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Systolic Blood Pressure Variability is Associated with Increased Multiple Sclerosis Disability

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SYSTOLIC BLOOD PRESSURE VARIABILITY IS ASSOCIATED WITH INCREASED MULTIPLE SCLEROSIS DISABILITY

Running title: Blood-pressure Variability and MS Disability

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ABSTRACT

Objective: To examine the relationship between visit-to-visit systolic blood pressure (SBP) variability and patient-reported outcome measure of disability in multiple sclerosis (MS) patients.

Design: A retrospective cohort study of individuals with MS who completed a Patient Determined Disease Steps (PDDS) scale between 2011 – 2015 at a multiple sclerosis specialty clinic.

Participants: Individuals with MS for whom both a completed PDDS scale and ≥3 SBP measures within the prior 12 months of the survey were available.

Main Outcome Measure: Participants were grouped into three classes of disability (No or Mild (PDDS 0 - 1), Moderate (2 - 3), Severe (4 - 7)). SBP variability was calculated as within-subject standard deviations using all SBP measures taken during the past 12 months. SBP variability was analyzed by Tertile groups.

Results: Ninety-two subjects were included in this analysis. Compared to those in Tertile 1 (lowest variability), subjects in Tertile 2 were 3.8 times more likely (OR = 3.77; 95% CI, 1.20 – 11.87) and those in Tertile 3 (highest variability) were 5.5 times more likely (OR = 5.48; 95% CI, 1.65 – 18.15; p = 0.005) to be in a higher disability group (p for trend = 0.006), independent of mean SBP.

Conclusions: Our results show a significant gradient relationship between SBP variability and MS-related disability. More research is needed to determine the underlying pathophysiological relationship between SBP variability and MS disability progression.

Keywords: multiple sclerosis, disability progression, blood pressure variability, cardiovascular comorbidities

Article Summary

Strengths and Limitations of This Study

- This is a first study to look at the relationship between the Systolic Blood Pressure (SBP) variability and MS-related disability outcomes.
- This study paired prospectively collected patient-reported outcomes with retrospectively collected data, which allowed us to leverage existing data to take a first look at this novel question.
- Our analysis included a multi-faceted approach including - patient-reported measures, clinical outcomes (blood pressure), and concurrent co-morbid diagnosis.
- The retrospective collection of the paired clinical data limited the standardization of the number and inter-interval timing of blood pressure measurements, as well as the total number of subjects available for analysis.

1. Introduction

Multiple Sclerosis (MS) is an inflammatory and degenerative disorder of the central nervous system. Individuals with MS commonly experience some degree of disability progression independent of inflammatory driven events. The underlying mechanisms driving this inflammatory-independent disease progression remains poorly understood. It is likely that there is no single factor that drives MS progression. Instead it is believed to be a multi-faceted process with variable importance and influence of factors for any individual person. Posited factors include medical co-morbidities, as well as environmental factors such as smoking or vitamin D exposure.

In MS patients, co-morbid cardiovascular disease is associated with worsened disease progression and reduced quality of life, although the mechanism remains uncertain.[1-5] Visit-to-visit systolic blood pressure (SBP) variability is an emerging risk factor for a wide array of health outcomes including cardiovascular disease (CVD), kidney failure, cognitive dysfunction, diabetic complications, and all-cause mortality.[6-10] Excessive SBP variability (≥ 10 within-subject standard deviation) has been associated with many of these outcomes independent of mean blood pressure and hypertension.[8,11,12] Evidence suggests that visit-to-visit blood pressure variability may have stronger effects on cardiovascular outcomes than that of measures taken during a single visit or by 24-hour ambulatory monitoring devices.[13-15] While various vascular comorbidities have been previously studied in the progression of MS, the relationship between SBP variability and MS progression has yet to be explored.

We conducted a retrospective cohort study to examine the relationship between SBP variability and self-reported MS disability. We hypothesized that higher SBP variability is associated with greater degree of disability among individuals with MS.

2. Material and Methods

Study Design and Sample

We conducted a retrospective cohort study of individuals with MS who participated in research between 2011 and 2015 at the University of Virginia School of Medicine (UVA) and had previously prospectively completed the Patient Determined Disease Steps (PDDS) scale, a validated patient-reported outcome measure of MS disability.[16-18] The PDDS is a self-report tool of MS disability in which participants indicate their level of disability between 0 (‘normal’) and 8 (‘bedridden’), where 4 indicates “early cane” use. SBP measurements were obtained from

medical records and only those subjects with ≥ 3 available SBP measurements captured within the 12 months prior to PDDS completion were included in the analysis. This study was approved by the UVA institutional review board.

Visit-to-visit variability of systolic blood pressure

All available SBP measures within 12-months pre- and post- PDDS survey data were extracted from the electronic medical records system. Within-subject means and standard deviations of SBP were computed. Coefficient of variation was calculated by dividing the standard deviation by the mean to categorize the sample into tertile groups.

Covariates

Demographic data (age, sex, and race/ethnicity) were collected. We searched with Clinical Data Repository (CDR), a data warehouse containing clinical information from patients treated at the University of Virginia, for the 12-month period prior to the PDDS survey to identify co-existing conditions including- cardiovascular (ICD-9-CM codes, 410.xx – 414.xx, 428.xx, 431.xx, 434.xx, and 436.xx), peripheral vascular (443.9), diabetes (250.xx, 357.2, 362.01), depression (311.xx, 300.4, 296.20, 296.80, 296.89, 296.90), and hypertension (401.x). In addition to the diagnostic codes, we classified hypertension in patients using the 140/90 mm Hg per ACC/AHA guideline.[19] We also extracted body mass index (BMI) data within six months of the PDDS survey completion date.

Statistical Analysis

We used multivariable regression analysis to examine the relationship between SBP variability and the PDDS disability rating. To best utilize the ordinal nature of our response variable (PDDS score)[16,17], we estimated an ordinal logistic regression[20] and found that it did not

satisfy the proportional odds assumption.[20,21] We tried several groupings to satisfy the assumption and decided on three groups based on the PDDS scores as follows: No or Mild Disability (PDDS scores 0 or 1), Moderate Disability (PDDS scores 2 or 3), and Severe Disability (PDDS scores 4 or higher). The disability outcomes in these new groups were modeled using ordinal logistic regression as a function of SBP variability, adjusting for patient demographic data (age, sex, and race/ethnicity) and mean SBP.

As a sensitivity analysis, we estimated two additional models. First, we defined the PDDS score 3 or above as presence of severe disability and modeled the binary response (0 = No or Mild Disability; 1 = Moderate to Severe Disability) using a logistic regression (Table 4). Second, we treated the PDDS score as a continuous variable and estimated a linear regression that are identically specified as the ordinal logistic regression model (Table 5).

We further tested whether co-existing conditions affect the association by including depression, hypertension, and sleep disturbances as additional control variables (Table e-1). Because SBP variability is found to be correlated with the number of measures used in computing the within-subject standard deviations, we controlled for the number of BP measures in another sensitivity analysis (Table e-2).

Finally, we tested whether PDDS scores can predict SBP variability before the study (Table e-3) and whether PDDS scores can predict SBP variability after the survey (Table e-4) by estimating linear regressions to predict pre- and post-survey SBP variability as a function of PDDS scores, adjusting for age, sex, race, and other covariates.

We used Stata SE v. 15.1 (StataCorp, College Station, TX) for all statistical analysis.

3. Results

A total of 218 PDDS surveys were identified from available study data. Among these, 17 subjects had completed more than one PDDS survey; in such cases, the first available survey date with corresponding ≥ 3 SBP measures was utilized. No subject contributed more than once to the final data set. Of the resultant subjects, only 94 had the requisite ≥ 3 blood pressure measures in the 12-months prior to the survey completion date. Two additional subjects were excluded due to lack of available records to permit BMI calculation (absent height and/or weight).

The resultant 92 subjects included in the final analysis had a mean age of 44.7±12.2 years at the time of PDDS survey completion. They were predominantly white (82.6%) and 54% female. Their mean SBP was 124.1±13.2 mm Hg overall and were highest in Tertile 1 (128.0±13.0 mm Hg) and lowest in Tertile 2 (125.8±13.0 mm Hg). Their within-subject SBP standard deviation was 9.9±4.6 mm Hg overall but changed from 5.8±2.1 mm Hg (interquartile range [IQR] 4.4 – 7.4 mm Hg) to 9.2±1.4 mm Hg (IQR 11.7 – 17.7 mm Hg) in Tertile 2, and 14.8±3.9 (IQR 8.5 – 10.2 mm Hg) in Tertile 3. Their mean BMI was 29.0 kg/m^2. A total of 19 (20.7%) had depression, 28 (30.4%) had hypertension (11 patients with a diagnosis in ICD-9-CM and 17 patients with elevated mean BP). We could not identify any subject with vascular comorbidities except for one who had acute myocardial infarction and was in Tertile 2. For this reason, vascular comorbidities have not been used in any subsequent analyses. The mean and median PDDS score was 2.2±1.89 and 2 (IQR 0 – 4). Forty patients (43.5%) had no or mild disability, 27 (29.4%) had moderate disability, and 25 (27.2%) had severe disability (Table 1).

Participants included in the analysis were not significantly different from those excluded (n = 126) in terms of PDDS score, patient sex, race and body mass index (Table 2). However,

included subjects were older (48.7 vs 44.7 years; p = 0.016), less hypertensive (30.4% vs 52.4%; p = 0.001) and more depressed (20.7% vs 5.6%; p < 0.001).

Results from multivariable analyses are shown in Table 3, Compared to subjects in Tertile 1 (lowest variability), those in Tertile 2 were 3.8 times more likely (OR = 3.77; 95% CI, 1.20 – 11.87; p = 0.023) and those in Tertile 3 (highest variability) were 5.5 times more likely (OR = 5.48; 95% CI, 1.65 – 18.15; p = 0.005) to be in a higher disability group, independent of mean SBP, age, sex, and race/ethnicity. This relationship did not significantly change when BMI and other comorbidities such as hypertension and depression were included in the model (Table e-1).

For sensitivity analyses, we checked the robustness of this association by estimating a logistic regression that predicted the binary indicator of PDDS score 3 or above (moderate or severe disability) and a linear regression that predicted the original PDDS score as a continuous variable (Tables 4 and 5). All sensitivity analyses showed that the significant gradient relationship between SBP variability and disability ratings assessed by PPDS scale persisted.

We checked whether the number of SBP measures used to compute the variability is a confounding factor between the variability and the PDDS outcome by estimating the model shown in Table 2 with the number of measures as an additional covariate (Table e-2). The significant gradient relationship persisted in this model as well (p for trend = 0.007).

Finally, we tested the potential multi-directionality of the relationship between PDDS scores and SBP variability by predicting the SBP variability before and after the study using PDDS scores. From the 92 included subjects, 89 subjects had available ≥3three post-survey SBP measures, for whom the pre- and post-survey SBP coefficients of variation were correlated at r = 0.10 (p = 0.349), while SBP means were correlated at r = 0.83 (p < 0.001). We estimated two

regression models that predict pre-survey and post-survey SBP coefficient of variation using PDDS scores, after controlling for age, sex, and race. PDDS scores did not predict pre-survey variability in any model specification (Table e-3). On the other hand, those with moderate disability had 0.03 higher post-survey coefficient of variation in SBP (95% CI, 0.01 – 0.05; p = 0.003) compared to those with no or mild disability but the severe disability group did not have significantly different SBP variability from the no or mild group. Mean SBP, number of BP measures, or any other comorbidities did not change this association (Table e-4). These tests of directionality of the association between SBP variability and PDDS scores are summarized in Figure 1.

4. Discussion

Our results demonstrate a significant and strong graded relationship between SBP variability and self-reported disability outcome measures (PDDS) among MS patients. Patients in Tertile 3 (highest variability) had an approximately six times higher risk of being in the higher disability group compared to those in Tertile 1 (lowest variability). This relationship was independent of age, sex, race/ethnicity, and mean SBP. This result was robust to different analytic methods such as logistic regression to predict PDDS score 3 or higher (presence of moderate to severe disability) and ordinary least squares regression that predicted the PDDS score as a continuous outcome.

