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Association of late-life changes in blood pressure and cognitive status

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Abstract

Background   Disagreement exists on the association between changes in blood pressure and cognitive impairment. We aimed to examine whether 4-year changes in systolic and diastolic blood pressure (SBP and DBP) are associated with cognitive status in a representative sample of older men and women. **Methods**   Analysis of longitudinal data from 854 participants of a population-based German sample (aged 60–87 years) was performed with standard cognitive screening and blood pressure measurements. Effects of changes in SBP and DBP (10 mmHg and 5 mmHg respectively as unit of regression effect measure) on cognitive status were evaluated using non-parametric and linear regression modeling. **Results**   No clear associations were seen between changes in SBP or in DBP and cognitive scores. Small effects were found after stratification for sex and hypertension awareness. Specifically, larger decreases in SBP were associated with higher cognitive scores in those men aware of their hypertension (10 mmHg decrease in SBP, β = –0.26, 95% CI: –0.51 to –0.02) and men with controlled hypertension (10 mmHg decrease in SBP, β = –0.44, 95% CI: –0.92 to –0.03). Additionally larger increases in DBP were associated with higher cognitive scores in men with controlled hypertension (5 mmHg increase in DBP, β = 0.67, 95% CI: 0.19–1.15). For women aware of their hypertension, larger decreases in DBP were associated with higher cognitive scores (5 mmHg decrease in DBP, β = –0.26; 95%CI: –0.51 to –0.01). **Conclusions**   Changes in blood pressure were only weakly associated with cognitive status. Specifically, decreases in SBP were associated with higher cognitive scores in men aware of their hypertension and especially those that were medically controlled.

1   Introduction

High blood pressure (BP) is a strong risk factor of cerebrovascular events, which are associated with decreased cognitive function, but it is also treatable. Previous studies examining the association between BP and cognitive function have provided conflicting results. In a recent review summarizing results of cross-sectional studies, there were four studies reporting an association between cognitive status [as defined by the Mini Mental State Examination (MMSE)] and high BP; three studies report in an association with low BP.[1] There were several other studies using other measurements for cognitive impairment which found not only positive and negative associations, but also no association or a U-shape relation with BP. Also the results of longitudinal studies which investigated the relation between late-life hypertension (participants older than 65 years) and cognition are inconsistent, with some studies reporting no significant effect,[2–4] whereas others show high BP as a risk factor for cognitive impairment,[5–7] or even a U-shape relation between both.[8]

Reason for these conflicting findings could be that the relationship between BP and cognition is complex. Several factors such as education, sex or mental health may confound the effect.[9] Therefore, the association between BP and cognitive function maybe because of a direct effect of the BP itself or adverse effects of treatment. To date, no study has comprehensively addressed all of these issues. The conflicting evidence on the association of changes in BP with cognitive function needs clarification. Thus, the major aims of this study were: (1) to study whether changes in BP over 4 years, systolic and diastolic BP (SBP and DBP) are associated with cognitive status, (2) to determine sex-differences, and (3) differences in hypertension awareness status in this association.

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2 Methods

2.1 Study population

CARLA (cardiovascular disease, living and ageing in Halle) is a population-based cohort study in Halle (Saale) in eastern Germany, which aims to examine the distribution of CVD, heart rate variability and CVD risk factors and their associations in an elderly East German population. A random sample of 5,000 men and women aged 45 to 80 years at the time of the sampling (July 2002) was drawn from the population registry of the city of Halle. For the baseline investigation 1,779 participants aged 45–83 years, were recruited between July 2002 and January 2006, with a response rate of 64%. The first follow-up examination for 1,436 participants was done between March 2007 and March 2010 (mean follow-up of 4 years, response rate = 92%). A more detailed description of the CARLA design has been already published.[10] Participants (n =139) with cardiovascular disease (self-reported myocardial infarction and/or definite by Minnesota code of the 10 s ECG,[10] and/or self-reported coronary artery bypass graft, and/or self-reported percutaneous transluminal coronary angioplasty, and/or self-reported physician-diagnosed stroke, and/or carotid surgery) at baseline were excluded from the analysis as these conditions have been shown to contribute to substantial decline in cognitive function in the older population.[11] Additionally, participants (n = 2), with MMSE scores below 10 (indicative of severe dementia) were excluded. Those participants were excluded because they could confound the effect of blood pressure changes on cognition.

