters
183 were the patient's forced expiratory volume in one second (FEV₁) and the ratio of the FEV₁ to
184 the forced vital capacity (FVC)³⁹. Patients with an FEV₁ to FVC ratio less than 0.7 were
185 classified as having COPD with severity stages determined by classification based on their
186 measured FEV₁ values as a percent of their predicted FEV₁ values. The percent predicted FEV₁
187 values were calculated using equations derived by Harkinson et al.⁴⁰ for the NHANES III dataset
188 which calculate predicted values for each subject based on the subject's age, height, race, and
189 gender. Utilizing standards from The Global Initiative for Chronic Obstructive Pulmonary
190 Disease (GOLD), subjects were classified into three COPD levels⁴¹ as well as symptoms,
191 restrictive, and normal classification groups (Table 1)⁴².

192

193 Two separate models were developed. The first model was developed to investigate the presence
194 of walking abnormalities in persons with COPD, using the presence of gait abnormality as a
195 dependent variable. Three variables in the NHANES III dataset address walking abnormalities.
196 The protocol for NHANES states that the physician should evaluate the patient for a limp or
197 shuffle (variable PEP1A1). According to the NHANES instructions this must be a chronic limp
198 on either leg that is a current condition. If a limp or shuffle were not present, the physician could
199 additionally evaluate the patient for any other walking abnormality (variable PEP1A2). If the
200 physician marked "yes" to either of these conditions, the overall finding for walking

201 abnormalities was marked as “yes” (variable PEP1). Only the overall finding for the locomotion
202 variable was used for analysis. This variable was coded as “yes, findings” if either one or both of
203 the other two variables (limp or shuffle and/or other walking abnormalities) were coded as “yes”.
204 The second model was developed to investigate the association of physical activity levels with
205 COPD status. The dependent variable for this model was a subjective measure of physical
206 activity. In the NHANES III Adult Household Survey, physical activity was assessed using the
207 following variable, “How active are you compared with men/women your age?” (variable
208 HAT28) In the NHANES data set, the data was coded as: more active, less active, about the
209 same, blank but applicable, and don't know.

210

211 Age, gender, and BMI were chosen as covariates. Descriptive statistics for all analysis variables
212 are presented in Table 2. In addition to the covariates, smoking status was added to the analysis.
213 Data from the NHANES III Adult Household Survey was used to create the smoking status
214 variable. A person was classified as “never” smoking if he/she reported smoking fewer than all
215 of 100 cigarettes, 20 cigars, or 20 pipefuls of tobacco in his/her lifetime. Among persons who
216 had smoked at least 100 cigarettes, 20 cigars, or 20 pipefuls of tobacco, those who reported they
217 were not currently smoking any of cigarettes, pipes, or cigars were classified as “former”
218 smokers, while those who indicated they were currently using at least one of these three options
219 were classified as “current” smokers.

220

221 Model Development: The SAS SURVEYLOGISTIC procedure was used to generate logistic
222 regression models with gait abnormality and physical activity as dependent variables and COPD
223 classification as the independent variable. Age, BMI, gender, and smoking status were added to

224 the model to control for their effects on the outcome variable. Significance was set at an alpha
225 level of 0.05. For the physical activity model, responses of “More active” and “About the same”
226 were combined into a single category and used as a reference for comparison against responses
227 of “Less active”.

228

229 **Results:**

230 Using COPD status as a predictor of the walking abnormalities without covariates, it was found
231 that each COPD classification compared against normal were significantly ($p < 0.05$) associated
232 to walking abnormalities. Upon adding the covariates into the model, SEVERE COPD (odds
233 ratio: 2.53, 95% CI: 1.2 to 5.3) remained significantly ($p = 0.01$) associated to walking
234 abnormalities. The covariates of age (odds ratio: 1.10, 95% CI: 1.1 to 1.1) and BMI (odds ratio:
235 1.06, 95% CI: 1.0 to 1.1) were also significantly ($p < 0.0001$) associated to walking
236 abnormalities. These results are presented in Table 3 and 4.

237

238 Furthermore, we found that SEVERE (odds ratio: 4.57, 95% CI: 2.6 to 7.9), MODERATE (odds
239 ratio: 1.83, 95% CI: 1.3 to 2.5), SYMPTOMS (odds ratio: 1.84, 95% CI: 1.5 to 2.3),
240 RESTRICTIVE (odds ratio: 2.43, 95% CI: 1.9 to 3.1), BMI (odds ratio: 1.0, 95% CI: 1.0 to 1.1),
241 and current smoker (odds ratio: 1.4, 95% CI: 1.2 to 1.8) were significantly ($p < 0.05$) associated
242 with less activity than other men/women their age. Age (odds ratio: 0.97, 95% CI: 0.96 to 0.98)
243 was significantly ($p < 0.0001$) associated with the response of more active or about the same
244 compared to other men/women their age. These results are presented in Table 5.

245

246 **Discussion:**

247 The purpose of this study was to investigate whether or not walking abnormalities are associated
248 with the presence of COPD using data from the NHANES III dataset. It was hypothesized that
249 walking abnormalities would be significantly associated with COPD severity, due to the
250 prevalence of peripheral dysfunction due to decrease physical activity levels noted in COPD. The
251 novel finding is that COPD is related to walking abnormalities. When using a comprehensive
252 classification scheme for COPD status, a significant association between severe COPD status
253 and walking abnormalities was observed. From clinical point of view, reduced physical activity
254 in daily life and impaired muscle strength are the mostly likely causes. This was confirmed as
255 demonstrated by decreased physical activity being significantly associated with all levels of
256 COPD severity. These results strengthen the novel findings by demonstrating the importance of
257 physical activity and the effect of inactivity on walking abnormalities. Thus, questions are raised
258 as to why persons with severe COPD would suffer from walking abnormalities and how is this
259 clinically relevant?