Another important finding in this study is that the association of excessive SBP variability with higher PDDS scores can occur in normotensive individuals. Indeed, overall, 70% of our cohort were normotensive (< 140/90 mm Hg) or without hypertension diagnosis. They also had lower rates of hypertension in higher SBP variability tertiles with the lowest proportion observed in Tertile 3 (19% vs 41% in Tertile 1), a group with the highest SBP variability. This

finding is consistent with previous studies by Sohn and his colleagues on diabetic complications.[8,11,12] Our results also demonstrate that mean SBP was not significantly associated with PDDS groups, suggesting there may be a different physiologic mechanism at play, not simply elevated blood pressures.[13]

Excessive visit-to-visit SBP variability has been associated with cardiovascular and several other health outcomes. To our knowledge, this is the first study to show that excessive visit-to-visit SBP variability may be a risk factor to MS disability progression. Previously, several large studies have identified a relationship between vascular comorbidities and MS outcomes, both clinical and patient-reported, using diagnostic codes (e.g., hypertension) or medications (anti-hypertensives) to classify patients.[1-4] Our results confirm the previous diagnosis-based research and extends that work, by identifying excessive SBP variability as a contributing factor to the previously identified relationship between blood-pressure changes and MS. Our results further suggest that a relevant hemodynamic mechanism in the interplay between cardiovascular disease and MS disability progression, is not simply hypertension (i.e., elevated mean BP), but also excessive SBP variability.

Pathophysiological mechanisms involved in the relationship between blood pressure variability and health outcomes are currently explained by arterial stiffness, endothelial dysfunction, and subclinical inflammation.[22-25] Several factors known to increase blood pressure variability include autonomic dysfunction[26], low hydration status[27], insulin dysregulation[28,29] and sleep-apena[30] are commonly found in patients with MS. Tettey et al. suggests that vascular comorbidities may activate the inflammatory cascade that ultimately leads to neurodegeneration which manifests in disability progression in MS.[2] They also suggested that cerebral endothelial dysfunction may be involved in "trans-endothelial migration of T-lymphocytes and monocytes to

the CNS with destructive and often neurodegenerative consequences."[2] Our results suggest that excessive SBP variability could be a relevant factor in that postulated inflammatory cascade in the vasculature and that may contribute to the cerebral endothelial dysfunction, which combine to produce the MS disability progression we observed in our study. More research is needed to test whether excessive SBP variability is indeed implicated in these pathways.

It is still premature to derive any MS-related clinical implications from our results. But it is advisable that MS patients be checked for SBP variability and those with excessive variability (e.g., within-subject standard deviation of 8 or higher) be recommended for careful vascular evaluation. Interestingly, we found that the majority of patients we identified as having hypertension according to the JNC7[31] and 2017 ACC/AHA criteria[19] did not have an actual diagnosis of hypertension. This suggests a potential under-diagnosis of hypertension, at least in our cohort.

This cross-sectional study was not designed to make any causal inferences between SBP variability and PDDS scores. However, our sensitivity analyses suggest that, while SBP variability was a strong and significant predictor of PDDS scores, the latter did not predict the former. Our data further suggest that the PDDS scores could significantly predict post-survey SBP variability but that the pre- and post-survey SBP variabilities were not correlated ($r = 0.10$; $p = 0.349$). This lends credence to the notion that SBP variability can in fact be a prognostic factor for future disability progression and that there may be a vicious cycle of increasing SBP variability and worsening disability feeding each other dynamically over time.

There are limitations to our work. This is a retrospective study in design and we relied on the CDR for our health system as a source of blood pressure measures and comorbid conditions. Accuracy of these values is not known. Second, we were limited in sample size, mainly because

the majority of patients in the original study sample were excluded because they lacked the requisite number of SBP measures. A bivariate comparison of the included vs excluded patients in Table 2 showed that they are similar in demographic factors, with the noted exception of age and depression, both of which were higher in the included population. These factors may have resulted in higher visit frequency leading to more available SBP values in those meeting eligibility criteria. Interestingly, the included population had lower incidence of hypertension compared to excluded subjects, as identified by ICD-9-CM codes or BP measures taken during the one-year period prior to the survey completion. We were only able to capture BP measures documented in our institutional electronic-medical records and there may have been additional values measured by other providers that were not captured in our data. In addition, while validated, PDDS is a patient-reported outcome that may have unknown response bias. Despite these limitations, we believe our results represent an important first step in studying this relationship.

In conclusion, our results show that excessive SBP variability is associated with increased disability in MS patients, independent of mean SBP, hypertension diagnosis, depression, and obesity. This may represent a novel mechanism which may mediate the relationship between vascular dysfunction and progression of MS disability. Further prospective studies are needed to confirm whether excessive SBP variability is linked to the subclinical inflammation markers and/or cerebral endothelial dysfunction, and other markers of disease progression.

Declaration of Conflicting Interests

Myla D. Goldman has served as a consultant for ADAMAS, Celgene, EMD Serono, Novartis Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals. She has received research funding from Biogen Idec, Novartis Pharmaceuticals, National MS Society, MedDay Pharmaceuticals, and PCORI.

Seulgi Min reports no disclosures.

Jennifer M. Lobo reports no disclosures.

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Data Availability Statement

Anonymized data not published within this article are available from the corresponding author (MDG) on reasonable request.

Author Statement

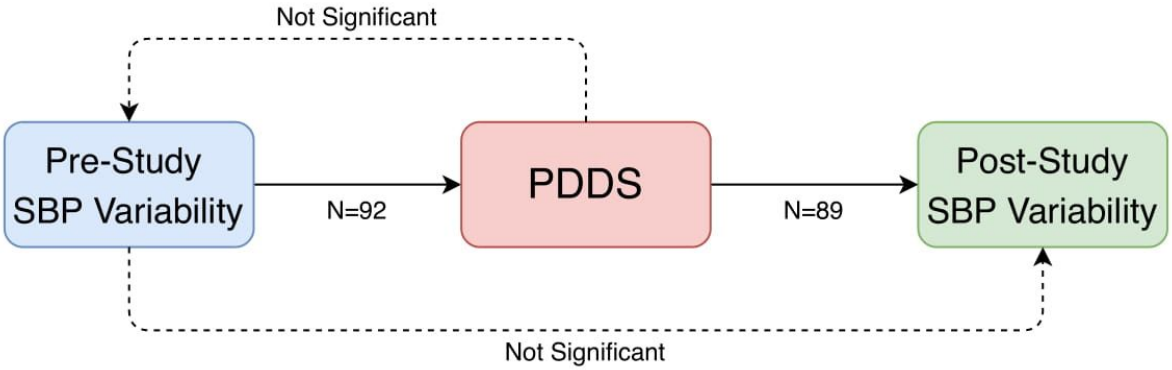
Myla D. Goldman, MD, MSc - Study concept and design, acquisition of data, analysis and interpretation of data, and drafting/revising the manuscript

Seulgi Min, BA - Acquisition of data, drafting/revising the manuscript

Jennifer M. Lobo, PhD - Diagram creation, drafting/revising the manuscript

Min-Woong Sohn, PhD - Study concept and design, analysis and interpretation of data, statistical analysis, and drafting/revising the manuscript

Figure 1. Summary of the significant relationships (solid arrows) and nonsignificant relationships (dashed arrows) between SBP variability and PDDS scores



* Pre-survey SBP variability was significantlypredictive of PDDS score (p = 0.015), and PDDS scores were predictive of Post-surveySBP variability (p = 0.011). PDDS scores did not predict pre-survey SBPvariability, and pre-survey SBP variability did not predict post-study SBPvariability. The p-values were obtained from a Wald test with 2 degrees offreedom (Pre-survey variability to PDDS) and from an F test with 2 and 83degrees of freedom (PDDS to Post-survey variability).

Table 1. Characteristics of Study Cohort (N = 92) *

Variable	Tertiles of SBP coefficient of variation				
	All	1 (Lowest Variability)	2	3 (Highest Variability)	P-Value
	N (%)	N (%)	N (%)	N (%)	
All, n (Row %)	92 (100.00%)	31 (33.70%)	30 (32.61%)	31 (33.70%)	
Age, mean (SD)	44.71 (12.16)	45.03 (14.29)	45.93 (12.54)	43.19 (9.41)	0.673
Female	50 (54.35%)	18 (58.06%)	20 (66.67%)	12 (38.71%)	0.080
White Race	76 (82.61%)	29 (93.55%)	25 (83.33%)	22 (70.97%)	0.063
Within-subject SBP					
Mean (mm Hg), mean (SD)	124.05 (13.19)	128.01 (12.98)	118.16 (11.86)	125.78 (13.00)	0.008
Standard deviation (mm Hg), mean (SD)	9.94 (4.59)	5.82 (2.05)	9.17 (1.41)	14.79 (3.91)	< 0.001
Maximum (mm Hg), mean (SD)	137.95 (15.11)	135.74 (13.70)	132.60 (12.37)	145.32 (16.34)	0.002
Minimum (mm Hg), mean (SD)	110.68 (14.19)	120.45 (13.11)	105.43 (11.24)	106.00 (12.95)	< 0.001
Number of measures, mean (SD)	7.93 (5.53)	6.29 (3.97)	10.33 (6.18)	7.26 (5.57)	0.011
Body mass index (kg/m²), mean (SD)	29.03 (6.02)	28.73 (5.64)	28.04 (5.25)	30.28 (6.99)	0.330
Depression	19 (20.65%)	4 (12.90%)	11 (36.67%)	4 (12.90%)	0.031
Hypertension	28 (30.43%)	13 (41.94%)	9 (30.00%)	6 (19.35%)	0.154
PDDS Score, mean (SD)	2.22 (1.89)	1.52 (1.95)	2.73 (1.70)	2.42 (1.86)	0.031
PDDS Score, median (Interquartile Range)	2 (0 – 4)	0 (0 – 3)	3 (1 – 4)	2 (1 - 4)	
PDDS Score (3 Groups)					
No or Mild (0, 1)	40 (43.48%)	19 (61.29%)	9 (30.00%)	12 (38.71%)	0.163
Moderate (2, 3)	27 (29.35%)	6 (19.35%)	11 (36.67%)	10 (32.26%)	
Severe (4 or higher)	25 (27.17%)	6 (19.35%)	10 (33.33%)	9 (29.03%)	

* SBP = systolic blood pressure; SD = standard deviation; PDDS = patient determined disease steps. All percentages are either column percentages (Col %) or row percentages (Row %). P-values for continuous variables were computed using one-way ANOVA and those for categorical variables were based on Pearson chi-square tests.

Table 2. Comparison of the included and excluded patients in the original cohort*

Variables	All	Excluded	Included	P-Value
	N (Col %)	N (Row %)	N (Row %)	
All	218 (100.00%)	126 (57.80%)	92 (42.20%)	
Age, mean (SD)	47.04 (12.24)	44.71 (12.16)	48.74 (12.06)	0.016
Female	113 (51.83%)	63 (50.00%)	50 (54.35%)	0.526
White Race	181 (83.03%)	105 (83.33%)	76 (82.61%)	0.888
BMI (kg/m²), mean (SD)	28.25 (6.19)	29.03 (6.02)	27.59 (6.29)	0.102
Hypertension	94 (43.12%)	66 (52.38%)	28 (30.43%)	0.001
Diabetes	6 (2.75%)	4 (3.17%)	2 (2.17%)	0.656
Depression	26 (11.93%)	7 (5.56%)	19 (20.65%)	< 0.001
PDDS Score, mean (SD)	2.05 (1.81)	2.22 (1.89)	1.93 (1.75)	0.247
PDDS Score (3 Groups)				
No or Mild (0, 1)	95 (43.58%)	55 (43.65%)	40 (43.48%)	0.212
Moderate (2, 3)	75 (34.40%)	48 (38.10%)	27 (29.35%)	
Severe (4 or higher)	48 (22.02%)	23 (18.25%)	25 (27.17%)	

* SD = standard deviation; BMI = body mass index; PDDS = patient determined disease steps.

Table 3. Ordinal logistic regression results for MS patients in a higher disability group (N = 92)*

Variables	OR (95% CI)	P-Value
SBP variability tertiles [1 (Lowest Variability)]		
2	3.774 (1.200 - 11.865)	0.023
3 (Highest Variability)	5.477 (1.653 - 18.148)	0.005
Age	1.096 (1.049 - 1.145)	< 0.001
Female [Male]	2.993 (1.197 - 7.484)	0.019
White Race [Other race/ethnicity]	1.331 (0.412 - 4.299)	0.633
Within-subject mean SBP (mm Hg)	1.004 (0.970 - 1.040)	0.807

* Disability groups were defined as No or Mild (PDDS scores 0 or 1), Moderate (2 or 3), and Severe (4 or higher). Reference groups are in angle brackets.