2.2 Outcome

Cognitive function in individuals 60 years or older, was measured with the MMSE at the first follow-up, 2007–2010.[12] The MMSE includes 10 items, which measure orientation (10 points), registration (3 points), attention and calculation (5 points), recall (3 points), naming and repetition (3 points), comprehension (3 points), reading ability (1 point), writing ability (1 point), and design copy (1 point). The score ranges from 0 to 30, with a higher score indicative of better cognitive performance.

2.3 Exposure

BP measurements were performed in sitting position after 5-min resting using the OMRON HEM-705CP device. The average of the second and third of three measurements was used for the analyses. Those participants with SBP equal or greater than 140 mmHg and/or DBP equal or greater than 90 mmHg at baseline were considered hyper-tensive. Those participants who said they had a physician diagnosed hypertension were considered aware. Those participants under antihypertensive medication without hypertension (SBP lower than 140 and DBP lower than 90 mmHg) were considered controlled. These categories were pre-specified before data analysis. Use of antihypertensive medication was defined according to the anatomic therapeutic chemical classification system (ATC codes C02, C03, C07, C08, and C09). Individual absolute changes in systolic or diastolic BP were calculated as the difference between the follow-up and the baseline value.

2.4 Covariates

Socio-demographic variables: sex, age and education years [following the International Standard Classification of Education (ISCED) 97-Classification], were determined in the standardized interview. Cardiovascular risk factors were assessed during the personal interview and clinical examination. During the personal interview, the participants were asked about their smoking habits (pack-years tobacco) and alcohol drinking habits (grams a day for each alcoholic beverage). Body mass index (BMI) was calculated as weight in kilogram divided by the height in meter squared. Laboratory analyses of non-fasting venous blood samples included serum total cholesterol. Depressed mood was assessed at follow-up with the German version of the Center for Epidemiological Studies–Depression (Allgemein Depression Skala, ADS) with 20 items.[13,14] Respondents indicate on a scale from 0 (rarely) to 3 (most of the time), how often they experienced each symptom during last week (sleep disturbances, poor appetite, feelings of loneliness, etc.). The total score ranges from 0 to 60; higher scores indicate more depressive symptomatology.

2.5 Statistical analyses

The present study includes 854 participants at follow-up (97% of the follow-up participants over 60 years). We identified minimally sufficient adjustment sets using directed acyclic graphs (DAG) that represent the relations among the exposure, outcome, and other variables.[15] All previously mentioned covariates were considered as potential confounders for the relation of changes in BP and cognitive status. The minimally sufficient adjustment set for the total effect in the association of BP on cognition included sex, education years and baseline values for age, total cholesterol levels, alcohol consumption, smoked pack-cigarettes per year, antihypertensive medication and systolic and diastolic BP.

Prior to model-fitting, we assessed the linearity of the associations between changes in BP and cognitive

status using generalized additive models. Since all variables showed a linear association, linear regression models were used to estimate those associations. Exposures were analyzed continuously, changes in SBP per 10 mmHg increase, and changes in DBP per 5 mmHg increase; both previously reported as clinically relevant.[16] In order to assess the influence of prevalent hypertension and hypertension awareness, we performed the analyses of the association of changes in BP with cognitive status: (1) in the whole population, (2) in subgroups of subjects with/without hypertension at baseline, (3) in subgroups of participants aware/unaware of hypertension at baseline and (4) in subgroups of participants with hypertension controlled/uncontrolled by antihypertensive medication at baseline. Covariates in these models were the same as those used previously. All analyses were performed using SAS 9.3. (SAS Inc., Cary, NC, USA).