260

261 One potential explanation for the association between walking abnormalities and COPD severity
262 could be the result of decreased physical activity. It has been shown that decreased levels of
263 physical activity result in decreased muscle fiber cross-sectional area, reduction in mitochondrial
264 density, capillary density, and amount of contractile proteins, and increased susceptibility to
265 assuming properties of type II fibers ⁴³. Skeletal muscle dysfunction present in COPD includes
266 loss of body cell mass and protein degradation, impaired energy production and metabolic
267 performance, increased susceptibility to leg fatigue, and leg weakness leading to reduced activity
268 ^{2, 6-8, 14, 15, 26-32}. These dysfunctions in the muscular system may impact walking patterns, causing an
269 irregular walking pattern, and further causing decreased levels of physical activity. Mechanisms

270 leading to reduced physical activity levels of COPD patients have been debated, though it has
271 been demonstrated that activity may be limited in COPD patients due to peripheral muscle
272 fatigue ²⁴. Recently, using surface electromyography COPD patients demonstrated muscle
273 contractile fatigue in the rectus femoris and vastus lateralis during a 6 minute walk test of COPD
274 patients ⁴⁴. There is a growing body of evidence that peripheral muscle fatigue is associated to
275 structural and mechanical abnormalities of skeletal muscle in COPD patients. For instance, it has
276 been documented that skeletal muscle contractile fatigue is affected by metabolic changes in the
277 skeletal muscle, redox status, systemic inflammation, and lactic acid accumulation ⁴⁵⁻⁴⁸. It is
278 possible that fatigue is the result of mitochondrial changes in COPD skeletal muscle that are
279 related to a greater presence of type II muscle fibers ^{4,49}. It has been demonstrated that sedentary
280 controls also demonstrate a profile of increased number of type II muscle fibers ⁵⁰; therefore, it is
281 possible disuse may be the mechanism for mitochondrial changes in COPD patients leading to
282 further decrements in activity levels. This is further strengthened by studies that have
283 demonstrated that limitation in mechanical efficiency and submaximal exercise is related to an
284 increased percentage of type II fibers and muscle disuse as opposed to peripheral muscle
285 oxygenation, respectively ^{51,52}. Further, studies have demonstrated positive effects of exercise
286 training on COPD patients ⁵³⁻⁵⁷. These positive effects include increased muscular size, strength,
287 power, endurance, mitochondrial capacity, and restoration of protein levels ⁵⁸⁻⁶¹.

288

289 Alternatively, systemic inflammation in organ systems outside of the lungs, distinct from local
290 pulmonary inflammation may potentially be another mechanism to walking abnormalities in
291 COPD. This inflammation, characterized by oxidative stress, increased levels of cytokines and
292 leukocytes, has been speculated as an underlying mechanism of abnormal skeletal muscle

293 structure and function in COPD ^{2, 3, 5, 45-47}. Whether the abnormalities in gait in COPD patients
294 demonstrated in the present study result from inactivity or from other processes remains to be
295 determined.

296
297 There are limitations associated with this study. NHANES III dataset allows for limited
298 investigations into the association of COPD and walking abnormalities. Walking abnormalities
299 in this dataset are poorly defined and include overall observations of walking patterns, such as
300 the presence of a limp or shuffle. Future studies should investigate mechanical abnormalities
301 using a biomechanical analysis in order to thoroughly understand the muscular joint responses
302 and contributions to walking patterns. In addition, the variable used to define physical activity
303 levels was subjectively provided. Subjects were asked their opinion on their activity level as
304 compared to other adults their same age. Use of accelerometers and pedometers provide
305 objective measures of physical activity ¹⁰⁻¹³.

306
307 This analysis of the NHANES III dataset is the first study that investigated whether or not
308 walking abnormalities are associated with COPD status. The novel finding of this study is that
309 COPD is related to gait abnormalities. From clinical point of view, reduced physical activity in
310 daily life and impaired muscle strength are the mostly likely causes. There has been much debate
311 in the literature as to the peripheral effects of COPD and whether or not mechanical outcomes
312 are associated with severity of the disease. Further studies should employ objective analyses to
313 investigate mechanical outcomes of COPD patients to determine these associations. The
314 biomechanical analysis of walking abnormalities would provide procedures and measures that
315 can clearly examine the locomotion of COPD patients by identifying physical deficiencies and

316 determining the severity of their mechanical limitations. In conclusion, this study provides
317 preliminary evidence that a decline in mechanical outcomes (e.g. walking abnormalities) is
318 associated with persons that have severe COPD.

319

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325

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489

490

491 **Table Captions.**

492 **Table 1.** Classification of subjects based upon GOLD standards.⁴²

493

494 **Table 2.** Descriptive Statistics for Continuous and Categorical Variables.

495

496 **Table 3.** Logistic Regression of Walking Abnormalities by COPD Status. N=8,405

497 (84,234,791)

498 1. Reference category is Normal.

499

500 **Table 4.** Logistic Regression of Walking Abnormalities by COPD Status, Age, BMI, Sex, and

501 Smoking Status. N=8,389 (84,146,857) (Note: * indicates $p < 0.05$)

502 1. Reference category is Normal.

503 2. Reference category is Never Smoked.

504

505 **Table 5.** Logistic Regression of Physical Activity compared to men/women of comparable age

506 by COPD Status, Age, BMI, Sex, and Smoking Status. N=8,193 (82,225,630) (Note: * indicates

507 $p < 0.05$)

508 1. Reference category is Normal.

509 2. Reference category is Never Smoked.

510