Table 4. Logistic regression results for patients having PDDS scores ≥3 (N = 92)*

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value
SBP variability tertiles [1 (Lowest Variability)]						
2	7.098 (1.745 - 28.862)	0.006	7.767 (1.822 - 33.105)	0.006	7.662 (1.783 - 32.928)	0.006
3 (Highest Variability)	4.564 (1.210 - 17.213)	0.025	4.338 (1.124 - 16.749)	0.033	4.273 (1.106 - 16.514)	0.035
Age	1.106 (1.047 - 1.168)	< 0.001	1.107 (1.047 - 1.170)	< 0.001	1.109 (1.048 - 1.174)	< 0.001
Female [Male]	2.079 (0.718 - 6.020)	0.177	2.186 (0.741 - 6.444)	0.156	2.215 (0.751 - 6.536)	0.150
White Race [Other race/ethnicity]	1.972 (0.446 - 8.723)	0.371	1.867 (0.427 - 8.159)	0.407	1.984 (0.445 - 8.835)	0.369
Within-subject mean SBP (mm Hg)	1.003 (0.962 - 1.045)	0.901	1.002 (0.961 - 1.044)	0.929	0.994 (0.947 - 1.044)	0.818
Hypertension			0.637 (0.199 - 2.038)	0.447	0.605 (0.188 - 1.950)	0.400
Depression			0.632 (0.179 - 2.230)	0.476	0.617 (0.174 - 2.188)	0.454
Body mass index (kg/m²)					1.032 (0.932 - 1.143)	0.542
Pseudo R^2	0.265		0.273		0.276	
Hosmer-Lemeshow Test (df), p-value	2.691 (8); p = 0.9522		7.885 (8); p = 0.4448		6.6506 (8); p = 0.5748	
Area under the ROC Curve	0.823		0.826		0.831	
AIC	107.184		110.186		111.814	
BIC	124.836		132.883		137.032	

* PDDS = patient determined disease steps; SBP = systolic blood pressure. AIC = Akaike information criterion; BIC = Bayesian information criterion. Reference groups are in angle brackets. P-values in these sensitivity analyses were NOT corrected for multiple comparison.

Table 5. Ordinary least squares models to predict PDDS scores (N = 92)*

Variable	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value
Intercept	-2.524 (-5.944 - 0.896)	0.146	-2.536 (-6.032 - 0.961)	0.153	-2.556 (-6.069 - 0.958)	0.152
SBP variability tertiles [1 (Lowest Variability)]						
2	1.132 (0.280 - 1.985)	0.010	1.153 (0.263 - 2.044)	0.012	1.128 (0.228 - 2.028)	0.015
3 (Highest Variability)	1.245 (0.426 - 2.065)	0.003	1.247 (0.402 - 2.092)	0.004	1.213 (0.355 - 2.072)	0.006
Age	0.074 (0.045 - 0.104)	< 0.001	0.075 (0.045 - 0.105)	< 0.001	0.075 (0.045 - 0.105)	< 0.001
Female [Male]	0.630 (-0.056 - 1.316)	0.071	0.625 (-0.071 - 1.321)	0.078	0.623 (-0.076 - 1.322)	0.080
White Race [Other race/ethnicity]	0.371 (-0.553 - 1.294)	0.427	0.363 (-0.575 - 1.302)	0.443	0.393 (-0.556 - 1.342)	0.413
Within-subject mean SBP (mm Hg)	0.000 (-0.028 - 0.028)	0.990	0.000 (-0.028 - 0.028)	0.996	-0.004 (-0.036 - 0.028)	0.805
Hypertension			0.016 (-0.718 - 0.750)	0.965	-0.009 (-0.751 - 0.734)	0.982
Depression			-0.079 (-0.925 - 0.766)	0.853	-0.085 (-0.935 - 0.764)	0.842
Body mass index (kg/m²)					0.017 (-0.047 - 0.080)	0.597
R^2	0.368		0.368		0.370	
Adjusted R^2	0.323		0.307		0.301	
AIC	351.224		355.183		356.868	
BIC	371.398		380.400		384.607	

* PDDS = patient determined disease steps; SBP = systolic blood pressure. AIC = Akaike information criterion; BIC = Bayesian information criterion. Reference groups are in angle brackets. P-values in these sensitivity analyses were NOT corrected for multiple comparison.

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Table e-1. Ordinal logistic regression for MS patients in a higher disability group with BMI and comorbid conditions (N = 92)*

Variables	Estimate (95% CI)	P-Value
Tertiles of SBP coefficient of variation		
2	3.480 (1.077 - 11.251)	0.037
3 (Highest Variability)	5.193 (1.531 - 17.616)	0.008
Age	1.100 (1.051 - 1.150)	< 0.001
Female	3.177 (1.249 - 8.078)	0.015
White Race	1.495 (0.450 - 4.963)	0.512
Within-subject mean SBP (mm Hg)	0.991 (0.952 - 1.031)	0.647
Hypertension	0.930 (0.356 - 2.430)	0.882
Depression	1.183 (0.426 - 3.289)	0.747
Body mass index (kg/m²)	1.057 (0.974 - 1.147)	0.186

* SBP = systolic blood pressure. Reference groups are in angle brackets.

Table e-2. Ordinal logistic regression for MS patients in a higher disability group with the number of SBP measures as a covariate (N = 92)*

Variables	Estimate (95% CI)	P-Value
SBP variability tertiles [1 (Lowest Variability)		
2	3.090 (0.959 - 9.956)	0.059
3 (Highest Variability)	5.204 (1.576 - 17.182)	0.007
Age	1.101 (1.053 - 1.151)	0.000
Female [Male]	2.598 (1.023 - 6.595)	0.045
White Race [Other race/ethnicity]	1.333 (0.411 - 4.319)	0.632
Within-subject mean SBP (mm Hg)	1.013 (0.977 - 1.050)	0.489
Within-subject SBP measures	1.084 (0.990 - 1.188)	0.083

* SBP = systolic blood pressure. Reference groups are in angle brackets.

Table e-3. Ordinary least squares models to predict SBP variability before the study (N = 92)*

Variables	Model 1		Model 2		Model 2	
	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value
Intercept	0.098 (0.069 - 0.128)	0.000	0.042 -(0.027 - 0.110)	0.232	0.076 -(0.004 - 0.155)	0.063
PDDS severity [1 (No or Mild)]						
2 (Moderate)	0.010 (-0.009 - 0.029)	0.286	0.011 (-0.008 - 0.030)	0.256	0.009 (-0.011 - 0.029)	0.383
3 (Severe)	0.019 (-0.001 - 0.039)	0.059	0.019 (-0.001 - 0.040)	0.063	0.018 (-0.003 - 0.039)	0.095
Age (per 100 y)	0.000 (-0.001 - 0.001)	0.567	0.000 (-0.001 - 0.000)	0.340	0.000 (-0.001 - 0.000)	0.431
Female	-0.004 (-0.019 - 0.010)	0.544	-0.006 (-0.020 - 0.009)	0.424	-0.005 (-0.020 - 0.010)	0.525
White Race	-0.018 (-0.038 - 0.002)	0.075	-0.017 (-0.037 - 0.003)	0.097	-0.016 (-0.037 - 0.004)	0.123
Within-subject mean SBP (mm Hg)			0.001 (0.000 - 0.001)	0.056	0.000 (-0.001 - 0.001)	0.666
Within-subject BP measures			0.000 (-0.001 - 0.001)	0.958	0.000 (-0.001 - 0.002)	0.824
BMI (kg/m^2)					0.000 (-0.001 - 0.002)	0.617
Depression					0.000 (-0.018 - 0.017)	0.972
Sleep Disturbance					0.000 (-0.027 - 0.027)	0.982
Hypertension					-0.014 (-0.030 - 0.002)	0.086

* PDDS = patient determined disease steps; SBP = systolic blood pressure; BMI = body mass index. Reference groups are in angle brackets.

Table e-4. Ordinary least squares models to predict SBP variability post study (N = 89)*

Variables	Model 1		Model 2		Model 2	
	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value
Intercept	0.072 (0.041 - 0.103)	< 0.001	0.008 -(0.069 - 0.084)	0.840	0.004 -(0.075 - 0.082)	0.928
PDDS scores [1 (No or Mild)]						
2 (Moderate)	0.031 (0.011 - 0.051)	0.003	0.030 (0.010 - 0.050)	0.004	0.028 (0.007 - 0.049)	0.010
3 (Severe)	0.021 (0.000 - 0.042)	0.052	0.018 (-0.004 - 0.040)	0.101	0.018 (-0.004 - 0.040)	0.113
Age (per 100 y)	0.001 (-0.076 - 0.077)	0.990	-0.005 (-0.082 - 0.072)	0.892	-0.006 (-0.086 - 0.074)	0.884
Female	-0.007 (-0.023 - 0.008)	0.357	-0.009 (-0.024 - 0.007)	0.265	-0.009 (-0.024 - 0.007)	0.278
White Race	-0.005 (-0.026 - 0.016)	0.655	-0.002 (-0.023 - 0.019)	0.862	-0.002 (-0.023 - 0.020)	0.873
Within-subject mean SBP (mm Hg)			0.000 (0.000 - 0.001)	0.103	0.000 (0.000 - 0.001)	0.236
Within-subject BP measures			0.001 (0.000 - 0.002)	0.228	0.001 (-0.001 - 0.002)	0.393
BMI (kg/m^2)					0.000 (-0.001 - 0.002)	0.539
Depression					0.011 (-0.008 - 0.030)	0.272
Sleep Disturbance					0.005 (-0.022 - 0.032)	0.709
Hypertension					0.001 (-0.016 - 0.018)	0.875

* PDDS = patient determined disease steps; SBP = systolic blood pressure; BMI = body mass index. Reference groups are in angle brackets.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4-5

Bias	#9	Describe any efforts to address potential sources of bias	5-6
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4-5
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5-6
Statistical methods	#12c	Explain how missing data were addressed	5-6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	N/A
Statistical methods	#12e	Describe any sensitivity analyses	5-6
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
Participants	#13b	Give reasons for non-participation at each stage	6

Participants	#13c	Consider use of a flow diagram	N/A
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6-7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	6-7
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
Main results	#16b	Report category boundaries when continuous variables were categorized	7-8, Table 1
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8

Discussion

Key results	#18	Summarise key results with reference to study objectives	8-9
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	11-12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

BMJ Open

A retrospective cohort study of the relationship between systolic blood pressure variability and multiple sclerosis disability

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A retrospective cohort study of the relationship between systolic blood pressure variability and multiple sclerosis disability

Running title: Blood pressure variability and MS disability

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ABSTRACT

Objective: To examine the relationship between visit-to-visit systolic blood pressure (SBP) variability and patient-reported outcome measure of disability in multiple sclerosis (MS) patients.

Design: A retrospective cohort study of individuals with MS who completed a Patient Determined Disease Steps (PDDS) scale between 2011 – 2015 at a multiple sclerosis specialty clinic.

Participants: Individuals with MS for whom both a completed PDDS scale and ≥3 SBP measures within the prior 12 months of the survey were available.

Main Outcome Measure: Participants were grouped into three classes of disability (No or Mild (PDDS 0 - 1), Moderate (2 - 3), Severe (4 - 7)). SBP variability was calculated as within-subject standard deviations using all SBP measures taken during the past 12 months. SBP variability was analyzed by Tertile groups.

Results: Ninety-two subjects were included in this analysis. Mean PDDS score was 2.22±1.89. Compared to subjects in Tertile 1 (lowest variability), the odds of being in a higher disability group was 3.5 times higher (OR = 3.48; 95% CI, 1.08 – 11.25; p = 0.037) in Tertile 2 and 5.2 times higher (OR = 5.19; 95% CI, 1.53 – 17.61; p = 0.008) in Tertile 3 (highest variability), independent of mean SBP, age, sex, race/ethnicity, BMI, and comorbidities (p for trend = 0.008). Mean PDDS scores were 1.52±1.18 in Tertile 1, 2.73±1.02 in Tertile 2 and 2.42±0.89 in Tertile 3 after adjusting for the same covariates.

Conclusions: Our results show a significant gradient relationship between SBP variability and MS-related disability. More research is needed to determine the underlying pathophysiological relationship between SBP variability and MS disability progression.

Keywords: multiple sclerosis, disability progression, blood pressure variability, cardiovascular comorbidities

Article Summary

Strengths and Limitations of This Study

- This is a first study to look at the relationship between the systolic blood pressure (SBP) variability and MS-related disability outcomes.
- This study paired prospectively collected patient-reported outcomes with retrospectively collected data, which allowed us to leverage existing data to take a first look at this novel question.
- Our analysis included a multi-faceted approach including - patient-reported measures, clinical outcomes (blood pressure), and concurrent co-morbid diagnosis.
- The retrospective collection of the paired clinical data limited the standardization of the number and inter-interval timing of blood pressure measurements, as well as the total number of subjects available for analysis.

1. Introduction

Multiple Sclerosis (MS) is an inflammatory and degenerative disorder of the central nervous system. Individuals with MS commonly experience some degree of disability progression independent of inflammatory driven events. The underlying mechanisms driving this inflammatory-independent disease progression remains poorly understood. It is likely that there is no single factor that drives MS progression. Instead it is believed to be a multi-faceted process with variable importance and influence of factors for any individual person. Posited factors include medical co-morbidities, as well as environmental factors such as smoking or vitamin D exposure.