Twenty-seven (3%) of the 881 follow-up participants with MMSE (60 years or older) had missing data for relevant covariates, thus 854 subjects were included in the analysis. No relevant differences in SBP, DBP, at baseline and at follow-up, MMSE, sex, depression score or age were found between participants with missing or full information.

3 Results

Table 1 shows characteristics of the study participants. Participants had at baseline a mean age of 67.2 years (95% CI: 66.7–67.6) and 53% were male. The mean scores for the cognitive status test (MMSE) were identical for men and women (27.3). Slightly higher SBP and DBP at baseline and follow-up were found for men than for women. For men, changes in SBP ranged between −54 and 84 mmHg (mean: 8.0, 95% CI: 6.1–9.9) and changes in DBP ranged between −31 and 45 mmHg (mean: 6.8, 95% CI: 5.9–7.7); whereas for women, changes in SBP ranged between −85 and 76 mmHg (mean: 5.0, 95% CI: 3.0–7.1) and changes in DBP ranged between −19 and 35 mmHg (mean: 4.6, 95% CI: 3.7–5.4). As expected, men had more years of formal education than women, and higher consumption of alcohol and cigarettes. In contrast, women had higher scores in the depression scale than men. 85% and 78% of the participants were at baseline hypertensive (men and women respectively) and the percentage increased slightly for women after 4-years of follow-up (83%). This could be due to the fact that more participants took antihypertensive medication at follow-up (from 47% at baseline to 65% at follow-up for men and from 52% at baseline to 66% at follow-up for women). This increase was most notorious for ACE-inhibitors and beta-blockers.

Table 1. Characteristics of study participants, sex-stratified.

	Men (*n* = 455)	Women (*n* = 399)
Age at baseline, yrs	67.4 (66.7–68.0)	66.9 (66.2–67.6)
Education years, mean	15.6 (15.4–15.8)	14.0 (13.8–14.2)
Cognitive status (MMSE) at follow-up	27.3 (27.1–27.5)	27.3 (27.1–27.5)
SBP, mmHg		
Baseline	148.6 (146.9–150.4)	143.6 (141.4–145.8)
Follow-up	140.7 (138.8–142.5)	138.6 (136.7–140.5)
DBP, mmHg		
Baseline	86.7 (85.7–87.7)	83.4 (82.3–84.5)
Follow-up	79.9 (78.9–80.8)	78.8 (77.9–79.8)
*Hypertension		
Baseline	387 (85.1%; 81.8%–88.3%)	312 (78.2%; 74.1%–82.3%)
Follow-up	388 (85.3%; 82.0%–88.5%)	330 (82.7%; 79.0%–86.4%)
Total cholesterol, mmol/L,		
Baseline	5.4 (5.3–5.5)	5.9 (5.8–6.0)
Follow-up	5.2 (5.1–5.3)	5.8 (5.7–5.9)
BMI, Kg/m²		
Baseline	28.2 (27.9–28.6)	28.5 (28.0–29.0)
Follow-up	28.3 (27.9–28.6)	28.8 (28.4–29.3)
Pack-years		
Baseline	12.9 (11.5–14.2)	3.2 (2.4–4.0)
Follow-up	13.2 (11.8–14.7)	3.4 (2.6–4.3)
Alcohol intake, mg/day,		
Baseline	17.9 (16.2–19.6)	4.1 (3.4–4.7)
Follow-up	14.6 (13.1–16.2)	3.6 (2.9–4.3)
*,#Antihypertensive medication, baseline	215 (47.3%; 42.6%–51.9%)	206 (51.6%; 46.7%–56.6%)
Number of antihypertensives per participant	1.6 (1.5–1.7)	1.6 (1.5–1.7)
*Anti-arrhythmias	3 (0.7%; 0–1.4%)	4 (1.0%; 0–2.0%)
*ACE-inhibitors	161 (35.4%; 31.0%–39.8%)	132 (33.1%; 28.4%–37.7%)
*Beta-blockers	132 (29.0%; 24.8%–33.2%)	133 (33.3%; 28.7%–38.0%)
*Diuretics	39 (8.6%; 6.0%–11.2%)	34 (8.5%; 5.8%–11.3%)
*Calcium-channel blockers	74 (16.3%; 12.9%–19.7%)	60 (15.0%; 11.5%–18.6%)
*,#Antihypertensive medication Follow-up	296 (65.1%; 60.7%–69.5%)	263 (65.9%; 61.2%–70.6%)
Number of antihypertensives per participant	1.8 (1.7–1.9)	1.9 (1.8–2.0)
*Anti-arrhythmics	5 (1.1%; 0.1%–2.1%)	3 (0.8%; 0–1.6%)
*ACE-inhibitors	237 (52.1%; 47.5%–56.7%)	198 (49.6%; 44.7%–54.6%)
*Beta-blockers	177 (38.9%; 34.4%–43.4%)	187 (46.9%; 41.9%–51.8%)
*Diuretics	54 (11.9%; 8.9%–14.9%)	57 (14.3%; 10.8%–17.7%)
*Calcium-channel blockers	97 (21.3%; 17.5%–25.1%)	80 (20.1%; 16.1%–24.0%)
Depression (CES-D)		
Baseline	7.5 (6.9–8.0)	10.2 (9.5–11.0)
Follow-up	7.6 (7.0–8.2)	10.5 (9.7–11.4)