Co-morbid cardiovascular disease (CVD) is more prevalent in MS relative to healthy populations. In MS patients, CVD is associated with worsened disease progression and reduced quality of life, although the mechanism remains uncertain.[1-5] Visit-to-visit systolic blood pressure (SBP) variability is an emerging risk factor for a wide array of health outcomes including CVD, kidney failure, cognitive dysfunction, diabetic complications, and all-cause mortality.[6-10] Excessive SBP variability (≥ 10 within-subject standard deviation) has been associated with many of these outcomes independent of mean blood pressure and hypertension.[8,11,12] Evidence suggests that visit-to-visit blood pressure variability may have stronger effects on cardiovascular outcomes than that of measures taken during a single visit or by 24-hour ambulatory monitoring devices.[13-15] While various vascular comorbidities have been previously studied in the progression of MS, the relationship between SBP variability and MS progression has yet to be explored.

We conducted a retrospective cohort study to examine the relationship between SBP variability and self-reported MS disability. We hypothesized that higher SBP variability is associated with greater degree of disability among individuals with MS.

2. Material and Methods

Study Design and Sample

We conducted a retrospective cohort study of individuals with MS who participated in research between 2011 and 2015 at the University of Virginia School of Medicine (UVA) and had previously prospectively completed the Patient Determined Disease Steps (PDDS) scale, a validated patient-reported outcome measure of MS disability.[16-18] The PDDS is a self-report tool of MS disability in which participants indicate their level of disability between 0 (‘normal’) and

8 ('bedridden'), where 4 indicates "early cane" use. SBP measurements were obtained from medical records and only those subjects with ≥ 3 available SBP measurements captured within the 12 months prior to PDDS completion were included in the analysis. This study was approved by the UVA institutional review board.

Visit-to-visit variability of systolic blood pressure

All available SBP measures within 12-months pre- and post-PDDS survey data were extracted from the electronic medical records system. Within-subject means and standard deviations of SBP were computed. Coefficient of variation was calculated by dividing the standard deviation by the mean to obtain a measure of variability that was more independent of the mean than standard deviation. We used the within-subject coefficients of variation to divide the study sample into three equal-sized groups (tertiles), whose SBPCV ranges are 0.012 - 0.064 for Tertile 1 (the lowest variability group), 0.065 – 0.087 for Tertile 2, and 0.089 – 0.172 for Tertile 3 (the highest variability group).

Covariates

Demographic data (age, sex, and race/ethnicity) were collected. We searched with Clinical Data Repository (CDR), a data warehouse containing clinical information from patients treated at the University of Virginia, for the 12-month period prior to the PDDS survey to identify co-existing conditions including cardiovascular disease (ICD-9-CM codes, 410.xx – 414.xx, 428.xx, 431.xx, 434.xx, and 436.xx), peripheral vascular disease (443.9), diabetes (250.xx, 357.2, 362.01), depression (311.xx, 300.4, 296.20, 296.80, 296.89, 296.90), and hypertension (401.x). In addition to the diagnostic codes, we classified hypertension in patients using the 140/90 mm Hg per ACC/AHA guideline.[19] We also extracted body mass index (BMI) data within six months of the PDDS survey completion date.

Statistical Analysis

We used multiple regression analysis to examine the relationship between SBP variability and the PDDS disability rating. To best utilize the ordinal nature of our response variable (PDDS score)[16,17], we estimated an ordinal logistic regression[20] and found that it did not satisfy the proportional odds assumption.[20,21] We tried several medically meaningful groupings to satisfy the assumption and decided on three groups based on the PDDS scores as follows: No or Mild Disability (PDDS scores 0 or 1), Moderate Disability (PDDS scores 2 or 3), and Severe Disability (PDDS scores 4 or higher). The disability outcomes in these new groups were modeled using ordinal logistic regression as a function of SBP variability, adjusting for patient demographic data (age, sex, and race/ethnicity), mean SBP, BMI, hypertension, and depression.

As a sensitivity analysis, we estimated two additional models. First, we defined the PDDS score 3 or above as presence of severe disability and modeled the binary response (0 = No or Mild Disability; 1 = Moderate to Severe Disability) using a logistic regression (Table e-1). Second, we treated the PDDS score as a continuous variable and estimated a linear regression that are identically specified as the ordinal logistic regression model (Table e-2). Because SBP variability is found to be correlated with the number of measures used in computing the within-subject standard deviations, we controlled for the number of BP measures in another sensitivity analysis (Table e-3).

Finally, we tested whether PDDS scores can predict SBP variability before the study (Table e-4) and whether PDDS scores can predict SBP variability after the survey (Table e-5) by estimating linear regressions to predict pre- and post-survey SBP variability as a function of PDDS scores, adjusting for age, sex, race, and other covariates.

We used Stata SE v. 15.1 (StataCorp, College Station, TX) for all statistical analysis.

Patient and Public Involvement

No patient involved.

3. Results

A total of 218 PDDS surveys were identified from available study data. Among these, 17 subjects had completed more than one PDDS survey; in such cases, the first available survey date with corresponding ≥ 3 SBP measures was utilized. No subject contributed more than once to the final data set. When the same respondent participated in the PDDS survey more than once, we used the first survey. Of the resultant subjects, only 94 had the requisite ≥ 3 blood pressure measures in the 12-months prior to the survey completion date. Two additional subjects were excluded due to lack of available records to permit BMI calculation (absent height and/or weight).

The resultant 92 subjects included in the final analysis had a mean age of 44.7±12.2 years at the time of PDDS survey completion. They were predominantly white (82.6%) and 54% female. Their mean SBP was 124.1±13.2 mm Hg overall and were highest in Tertile 1 (128.0±13.0 mm Hg) and lowest in Tertile 2 (125.8±13.0 mm Hg). Their within-subject SBP standard deviation was 9.9±4.6 mm Hg overall but changed from 5.8±2.1 mm Hg (interquartile range [IQR] 4.4 – 7.4 mm Hg) to 9.2±1.4 mm Hg (IQR 11.7 – 17.7 mm Hg) in Tertile 2, and 14.8±3.9 (IQR 8.5 – 10.2 mm Hg) in Tertile 3. Their mean BMI was 29.0 kg/m^2. A total of 19

(20.7%) had depression, 28 (30.4%) had hypertension (11 patients with a diagnosis in ICD-9-CM and 17 patients with elevated mean BP). We could not identify any subject with vascular comorbidities except for one who had acute myocardial infarction and was in Tertile 2. For this reason, vascular comorbidities have not been used in any subsequent analyses. The mean and median PDDS score was 2.2±1.89 and 2 (IQR 0 – 4). Forty patients (43.5%) had no or mild disability, 27 (29.4%) had moderate disability, and 25 (27.2%) had severe disability (Table 1).

Participants included in the analysis were not significantly different from those excluded (n = 126) in terms of PDDS score, patient sex, race and body mass index (Table 2). However, included subjects were older (48.7 vs 44.7 years; p = 0.016), less hypertensive (30.4% vs 52.4%; p = 0.001) and more depressed (20.7% vs 5.6%; p < 0.001).

Results from multiple regression analyses are shown in Table 3. Compared to subjects in Tertile 1 (lowest variability), the odds of being in a higher disability group was 3.5 times higher (OR = 3.48; 95% CI, 1.08 – 11.25; p = 0.037) in Tertile 2 and 5.2 times higher (OR = 5.19; 95% CI, 1.53 – 17.61; p = 0.008) in Tertile 3 (highest variability), independent of mean SBP, age, sex, race/ethnicity, BMI, hypertension and depression (p for trend = 0.008). Mean PDDS scores were 1.52±1.18 in Tertile 1, 2.73±1.02 in Tertile 2 and 2.42±0.89 in Tertile 3 after adjusting for the same covariates as the model shown in Table 3.

For sensitivity analyses, we checked the robustness of this association by estimating a logistic regression that predicted the binary indicator of PDDS score 3 or above (moderate or severe disability) and a linear regression that predicted the original PDDS score as a continuous variable (Tables e-1 and e-2). All sensitivity analyses showed that the significant gradient relationship between SBP variability and disability ratings assessed by PPDS scale persisted.

We checked whether the number of SBP measures used to compute the variability is a confounding factor between the variability and the PDDS outcome by estimating the model shown in Table 2 with the number of measures as an additional covariate (Table e-3). The significant gradient relationship persisted in this model as well (p for trend = 0.007).

Finally, we tested the potential multi-directionality of the relationship between PDDS scores and SBP variability by predicting the SBP variability before and after the study using PDDS scores. From the 92 included subjects, 89 subjects had available ≥3 post-survey SBP measures, for whom the pre- and post-survey SBP coefficients of variation were correlated at r = 0.10 (p = 0.349), while SBP means were correlated at r = 0.83 (p < 0.001). We estimated two regression models that predict pre-survey and post-survey SBP coefficient of variation using PDDS scores, after controlling for age, sex, and race. PDDS scores did not predict pre-survey variability in any model specification (Table e-4). On the other hand, those with moderate disability had 0.03 higher post-survey coefficient of variation in SBP (95% CI, 0.01 – 0.05; p = 0.003) compared to those with no or mild disability but the severe disability group did not have significantly different SBP variability from the no or mild group. Mean SBP, number of BP measures, or any other comorbidities did not change this association (Table e-5). These tests of directionality of the association between SBP variability and PDDS scores are summarized in Figure 1.

4. Discussion

Our results demonstrate a significant and strong graded relationship between SBP variability and self-reported disability outcome measures (PDDS) among MS patients. Patients in Tertile 3 (highest variability) had an approximately six times higher risk of being in the higher disability group compared to those in Tertile 1 (lowest variability). This relationship was

independent of mean SBP, BMI, hypertension, depression, and patient demographic factors. This result was robust to different analytic methods such as logistic regression to predict PDDS score 3 or higher (presence of moderate to severe disability) and ordinary least squares regression that predicted the PDDS score as a continuous outcome.

Another important finding in this study is that the association of excessive SBP variability with higher PDDS scores can occur in normotensive individuals. Indeed, overall, 70% of our cohort were normotensive (< 140/90 mm Hg) or without hypertension diagnosis. They also had lower rates of hypertension in higher SBP variability tertiles with the lowest proportion observed in Tertile 3 (19% vs 41% in Tertile 1), a group with the highest SBP variability. This finding is consistent with previous studies by Sohn and his colleagues on diabetic complications.[8,11,12] Our results also demonstrate that mean SBP was not significantly associated with PDDS groups, suggesting there may be a different physiologic mechanism at play, not simply elevated blood pressures.[13]

Excessive visit-to-visit SBP variability has been associated with cardiovascular and several other health outcomes. To our knowledge, this is the first study to show that excessive visit-to-visit SBP variability may be a risk factor to MS disability progression. Previously, several large studies have identified a relationship between vascular comorbidities and MS outcomes, both clinical and patient-reported, using diagnostic codes (e.g., hypertension) or medications (anti-hypertensives) to classify patients.[1-4] Our results confirm the previous diagnosis-based research and extends that work, by identifying excessive SBP variability as a contributing factor to the previously identified relationship between blood-pressure changes and MS. Our results further suggest that a relevant hemodynamic mechanism in the interplay

between cardiovascular disease and MS disability progression, is not simply hypertension (i.e., elevated mean BP), but also excessive SBP variability.

Pathophysiological mechanisms involved in the relationship between blood pressure variability and health outcomes are currently explained by arterial stiffness, endothelial dysfunction, and subclinical inflammation.[22-25] Several factors known to increase blood pressure variability include autonomic dysfunction[26], low hydration status[27], insulin dysregulation[28,29] and sleep-apena[30] are commonly found in patients with MS. Tettey et al. suggests that vascular comorbidities may activate the inflammatory cascade that ultimately leads to neurodegeneration which manifests in disability progression in MS.[2] They also suggested that cerebral endothelial dysfunction may be involved in "trans-endothelial migration of T-lymphocytes and monocytes to the CNS with destructive and often neurodegenerative consequences."[2] Our results suggest that excessive SBP variability could be a relevant factor in that postulated inflammatory cascade in the vasculature and that may contribute to the cerebral endothelial dysfunction, which combine to produce the MS disability progression we observed in our study. More research is needed to test whether excessive SBP variability is indeed implicated in these pathways.

It is still premature to derive any MS-related clinical implications from our results. But it is advisable that MS patients be checked for SBP variability and those with excessive variability (e.g., within-subject standard deviation of 8 or higher) be recommended for careful vascular evaluation. Interestingly, we found that the majority of patients we identified as having hypertension according to the JNC7[31] and 2017 ACC/AHA criteria[19] did not have an actual diagnosis of hypertension. This suggests a potential under-diagnosis of hypertension, at least in our cohort.

This cross-sectional study was not designed to make any causal inferences between SBP variability and PDDS scores. However, our sensitivity analyses suggest that, while SBP variability was a strong and significant predictor of PDDS scores, the latter did not predict the former. Our data further suggest that the PDDS scores could significantly predict post-survey SBP variability but that the pre- and post-survey SBP variabilities were not correlated ($r = 0.10$; $p = 0.349$). This lends credence to the notion that SBP variability can in fact be a prognostic factor for future disability progression and that there may be a vicious cycle of increasing SBP variability and worsening disability feeding each other dynamically over time.

There are limitations to our work. This is a retrospective study in design and we relied on the CDR for our health system as a source of blood pressure measures and comorbid conditions. Accuracy of these values is not known. Second, we were limited in sample size, mainly because the majority of patients in the original study sample were excluded because they lacked the requisite number of SBP measures. A bivariate comparison of the included vs excluded patients in Table 2 showed that they are similar in demographic factors, with the noted exception of age and depression, both of which were higher in the included population. These factors may have resulted in higher visit frequency leading to more available SBP values in those meeting eligibility criteria. Interestingly, the included population had lower incidence of hypertension compared to excluded subjects, as identified by ICD-9-CM codes or BP measures taken during the one-year period prior to the survey completion. We were only able to capture BP measures documented in our institutional electronic-medical records and there may have been additional values measured by other providers that were not captured in our data. We were not able to control for some potential confounders, including MS disease duration, disease modifying treatments, and some comorbid conditions that might have affected disability outcomes in our

data. In addition, while validated, PDDS is a patient-reported outcome that may have unknown response bias. Despite these limitations, we believe our results represent an important first step in studying this relationship.

In conclusion, our results show that excessive SBP variability is associated with increased disability in MS patients, independent of mean SBP, hypertension diagnosis, depression, and obesity. This may represent a novel mechanism which may mediate the relationship between vascular dysfunction and progression of MS disability. Further prospective studies are needed to confirm whether excessive SBP variability is linked to the subclinical inflammation markers and/or cerebral endothelial dysfunction, and other markers of disease progression.

Declaration of Conflicting Interests

Myla D. Goldman has served as a consultant for ADAMAS, Celgene, EMD Serono, Novartis Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals. She has received research funding from Biogen Idec, Novartis Pharmaceuticals, National MS Society, MedDay Pharmaceuticals, and PCORI.

Seulgi Min reports no disclosures.

Jennifer M. Lobo reports no disclosures.

Min-Woong Sohn reports no disclosures.

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Data Availability Statement

Anonymized data not published within this article are available from the corresponding author (MDG) on reasonable request.

Author Statement

Myla D. Goldman, MD, MSc - Study concept and design, acquisition of data, analysis and interpretation of data, and drafting/revising the manuscript

Seulgi Min, BA - Acquisition of data, drafting/revising the manuscript

Jennifer M. Lobo, PhD - Diagram creation, drafting/revising the manuscript

Min-Woong Sohn, PhD - Study concept and design, analysis and interpretation of data, statistical analysis, and drafting/revising the manuscript

Figure 1. Summary of the significant relationships (solid arrows) and nonsignificant relationships (dashed arrows) between SBP variability and PDDS scores*

<<Figure 1 Here>>

* Pre-survey SBP variability was significantly predictive of PDDS scores ($p = 0.015$), and PDDS scores were predictive of post-survey PDDS variability ($p = 0.011$). PDDS scores did not predict pre-survey SBP variability, and pre-survey SBP variability did not predict post-survey SBP variability. The p-values were obtained from a Wald test with 2 degrees of freedom (pre-survey variability to PDDS) and from an F test with 2 and 83 degrees of freedom (PDDS to post-survey variability).

Table 1. Characteristics of Study Cohort (N = 92) *

Variable	Tertiles of SBP coefficient of variation				
	All	1 (Lowest Variability)	2	3 (Highest Variability)	P-Value
	N (%)	N (%)	N (%)	N (%)	
All, n (Row %)	92 (100.00%)	31 (33.70%)	30 (32.61%)	31 (33.70%)	
Age, mean (SD)	44.71 (12.16)	45.03 (14.29)	45.93 (12.54)	43.19 (9.41)	0.673
Female	50 (54.35%)	18 (58.06%)	20 (66.67%)	12 (38.71%)	0.080
White Race	76 (82.61%)	29 (93.55%)	25 (83.33%)	22 (70.97%)	0.063
Within-subject SBP					
Mean (mm Hg), mean (SD)	124.05 (13.19)	128.01 (12.98)	118.16 (11.86)	125.78 (13.00)	0.008
Standard deviation (mm Hg), mean (SD)	9.94 (4.59)	5.82 (2.05)	9.17 (1.41)	14.79 (3.91)	< 0.001
Maximum (mm Hg), mean (SD)	137.95 (15.11)	135.74 (13.70)	132.60 (12.37)	145.32 (16.34)	0.002
Minimum (mm Hg), mean (SD)	110.68 (14.19)	120.45 (13.11)	105.43 (11.24)	106.00 (12.95)	< 0.001
Number of measures, mean (SD)	7.93 (5.53)	6.29 (3.97)	10.33 (6.18)	7.26 (5.57)	0.011
Body mass index (kg/m²), mean (SD)	29.03 (6.02)	28.73 (5.64)	28.04 (5.25)	30.28 (6.99)	0.330
Depression	19 (20.65%)	4 (12.90%)	11 (36.67%)	4 (12.90%)	0.031
Hypertension	28 (30.43%)	13 (41.94%)	9 (30.00%)	6 (19.35%)	0.154
PDDS Score, mean (SD)	2.22 (1.89)	1.52 (1.95)	2.73 (1.70)	2.42 (1.86)	0.031
PDDS Score, median (Interquartile Range)	2 (0 – 4)	0 (0 – 3)	3 (1 – 4)	2 (1 - 4)	
PDDS Score (3 Groups)					
No or Mild (0, 1)	40 (43.48%)	19 (61.29%)	9 (30.00%)	12 (38.71%)	0.163
Moderate (2, 3)	27 (29.35%)	6 (19.35%)	11 (36.67%)	10 (32.26%)	
Severe (4 or higher)	25 (27.17%)	6 (19.35%)	10 (33.33%)	9 (29.03%)	

* SBP = systolic blood pressure; SD = standard deviation; PDDS = patient determined disease steps. All percentages are either column percentages (Col %) or row percentages (Row %). P-values for continuous variables were computed using one-way ANOVA and those for categorical variables were based on Pearson chi-square tests.

Table 2. Comparison of the included and excluded patients in the original cohort*

Variables	All	Excluded	Included	P-Value
	N (Col %)	N (Row %)	N (Row %)	
All	218 (100.00%)	126 (57.80%)	92 (42.20%)	
Age, mean (SD)	47.04 (12.24)	44.71 (12.16)	48.74 (12.06)	0.016
Female	113 (51.83%)	63 (50.00%)	50 (54.35%)	0.526
White Race	181 (83.03%)	105 (83.33%)	76 (82.61%)	0.888
BMI (kg/m²), mean (SD)	28.25 (6.19)	29.03 (6.02)	27.59 (6.29)	0.102
Hypertension	94 (43.12%)	66 (52.38%)	28 (30.43%)	0.001
Depression	26 (11.93%)	7 (5.56%)	19 (20.65%)	< 0.001
PDDS Score, mean (SD)	2.05 (1.81)	2.22 (1.89)	1.93 (1.75)	0.247
PDDS Score (3 Groups)				
No or Mild (0, 1)	95 (43.58%)	55 (43.65%)	40 (43.48%)	0.212
Moderate (2, 3)	75 (34.40%)	48 (38.10%)	27 (29.35%)	
Severe (4 or higher)	48 (22.02%)	23 (18.25%)	25 (27.17%)	

* SD = standard deviation; BMI = body mass index; PDDS = patient determined disease steps.

Table 3. Ordinal logistic regression results for MS patients in a higher disability group (N = 92)*

Variables	Estimate (95% CI)			P-Value
Tertiles of SBP coefficient of variation [1 (Lowest Variability)]				
2	3.480	(1.077 -	11.251)	0.037
3 (Highest Variability)	5.193	(1.531 -	17.616)	0.008
Age	1.100	(1.051 -	1.150)	< 0.001
Female [Male]	3.177	(1.249 -	8.078)	0.015
White Race [Other Races/Ethnicity]	1.495	(0.450 -	4.963)	0.512
Within-subject mean SBP (mm Hg)	0.991	(0.952 -	1.031)	0.647
Hypertension	0.930	(0.356 -	2.430)	0.882
Depression	1.183	(0.426 -	3.289)	0.747
Body mass index (kg/m²)	1.057	(0.974 -	1.147)	0.186

* Reference categories are in angle brackets. Disability groups were defined as No or Mild (PDDS scores 0 or 1), Moderate (2 or 3), and Severe (4 or higher).

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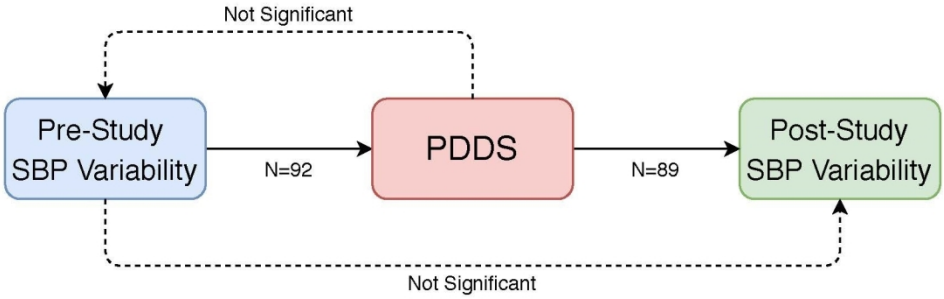

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Table e-1. Logistic regression results for patients having PDDS scores ≥3 (N = 92)*

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value
SBP variability tertiles [1 (Lowest Variability)]						
2	7.098 (1.745 - 28.862)	0.006	7.767 (1.822 - 33.105)	0.006	7.662 (1.783 - 32.928)	0.006
3 (Highest Variability)	4.564 (1.210 - 17.213)	0.025	4.338 (1.124 - 16.749)	0.033	4.273 (1.106 - 16.514)	0.035
Age	1.106 (1.047 - 1.168)	< 0.001	1.107 (1.047 - 1.170)	< 0.001	1.109 (1.048 - 1.174)	< 0.001
Female [Male]	2.079 (0.718 - 6.020)	0.177	2.186 (0.741 - 6.444)	0.156	2.215 (0.751 - 6.536)	0.150
White Race [Other race/ethnicity]	1.972 (0.446 - 8.723)	0.371	1.867 (0.427 - 8.159)	0.407	1.984 (0.445 - 8.835)	0.369
Within-subject mean SBP (mm Hg)	1.003 (0.962 - 1.045)	0.901	1.002 (0.961 - 1.044)	0.929	0.994 (0.947 - 1.044)	0.818
Hypertension			0.637 (0.199 - 2.038)	0.447	0.605 (0.188 - 1.950)	0.400
Depression			0.632 (0.179 - 2.230)	0.476	0.617 (0.174 - 2.188)	0.454
Body mass index (kg/m²)					1.032 (0.932 - 1.143)	0.542
Pseudo R^2	0.265		0.273		0.276	
Hosmer-Lemeshow Test (df), p-value	2.691 (8); p = 0.9522		7.885 (8); p = 0.4448		6.6506 (8); p = 0.5748	
Area under the ROC Curve	0.823		0.826		0.831	
AIC	107.184		110.186		111.814	
BIC	124.836		132.883		137.032	

* Reference categories are in angle brackets. P-values were NOT corrected for multiple comparison. PDDS scores ≥ 3 indicate moderate to severe disability. PDDS = patient determined disease steps; SBP = systolic blood pressure. AIC = Akaike information criterion; BIC = Bayesian information criterion.