Data are presented as mean (95% CI) unless other indicated. *Data are presented as *n* (mean percent, 95% CI); #Numbers do not add up, because some participants have multiple medications. ACE: angiotensin converting enzyme; BMI: body mass index; CES-D: center for epidemiologic studies depression; DBP: diastolic blood pressure; MMSE: mini-mental state examination; SBP: systolic blood pressure.

First, we checked with linear regression analysis the association between SBP and DBP at baseline and at follow-up and cognitive status (data not shown). Neither SBP nor of DBP at baseline or at follow-up were associated with cognitive status scores for men or women [β range between −0.01 (SE = 0.01) and 0.01 (SE = 0.01) for SBP and between −0.02 (SE = 0.02) and 0.03 (SE = 0.02) for DBP].

We then analysed the association between changes in BP and cognition. Generalized Additive Model analysis showed that the non-linearity assumption for the association between changes in BP and cognitive status could not be confirmed. Therefore, results from the linear analysis are shown. We could not observe associations between changes in SBP or in DBP and cognitive scores in both sexes (see Table 2).

However, in the age-stratified analysis it is shown that for men younger than 75 years almost an association could be seen between increases in SBP and lower cognitive scores (β = −0.18, 95% CI: −0.38 to 0.01).

Further analysis considered subgroups of participants with or without hypertension at baseline (Table 3). For participants, irrespective of sex and hypertensive status, no associations were found between changes in SBP or in DBP and cognition. In order to see whether awareness of hypertension at baseline exert an effect on this relationship, awareness of hypertension was taken into consideration (Table 3). No clear association was found for participants unaware of their hypertensive status in both sexes between changes in BP and cognition. For aware men, increases in

Table 2. Association between changes in blood pressure and cognitive status.