Table e-2. Ordinary least squares models to predict PDDS scores (N = 92)*

Variable	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value
Intercept	-2.524 (-5.944 - 0.896)	0.146	-2.536 (-6.032 - 0.961)	0.153	-2.556 (-6.069 - 0.958)	0.152
SBP variability tertiles [1 (Lowest Variability)]						
2	1.132 (0.280 - 1.985)	0.010	1.153 (0.263 - 2.044)	0.012	1.128 (0.228 - 2.028)	0.015
3 (Highest Variability)	1.245 (0.426 - 2.065)	0.003	1.247 (0.402 - 2.092)	0.004	1.213 (0.355 - 2.072)	0.006
Age	0.074 (0.045 - 0.104)	< 0.001	0.075 (0.045 - 0.105)	< 0.001	0.075 (0.045 - 0.105)	< 0.001
Female [Male]	0.630 (-0.056 - 1.316)	0.071	0.625 (-0.071 - 1.321)	0.078	0.623 (-0.076 - 1.322)	0.080
White Race [Other race/ethnicity]	0.371 (-0.553 - 1.294)	0.427	0.363 (-0.575 - 1.302)	0.443	0.393 (-0.556 - 1.342)	0.413
Within-subject mean SBP (mm Hg)	0.000 (-0.028 - 0.028)	0.990	0.000 (-0.028 - 0.028)	0.996	-0.004 (-0.036 - 0.028)	0.805
Hypertension			0.016 (-0.718 - 0.750)	0.965	-0.009 (-0.751 - 0.734)	0.982
Depression			-0.079 (-0.925 - 0.766)	0.853	-0.085 (-0.935 - 0.764)	0.842
Body mass index (kg/m²)					0.017 (-0.047 - 0.080)	0.597
R^2	0.368		0.368		0.370	
Adjusted R^2	0.323		0.307		0.301	
AIC	351.224		355.183		356.868	
BIC	371.398		380.400		384.607	

* Reference categories are in angle brackets. P-values were NOT corrected for multiple comparison. PDDS = patient determined disease steps; SBP = systolic blood pressure. AIC = Akaike information criterion; BIC = Bayesian information criterion.

Table e-3. Ordinal logistic regression for MS patients in a higher disability group with the number of SBP measures as a covariate (N = 92)*

Variables	Estimate (95% CI)	P-Value
SBP variability tertiles [1 (Lowest Variability)		
2	3.090 (0.959 - 9.956)	0.059
3 (Highest Variability)	5.204 (1.576 - 17.182)	0.007
Age	1.101 (1.053 - 1.151)	0.000
Female [Male]	2.598 (1.023 - 6.595)	0.045
White Race [Other race/ethnicity]	1.333 (0.411 - 4.319)	0.632
Within-subject mean SBP (mm Hg)	1.013 (0.977 - 1.050)	0.489
Number of within-subject SBP measures	1.084 (0.990 - 1.188)	0.083

* Reference categories are in angle brackets. SBP = systolic blood pressure.

Table e-4. Ordinary least squares models to predict SBP variability before the study (N = 92)*

Variables	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value
Intercept	0.098 (0.069 - 0.128)	0.000	0.042 (-0.027 - 0.110)	0.232	0.046 (-0.023 - 0.115)	0.189
PDDS severity [1 (No or Mild)]						
2 (Moderate)	0.010 (-0.009 - 0.029)	0.286	0.011 (-0.008 - 0.030)	0.256	0.011 (0.009 - 0.030)	0.274
3 (Severe)	0.019 (-0.001 - 0.039)	0.059	0.019 (-0.001 - 0.040)	0.063	0.019 (-0.002 - 0.040)	0.070
Age (per 100 y)	0.000 (-0.001 - 0.001)	0.567	0.000 (-0.001 - 0.000)	0.340	0.000 (-0.001 - 0.000)	0.244
Female [Male]	-0.004 (-0.019 - 0.010)	0.544	-0.006 (-0.020 - 0.009)	0.424	-0.005 (-0.020 - 0.009)	0.468
White Race [Other race/ethnicity]	-0.018 (-0.038 - 0.002)	0.075	-0.017 (-0.037 - 0.003)	0.097	-0.015 (-0.036 - 0.005)	0.137
Within-subject mean SBP (mm Hg)			0.001 (0.000 - 0.001)	0.056	0.001 (-0.000 - 0.001)	0.073
Number of within-subject SBP measures			0.000 (-0.001 - 0.001)	0.958	0.000 (-0.001 - 0.001)	0.918
BMI (kg/m^2)					-0.000 (-0.001 - 0.001)	0.896
Depression					0.001 (-0.017 - 0.018)	0.954
Hypertension					-0.013 (-0.029 - 0.001)	0.078

* Reference categories are in angle brackets. P-values are not corrected for multiple comparison. PDDS = patient determined disease steps; SBP = systolic blood pressure; BMI = body mass index.

Table e-5. Ordinary least squares models to predict SBP variability post study (N = 89)*

Variables	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value
Intercept	0.072 (0.041 - 0.103)	< 0.001	0.008 -(0.069 - 0.084)	0.840	0.004 (-0.073 - 0.082)	0.909
PDDS scores [1 (No or Mild)]						
2 (Moderate)	0.031 (0.011 - 0.051)	0.003	0.030 (0.010 - 0.050)	0.004	0.029 (0.008 - 0.050)	0.007
3 (Severe)	0.021 (0.000 - 0.042)	0.052	0.018 (-0.004 - 0.040)	0.101	0.018 (-0.004 - 0.040)	0.115
Age (per 100 y)	0.001 (-0.076 - 0.077)	0.990	-0.005 (-0.082 - 0.072)	0.892	0.000 (-0.001 - 0.001)	0.898
Female	-0.007 (-0.023 - 0.008)	0.357	-0.009 (-0.024 - 0.007)	0.265	-0.008 (-0.024 - 0.007)	0.285
White Race	-0.005 (-0.026 - 0.016)	0.655	-0.002 (-0.023 - 0.019)	0.862	-0.001 (-0.023 - 0.020)	0.891
Within-subject mean SBP (mm Hg)			0.000 (0.000 - 0.001)	0.103	0.000 (-0.000 - 0.001)	0.247
Within-subject BP measures			0.001 (0.000 - 0.002)	0.228	0.001 (-0.001 - 0.002)	0.396
BMI (kg/m^2)					0.000 (-0.001 - 0.002)	0.516
Depression					0.010 (-0.009 - 0.029)	0.280
Hypertension					0.001 (-0.016 - 0.018)	0.876

* Reference categories are in angle brackets. P-values are not corrected for multiple comparison. PDDS = patient determined disease steps; SBP = systolic blood pressure; BMI = body mass index.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	#3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4-5

Bias	#9	Describe any efforts to address potential sources of bias	5-6
Study size	#10	Explain how the study size was arrived at	4
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	4-5
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	5-6
Statistical methods	#12c	Explain how missing data were addressed	5-6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	N/A
Statistical methods	#12e	Describe any sensitivity analyses	5-6
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	6
Participants	#13b	Give reasons for non-participation at each stage	6

Participants	#13c	Consider use of a flow diagram	N/A
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6-7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	6-7
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	7
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
Main results	#16b	Report category boundaries when continuous variables were categorized	7-8, Table 1
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8

Discussion

Key results	#18	Summarise key results with reference to study objectives	8-9
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	11-12
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	10
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

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A retrospective cohort study of the relationship between systolic blood pressure variability and multiple sclerosis disability

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A retrospective cohort study of the relationship between systolic blood pressure variability and multiple sclerosis disability

Running title: Blood pressure variability and MS disability

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ABSTRACT

Objective: To examine the relationship between visit-to-visit systolic blood pressure (SBP) variability and patient-reported outcome measure of disability in multiple sclerosis (MS) patients.

Design: A retrospective cohort study of individuals with MS who completed a Patient Determined Disease Steps (PDDS) scale between 2011 – 2015 at a multiple sclerosis specialty clinic.

Participants: Individuals with MS for whom both a completed PDDS scale and ≥3 SBP measures within the prior 12 months of the survey were available.

Main Outcome Measure: Participants were grouped into three classes of disability (No or Mild (PDDS 0 - 1), Moderate (2 - 3), Severe (4 - 7)). SBP variability was calculated as within-subject standard deviations using all SBP measures taken during the past 12 months. SBP variability was analyzed by Tertile groups.

Results: Ninety-two subjects were included in this analysis. Mean PDDS score was 2.22±1.89. Compared to subjects in Tertile 1 (lowest variability), the odds of being in a higher disability group was 3.5 times higher (OR = 3.48; 95% CI, 1.08 – 11.25; p = 0.037) in Tertile 2 and 5.2 times higher (OR = 5.19; 95% CI, 1.53 – 17.61; p = 0.008) in Tertile 3 (highest variability), independent of mean SBP, age, sex, race/ethnicity, BMI, and comorbidities (p for trend = 0.008). Mean PDDS scores were 1.52±1.18 in Tertile 1, 2.73±1.02 in Tertile 2 and 2.42±0.89 in Tertile 3 after adjusting for the same covariates.

Conclusions: Our results show a significant gradient relationship between SBP variability and MS-related disability. More research is needed to determine the underlying pathophysiological relationship between SBP variability and MS disability progression.

Keywords: multiple sclerosis, disability progression, blood pressure variability, cardiovascular comorbidities

Article Summary

Strengths and Limitations of This Study

- This is a first study to look at the relationship between the systolic blood pressure (SBP) variability and MS-related disability outcomes.
- This study paired prospectively collected patient-reported outcomes with retrospectively collected data, which allowed us to leverage existing data to take a first look at this novel question.
- Our analysis included a multi-faceted approach including - patient-reported measures, clinical outcomes (blood pressure), and concurrent co-morbid diagnosis.
- The retrospective collection of the paired clinical data limited the standardization of the number and inter-interval timing of blood pressure measurements, as well as the total number of subjects available for analysis.

1. Introduction

Multiple Sclerosis (MS) is an inflammatory and degenerative disorder of the central nervous system. Individuals with MS commonly experience some degree of disability progression independent of inflammatory driven events. The underlying mechanisms driving this inflammatory-independent disease progression remains poorly understood. It is likely that there is no single factor that drives MS progression. Instead it is believed to be a multi-faceted process with variable importance and influence of factors for any individual person. Posited factors include medical co-morbidities, as well as environmental factors such as smoking or vitamin D exposure.

Co-morbid cardiovascular disease (CVD) is more prevalent in MS relative to healthy populations. In MS patients, CVD is associated with worsened disease progression and reduced quality of life, although the mechanism remains uncertain.[1-5] Visit-to-visit systolic blood pressure (SBP) variability is an emerging risk factor for a wide array of health outcomes including CVD, kidney failure, cognitive dysfunction, diabetic complications, and all-cause mortality.[6-10] Excessive SBP variability (≥ 10 within-subject standard deviation) has been associated with many of these outcomes independent of mean blood pressure and hypertension.[8,11,12] Evidence suggests that visit-to-visit blood pressure variability may have stronger effects on cardiovascular outcomes than that of measures taken during a single visit or by 24-hour ambulatory monitoring devices.[13-15] While various vascular comorbidities have been previously studied in the progression of MS, the relationship between SBP variability and MS progression has yet to be explored.

We conducted a retrospective cohort study to examine the relationship between SBP variability and self-reported MS disability. We hypothesized that higher SBP variability is associated with greater degree of disability among individuals with MS.

2. Material and Methods

Study Design and Sample

We conducted a retrospective cohort study of individuals with MS who participated in research between 2011 and 2015 at the University of Virginia School of Medicine (UVA) and had previously prospectively completed the Patient Determined Disease Steps (PDDS) scale, a validated patient-reported outcome measure of MS disability.[16-18] The PDDS is a self-report tool of MS disability in which participants indicate their level of disability between 0 (‘normal’) and

8 ('bedridden'), where 4 indicates "early cane" use. SBP measurements were obtained from medical records and only those subjects with ≥ 3 available SBP measurements captured within the 12 months prior to PDDS completion were included in the analysis. This study was approved by the UVA institutional review board.

Visit-to-visit variability of systolic blood pressure

All available SBP measures within 12-months pre- and post-PDDS survey data were extracted from the electronic medical records system. Within-subject means and standard deviations of SBP were computed. Coefficient of variation was calculated by dividing the standard deviation by the mean to obtain a measure of variability that was more independent of the mean than standard deviation. We used the within-subject coefficients of variation to divide the study sample into three equal-sized groups (tertiles), whose SBPCV ranges are 0.012 - 0.064 for Tertile 1 (the lowest variability group), 0.065 – 0.087 for Tertile 2, and 0.089 – 0.172 for Tertile 3 (the highest variability group).

Covariates

Demographic data (age, sex, and race/ethnicity) were collected. We searched with the Clinical Data Repository, a data warehouse containing clinical information from patients treated at the University of Virginia, for the 12-month period prior to the PDDS survey to identify co-existing conditions including cardiovascular disease (ICD-9-CM codes, 410.xx – 414.xx, 428.xx, 431.xx, 434.xx, and 436.xx), peripheral vascular disease (443.9), diabetes (250.xx, 357.2, 362.01), depression (311.xx, 300.4, 296.20, 296.80, 296.89, 296.90), and hypertension (401.x). In addition to the diagnostic codes, we classified hypertension in patients using the 140/90 mm Hg per ACC/AHA guideline.[19] We also extracted body mass index (BMI) data within six months of the PDDS survey completion date.

Statistical Analysis

We used multivariable regression analysis to examine the relationship between SBP variability and the PDDS disability rating. To best utilize the ordinal nature of our response variable (PDDS score)[16,17], we estimated an ordinal logistic regression[20] and found that it did not satisfy the proportional odds assumption.[20-22] We tried several medically meaningful groupings to satisfy the assumption based on the PDDS scores and decided on three groups that make psychological and medical sense as distinctive groups as follows: No or Mild Disability (PDDS scores 0 or 1), Moderate Disability (PDDS scores 2 or 3), and Severe Disability (PDDS scores 4 or higher). The disability outcomes in these new groups were modeled using ordinal logistic regression as a function of SBP variability, adjusting for patient demographic data (age, sex, and race/ethnicity), mean SBP, BMI, hypertension, and depression.

As a sensitivity analysis, we defined the PDDS score 3 or above as presence of severe disability and modeled the binary response (0 = No or Mild Disability; 1 = Moderate to Severe Disability) using a logistic regression (Table e-1). Because SBP variability is found to be correlated with the number of measures used in computing the within-subject standard deviations, we controlled for the number of BP measures in another sensitivity analysis (Table e-2).

Finally, we tested whether PDDS scores can predict SBP variability before the study (Table e-3) and whether PDDS scores can predict SBP variability after the survey (Table e-4) by estimating linear regressions to predict pre- and post-survey SBP variability as a function of PDDS scores, adjusting for age, sex, race, and other covariates.

We used Stata SE v. 15.1 (StataCorp, College Station, TX) for all statistical analysis.

Patient and Public Involvement

No patient involved.

3. Results

A total of 218 PDDS surveys were identified from available study data. Among these, 17 subjects had completed more than one PDDS survey; in such cases, the first available survey date with corresponding ≥ 3 SBP measures was utilized. No subject contributed more than once to the final data set. When the same respondent participated in the PDDS survey more than once, we used the first survey. Of the resultant subjects, only 94 had the requisite ≥ 3 blood pressure measures in the 12-months prior to the survey completion date. Two additional subjects were excluded due to lack of available records to permit BMI calculation (absent height and/or weight).

The resultant 92 subjects included in the final analysis had a mean age of 44.7±12.2 years at the time of PDDS survey completion. They were predominantly white (82.6%) and 54% female. Their mean SBP was 124.1±13.2 mm Hg overall and were highest in Tertile 1 (128.0±13.0 mm Hg) and lowest in Tertile 2 (125.8±13.0 mm Hg). Their within-subject SBP standard deviation was 9.9±4.6 mm Hg overall but changed from 5.8±2.1 mm Hg (interquartile range [IQR] 4.4 – 7.4 mm Hg) to 9.2±1.4 mm Hg (IQR 11.7 – 17.7 mm Hg) in Tertile 2, and 14.8±3.9 (IQR 8.5 – 10.2 mm Hg) in Tertile 3. Their mean BMI was 29.0 kg/m^2. A total of 19 (20.7%) had depression, 28 (30.4%) had hypertension (11 patients with a diagnosis in ICD-9-CM and 17 patients with elevated mean BP). We could not identify any subject with vascular

comorbidities except for one who had acute myocardial infarction and was in Tertile 2. For this reason, vascular comorbidities have not been used in any subsequent analyses. The mean and median PDDS score was 2.2±1.89 and 2 (IQR 0 – 4). Forty patients (43.5%) had no or mild disability, 27 (29.4%) had moderate disability, and 25 (27.2%) had severe disability (Table 1).

Participants included in the analysis were not significantly different from those excluded (n = 126) in terms of PDDS score, patient sex, race and body mass index (Table 2). However, included subjects were older (48.7 vs 44.7 years; p = 0.016), less hypertensive (30.4% vs 52.4%; p = 0.001) and more depressed (20.7% vs 5.6%; p < 0.001).

Results from ordinal logistic regression analyses are shown in Table 3. Compared to subjects in Tertile 1 (lowest variability), the odds of being in a higher disability group was 3.5 times higher (OR = 3.48; 95% CI, 1.08 – 11.25; p = 0.037) in Tertile 2 and 5.2 times higher (OR = 5.19; 95% CI, 1.53 – 17.61; p = 0.008) in Tertile 3 (highest variability), independent of mean SBP, age, sex, race/ethnicity, BMI, hypertension and depression (p for trend = 0.008). Mean PDDS scores were 1.52±1.18 in Tertile 1, 2.73±1.02 in Tertile 2 and 2.42±0.89 in Tertile 3 after adjusting for the same covariates as the model shown in Table 3.

For sensitivity analysis, we checked the robustness of this association by estimating a logistic regression that predicted the binary indicator of PDDS score 3 or above (moderate or severe disability) (Tables e-1). The sensitivity analysis showed a significant relationship between SBP variability and disability ratings assessed by PPDS scale persisted.

We checked whether the number of SBP measures used to compute the variability is a confounding factor between the variability and the PDDS outcome by estimating the model shown in Table 2 with the number of measures as an additional covariate (Table e-2). The significant gradient relationship persisted in this model as well (p for trend = 0.007).

Finally, we tested the potential multi-directionality of the relationship between PDDS scores and SBP variability by predicting the SBP variability before and after the study using PDDS scores. From the 92 included subjects, 89 subjects had available ≥3 post-survey SBP measures, for whom the pre- and post-survey SBP coefficients of variation were correlated at r = 0.10 (p = 0.349), while SBP means were correlated at r = 0.83 (p < 0.001). We estimated two regression models that predict pre-survey and post-survey SBP coefficient of variation using PDDS scores, after controlling for age, sex, and race. PDDS scores did not predict pre-survey variability in any model specification (Table e-3). On the other hand, those with moderate disability had 0.03 higher post-survey coefficient of variation in SBP (95% CI, 0.01 – 0.05; p = 0.003) compared to those with no or mild disability but the severe disability group did not have significantly different SBP variability from the no or mild group. Mean SBP, number of BP measures, or any other comorbidities did not change this association (Table e-4). These tests of directionality of the association between SBP variability and PDDS scores are summarized in Figure 1.

4. Discussion

Our results demonstrate a significant and strong graded relationship between SBP variability and self-reported disability outcome measures (PDDS) among MS patients. Patients in Tertile 3 (highest variability) had an approximately six times higher risk of being in the higher disability group compared to those in Tertile 1 (lowest variability). This relationship was independent of mean SBP, BMI, hypertension, depression, and patient demographic factors. This result was robust to different analytic methods such as logistic regression to predict PDDS score 3 or higher (presence of moderate to severe disability).

Another important finding in this study is that the association of excessive SBP variability with higher PDDS scores can occur in normotensive individuals. Indeed, overall, 70% of our cohort were normotensive (< 140/90 mm Hg) or without hypertension diagnosis. They also had lower rates of hypertension in higher SBP variability tertiles with the lowest proportion observed in Tertile 3 (19% vs 41% in Tertile 1), a group with the highest SBP variability. This finding is consistent with previous studies by Sohn and his colleagues on diabetic complications.[8,11,12] Our results also demonstrate that mean SBP was not significantly associated with PDDS groups, suggesting there may be a different physiologic mechanism at play, not simply elevated blood pressures.[13]

Excessive visit-to-visit SBP variability has been associated with cardiovascular and several other health outcomes. To our knowledge, this is the first study to show that excessive visit-to-visit SBP variability may be a risk factor to MS disability progression. Previously, several large studies have identified a relationship between vascular comorbidities and MS outcomes, both clinical and patient-reported, using diagnostic codes (e.g., hypertension) or medications (anti-hypertensives) to classify patients.[1-4] Our results confirm the previous diagnosis-based research and extends that work, by identifying excessive SBP variability as a contributing factor to the previously identified relationship between blood-pressure changes and MS. Our results further suggest that a relevant hemodynamic mechanism in the interplay between cardiovascular disease and MS disability progression, is not simply hypertension (i.e., elevated mean BP), but also excessive SBP variability.

Pathophysiological mechanisms involved in the relationship between blood pressure variability and health outcomes are currently explained by arterial stiffness, endothelial dysfunction, and subclinical inflammation.[23-26] Several factors known to increase blood pressure

variability include autonomic dysfunction[27], low hydration status[28], insulin dysregulation[29,30] and sleep-apena[31] are commonly found in patients with MS. Tettey et al. suggests that vascular comorbidities may activate the inflammatory cascade that ultimately leads to neurodegeneration which manifests in disability progression in MS.[2] They also suggested that cerebral endothelial dysfunction may be involved in "trans-endothelial migration of T-lymphocytes and monocytes to the CNS with destructive and often neurodegenerative consequences."[2] Our results suggest that excessive SBP variability could be a relevant factor in that postulated inflammatory cascade in the vasculature and that may contribute to the cerebral endothelial dysfunction, which combine to produce the MS disability progression we observed in our study. More research is needed to test whether excessive SBP variability is indeed implicated in these pathways.

It is still premature to derive any MS-related clinical implications from our results. But it is advisable that MS patients be checked for SBP variability and those with excessive variability (e.g., within-subject standard deviation of 8 or higher) be recommended for careful vascular evaluation. Interestingly, we found that the majority of patients we identified as having hypertension according to the JNC7[32] and 2017 ACC/AHA criteria[19] did not have an actual diagnosis of hypertension. This suggests a potential under-diagnosis of hypertension, at least in our cohort.

This cross-sectional study was not designed to make any causal inferences between SBP variability and PDDS scores. However, our sensitivity analyses suggest that, while SBP variability was a strong and significant predictor of PDDS scores, the latter did not predict the former. Our data further suggest that the PDDS scores could significantly predict post-survey SBP variability but that the pre- and post-survey SBP variabilities were not correlated ($r = 0.10$; $p = 0.349$). This lends credence to the notion that SBP variability can in fact be a prognostic

factor for future disability progression and that there may be a vicious cycle of increasing SBP variability and worsening disability feeding each other dynamically over time.

There are limitations to our work. This is a retrospective study in design and we relied on the Clinical Data Repository for our health system as a source of blood pressure measures and comorbid conditions. Accuracy of these values is not known. Second, we were limited in sample size, mainly because the majority of patients in the original study sample were excluded because they lacked the requisite number of SBP measures. Therefore, our results should be cautiously interpreted because of the potential for selection bias arising from requiring 3 or more SBP measures within 12 months prior PDDS measurement. However, a bivariate comparison of the included vs excluded patients in Table 2 showed that they are similar in demographic factors, with the noted exception of age and depression, both of which were higher in the included population. These factors may have resulted in higher visit frequency leading to more available SBP values in those meeting eligibility criteria. Interestingly, the included population had lower incidence of hypertension compared to excluded subjects, as identified by ICD-9-CM codes or BP measures taken during the one-year period prior to the survey completion. We were only able to capture BP measures documented in our institutional electronic-medical records and there may have been additional values measured by other providers that were not captured in our data. We were not able to control for some potential confounders, including MS disease duration, disease modifying treatments, and some comorbid conditions that might have affected disability outcomes in our data. In addition, while validated, PDDS is a patient-reported outcome that may have unknown response bias. Despite these limitations, we believe our results represent an important first step in studying this relationship.

In conclusion, our results show that excessive SBP variability is associated with increased disability in MS patients, independent of mean SBP, hypertension diagnosis, depression, and obesity. This may represent a novel mechanism which may mediate the relationship between vascular dysfunction and progression of MS disability. Further prospective studies are needed to confirm whether excessive SBP variability is linked to the subclinical inflammation markers and/or cerebral endothelial dysfunction, and other markers of disease progression.

Declaration of Conflicting Interests

Myla D. Goldman has served as a consultant for ADAMAS, Celgene, EMD Serono, Novartis Pharmaceuticals, Sanofi Genzyme, Teva Pharmaceuticals. She has received research funding from Biogen Idec, Novartis Pharmaceuticals, National MS Society, MedDay Pharmaceuticals, and PCORI.

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Data Availability Statement

Anonymized data not published within this article are available from the corresponding author (MDG) on reasonable request.

Author Statement

Myla D. Goldman, MD, MSc - Study concept and design, acquisition of data, analysis and interpretation of data, and drafting/revising the manuscript

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Figure 1. Summary of the significant relationships (solid arrows) and nonsignificant relationships (dashed arrows) between SBP variability and PDDS scores*

[Figure 1 Here]

* Pre-survey SBP variability was significantly predictive of PDDS scores ($p = 0.015$), and PDDS scores were predictive of post-survey PDDS variability ($p = 0.011$). PDDS scores did not predict pre-survey SBP variability, and pre-survey SBP variability did not predict post-survey SBP variability. The p-values were obtained from a Wald test with 2 degrees of freedom (pre-survey variability to PDDS) and from an F test with 2 and 83 degrees of freedom (PDDS to post-survey variability).

Table 1. Characteristics of Study Cohort (N = 92) *

Variable	Tertiles of SBP coefficient of variation				
	All	1 (Lowest Variability)	2	3 (Highest Variability)	P-Value
	N (%)	N (%)	N (%)	N (%)	
All, n (Row %)	92 (100.00%)	31 (33.70%)	30 (32.61%)	31 (33.70%)	
Age, mean (SD)	44.71 (12.16)	45.03 (14.29)	45.93 (12.54)	43.19 (9.41)	0.673
Female	50 (54.35%)	18 (58.06%)	20 (66.67%)	12 (38.71%)	0.080
White Race	76 (82.61%)	29 (93.55%)	25 (83.33%)	22 (70.97%)	0.063
Within-subject SBP					
Mean (mm Hg), mean (SD)	124.05 (13.19)	128.01 (12.98)	118.16 (11.86)	125.78 (13.00)	0.008
Standard deviation (mm Hg), mean (SD)	9.94 (4.59)	5.82 (2.05)	9.17 (1.41)	14.79 (3.91)	< 0.001
Maximum (mm Hg), mean (SD)	137.95 (15.11)	135.74 (13.70)	132.60 (12.37)	145.32 (16.34)	0.002
Minimum (mm Hg), mean (SD)	110.68 (14.19)	120.45 (13.11)	105.43 (11.24)	106.00 (12.95)	< 0.001
Number of measures, mean (SD)	7.93 (5.53)	6.29 (3.97)	10.33 (6.18)	7.26 (5.57)	0.011
Body mass index (kg/m²), mean (SD)	29.03 (6.02)	28.73 (5.64)	28.04 (5.25)	30.28 (6.99)	0.330
Depression	19 (20.65%)	4 (12.90%)	11 (36.67%)	4 (12.90%)	0.031
Hypertension	28 (30.43%)	13 (41.94%)	9 (30.00%)	6 (19.35%)	0.154
PDDS Score, mean (SD)	2.22 (1.89)	1.52 (1.95)	2.73 (1.70)	2.42 (1.86)	0.031
PDDS Score, median (Interquartile Range)	2 (0 – 4)	0 (0 – 3)	3 (1 – 4)	2 (1 - 4)	
PDDS Score (3 Groups)					
No or Mild (0, 1)	40 (43.48%)	19 (61.29%)	9 (30.00%)	12 (38.71%)	0.163
Moderate (2, 3)	27 (29.35%)	6 (19.35%)	11 (36.67%)	10 (32.26%)	
Severe (4 or higher)	25 (27.17%)	6 (19.35%)	10 (33.33%)	9 (29.03%)	

* SBP = systolic blood pressure; SD = standard deviation; PDDS = patient determined disease steps. All percentages are either column percentages (Col %) or row percentages (Row %). P-values for continuous variables were computed using one-way ANOVA and those for categorical variables were based on Pearson chi-square tests.

Table 2. Comparison of the included and excluded patients in the original cohort*

Variables	All	Excluded	Included	P-Value
	N (Col %)	N (Row %)	N (Row %)	
All	218 (100.00%)	126 (57.80%)	92 (42.20%)	
Age, mean (SD)	47.04 (12.24)	44.71 (12.16)	48.74 (12.06)	0.016
Female	113 (51.83%)	63 (50.00%)	50 (54.35%)	0.526
White Race	181 (83.03%)	105 (83.33%)	76 (82.61%)	0.888
BMI (kg/m²), mean (SD)	28.25 (6.19)	29.03 (6.02)	27.59 (6.29)	0.102
Hypertension	94 (43.12%)	66 (52.38%)	28 (30.43%)	0.001
Depression	26 (11.93%)	7 (5.56%)	19 (20.65%)	< 0.001
PDDS Score, mean (SD)	2.05 (1.81)	2.22 (1.89)	1.93 (1.75)	0.247
PDDS Score (3 Groups)				
No or Mild (0, 1)	95 (43.58%)	55 (43.65%)	40 (43.48%)	0.212
Moderate (2, 3)	75 (34.40%)	48 (38.10%)	27 (29.35%)	
Severe (4 or higher)	48 (22.02%)	23 (18.25%)	25 (27.17%)	

* SD = standard deviation; BMI = body mass index; PDDS = patient determined disease steps.

Table 3. Ordinal logistic regression results for MS patients in a higher disability group (N = 92)*

Variables	Estimate (95% CI)			P-Value
Tertiles of SBP coefficient of variation [1 (Lowest Variability)]				
2	3.480	(1.077 -	11.251)	0.037
3 (Highest Variability)	5.193	(1.531 -	17.616)	0.008
Age	1.100	(1.051 -	1.150)	< 0.001
Female [Male]	3.177	(1.249 -	8.078)	0.015
White Race [Other Races/Ethnicity]	1.495	(0.450 -	4.963)	0.512
Within-subject mean SBP (mm Hg)	0.991	(0.952 -	1.031)	0.647
Hypertension	0.930	(0.356 -	2.430)	0.882
Depression	1.183	(0.426 -	3.289)	0.747
Body mass index (kg/m²)	1.057	(0.974 -	1.147)	0.186

* Reference categories are in angle brackets. Disability groups were defined as No or Mild (PDDS scores 0 or 1), Moderate (2 or 3), and Severe (4 or higher).

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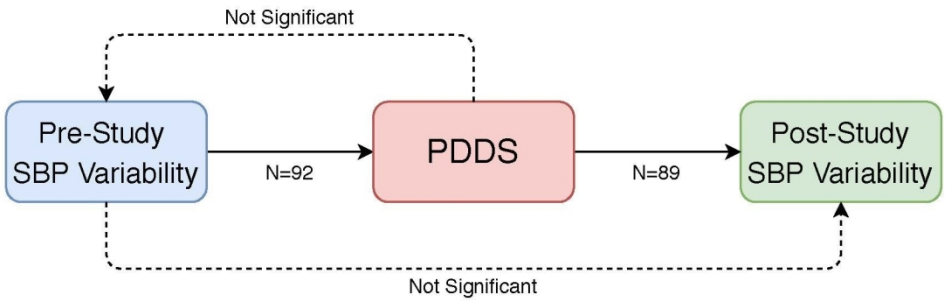

Figure 1. Summary of the significant relationships (solid arrows) and nonsignificant relationships (dashed arrows) between SBP variability and PDDS scores*

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Table e-1. Logistic regression results for patients having PDDS scores ≥3 (N = 92)*

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value	OR (95% CI)	P-Value
SBP variability tertiles [1 (Lowest Variability)]						
2	7.098 (1.745 - 28.862)	0.006	7.767 (1.822 - 33.105)	0.006	7.662 (1.783 - 32.928)	0.006
3 (Highest Variability)	4.564 (1.210 - 17.213)	0.025	4.338 (1.124 - 16.749)	0.033	4.273 (1.106 - 16.514)	0.035
Age	1.106 (1.047 - 1.168)	< 0.001	1.107 (1.047 - 1.170)	< 0.001	1.109 (1.048 - 1.174)	< 0.001
Female [Male]	2.079 (0.718 - 6.020)	0.177	2.186 (0.741 - 6.444)	0.156	2.215 (0.751 - 6.536)	0.150
White Race [Other race/ethnicity]	1.972 (0.446 - 8.723)	0.371	1.867 (0.427 - 8.159)	0.407	1.984 (0.445 - 8.835)	0.369
Within-subject mean SBP (mm Hg)	1.003 (0.962 - 1.045)	0.901	1.002 (0.961 - 1.044)	0.929	0.994 (0.947 - 1.044)	0.818
Hypertension			0.637 (0.199 - 2.038)	0.447	0.605 (0.188 - 1.950)	0.400
Depression			0.632 (0.179 - 2.230)	0.476	0.617 (0.174 - 2.188)	0.454
Body mass index (kg/m²)					1.032 (0.932 - 1.143)	0.542
Pseudo R^2	0.265		0.273		0.276	
Hosmer-Lemeshow Test (df), p-value	2.691 (8); p = 0.9522		7.885 (8); p = 0.4448		6.6506 (8); p = 0.5748	
Area under the ROC Curve	0.823		0.826		0.831	
AIC	107.184		110.186		111.814	
BIC	124.836		132.883		137.032	

* Reference categories are in angle brackets. P-values were NOT corrected for multiple comparison. PDDS scores ≥ 3 indicate moderate to severe disability. PDDS = patient determined disease steps; SBP = systolic blood pressure. AIC = Akaike information criterion; BIC = Bayesian information criterion.

Table e-2. Ordinal logistic regression for MS patients in a higher disability group with the number of SBP measures as a covariate (N = 92)*

Variables	Estimate (95% CI)	P-Value
SBP variability tertiles [1 (Lowest Variability)		
2	3.090 (0.959 - 9.956)	0.059
3 (Highest Variability)	5.204 (1.576 - 17.182)	0.007
Age	1.101 (1.053 - 1.151)	0.000
Female [Male]	2.598 (1.023 - 6.595)	0.045
White Race [Other race/ethnicity]	1.333 (0.411 - 4.319)	0.632
Within-subject mean SBP (mm Hg)	1.013 (0.977 - 1.050)	0.489
Number of within-subject SBP measures	1.084 (0.990 - 1.188)	0.083

* Reference categories are in angle brackets. SBP = systolic blood pressure.

Table e-3. Ordinary least squares models to predict SBP variability before the study (N = 92)*

Variables	Model 1		Model 2		Model 3	
	Estimate (95% CI)	**P-Value**	**Estimate (95% CI)**	**P-Value**	**Estimate (95% CI)**	**P-Value**
Intercept	0.098 (0.069 - 0.128)	0.000	0.042 (-0.027 - 0.110)	0.232	0.046 (-0.023 - 0.115)	0.189
PDDS severity [1 (No or Mild)]						
2 (Moderate)	0.010 (-0.009 - 0.029)	0.286	0.011 (-0.008 - 0.030)	0.256	0.011 (0.009 - 0.030)	0.274
3 (Severe)	0.019 (-0.001 - 0.039)	0.059	0.019 (-0.001 - 0.040)	0.063	0.019 (-0.002 - 0.040)	0.070
Age (per 100 y)	0.000 (-0.001 - 0.001)	0.567	0.000 (-0.001 - 0.000)	0.340	0.000 (-0.001 - 0.000)	0.244
Female [Male]	-0.004 (-0.019 - 0.010)	0.544	-0.006 (-0.020 - 0.009)	0.424	-0.005 (-0.020 - 0.009)	0.468
White Race [Other race/ethnicity]	-0.018 (-0.038 - 0.002)	0.075	-0.017 (-0.037 - 0.003)	0.097	-0.015 (-0.036 - 0.005)	0.137
Within-subject mean SBP (mm Hg)			0.001 (0.000 - 0.001)	0.056	0.001 (-0.000 - 0.001)	0.073
Number of within-subject SBP measures			0.000 (-0.001 - 0.001)	0.958	0.000 (-0.001 - 0.001)	0.918
BMI (kg/m^2)					-0.000 (-0.001 - 0.001)	0.896
Depression					0.001 (-0.017 - 0.018)	0.954
Hypertension					-0.013 (-0.029 - 0.001)	0.078

* Reference categories are in angle brackets. P-values are not corrected for multiple comparison. PDDS = patient determined disease steps; SBP = systolic blood pressure; BMI = body mass index.

Table e-4. Ordinary least squares models to predict SBP variability post study (N = 89)*

Variables	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value	Estimate (95% CI)	P-Value
Intercept	0.072 (0.041 - 0.103)	< 0.001	0.008 -(0.069 - 0.084)	0.840	0.004 (-0.073 - 0.082)	0.909
PDDS scores [1 (No or Mild)]						
2 (Moderate)	0.031 (0.011 - 0.051)	0.003	0.030 (0.010 - 0.050)	0.004	0.029 (0.008 - 0.050)	0.007
3 (Severe)	0.021 (0.000 - 0.042)	0.052	0.018 (-0.004 - 0.040)	0.101	0.018 (-0.004 - 0.040)	0.115
Age (per 100 y)	0.001 (-0.076 - 0.077)	0.990	-0.005 (-0.082 - 0.072)	0.892	0.000 (-0.001 - 0.001)	0.898
Female	-0.007 (-0.023 - 0.008)	0.357	-0.009 (-0.024 - 0.007)	0.265	-0.008 (-0.024 - 0.007)	0.285
White Race	-0.005 (-0.026 - 0.016)	0.655	-0.002 (-0.023 - 0.019)	0.862	-0.001 (-0.023 - 0.020)	0.891
Within-subject mean SBP (mm Hg)			0.000 (0.000 - 0.001)	0.103	0.000 (-0.000 - 0.001)	0.247
Within-subject BP measures			0.001 (0.000 - 0.002)	0.228	0.001 (-0.001 - 0.002)	0.396
BMI (kg/m^2)					0.000 (-0.001 - 0.002)	0.516
Depression					0.010 (-0.009 - 0.029)	0.280
Hypertension					0.001 (-0.016 - 0.018)	0.876

* Reference categories are in angle brackets. P-values are not corrected for multiple comparison. PDDS = patient determined disease steps; SBP = systolic blood pressure; BMI = body mass index.