	Men, β (95% CI), *n* = 455		Women, β (95% CI), *n* = 399	
Change in SBP (10 mmHg)	−0.14 (−0.31 to 0.03)		0.08 (−0.09–0.25)	
Change in DBP (5 mmHg)	0.09 (−0.09 to 0.27)		−0.14 (−0.35–0.06)	
	Men < 75 yrs (*n* = 355)	Men ≥ 75 yrs (*n* = 100)	Women < 75 yrs (*n* = 328)	Women ≥ 75 yrs (*n* = 71)
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
*Change in SBP (10 mmHg)	−0.18 (−0.38 to 0.01)	−0.03 (−0.40 to 0.34)	0.07 (−0.11 to 0.26)	0.12 (−0.39 to 0.62)
*Change in DBP (5 mmHg)	0.07 (−0.13 to 0.26)	0.16 (−0.58 to 0.26)	−0.15 (−0.37 to 0.07)	−0.18 (−0.74 to 0.39)

*Fully adjusted: BP, alcohol consumption, cholesterol level, smoked cigarette packs per year, depression score, antihypertensive medication, age and years of education at baseline. DBP: diastolic blood pressure; SBP: systolic blood pressure.

Table 3. Association between changes in blood pressure and cognitive status, considering hypertensive status and awareness.

	Men		Women	
	n	β (95% CI)	*n*	β (95% CI)
No hypertension	82		97	
Change in SBP (10 mmHg)		−0.03 (−0.43 to 0.36)		−0.10 (−0.67 to 0.46)
Change in DBP (5 mmHg)		−0.01 (−0.44 to 0.42)		−0.08 (−0.64 to 0.47)
Hypertension	373		302	
Change in SBP (10 mmHg)		−0.16 (−0.36 to 0.03)		0.12 (−0.06 to 0.31)
Change in DBP (5 mmHg)		0.12 (−0.08 to 0.31)		−0.17 (−0.39 to 0.05)
Unaware hypertension	118		69	
Change in SBP (10 mmHg)		0.14 (−0.23 to 0.51)		0.17 (−0.26 to 0.60)
Change in DBP (5 mmHg)		−0.09 (−0.41 to 0.24)		0.26 (−0.27 to 0.78)
Aware hypertension	255		233	
Change in SBP (10 mmHg)		−0.26 (−0.51 to −0.02)		0.12 (−0.09 to 0.32)
Change in DBP (5 mmHg)		0.20 (−0.06 to 0.46)		−0.26 (−0.51 to −0.01)
Uncontrolled hypertension	156		127	
Change in SBP (10 mmHg)		−0.26 (−0.59 to 0.06)		0.17 (−0.11 to 0.44)
Change in DBP (5 mmHg)		0.16 (−0.19 to 0.52)		−0.29 (−0.61 to 0.03)
Controlled hypertension	62		79	
Change in SBP (10 mmHg)		−0.44 (−0.92 to −0.03)		−0.02 (−0.46 to 0.43)
Change in DBP (5 mmHg)		0.67 (0.19 to 1.15)		−0.23 (−0.79 to 0.34)

DBP: diastolic blood pressure; SBP: systolic blood pressure; Fully adjusted models for men and women: BP, alcohol consumption, cholesterol level, smoked cigarette packs per year, depression score, antihypertensive medication (only in hypertension and awareness), age and years of education at baseline.

SBP (10 mmHg increment) were associated with lower cognitive scores (β = –0.26, 95% CI = –0.51 to –0.02), i.e., for each 10 mmHg decrease in SBP, the cognitive score increased by 0.3 points. Aware women with greater increases in DBP (5 mmHg increment) had lower cognitive test results (β = –0.26, 95% CI = –0.51 to –0.01). Finally, to analyse whether controlled BP through antihypertensive medication has an effect on this relationship, control of hypertension was taken into consideration (Table 3). No clear association was found between changes in SBP or in DBP and cognition for medically uncontrolled hypertensive participants, within both sexes, nor for medically controlled women. However, for medically controlled men, greater reductions in SBP (10 mmHg decrease) were associated with higher scores in cognition (β = –0.44, 95% CI: –0.92 to –0.03) and greater increases in DBP (5 mmHg increase) were associated with higher cognitive scores (β = 0.67, 95% CI: 0.19–1.15).

4   Discussion

In this study, we found a weak association between changes in BP and cognitive performance in late-adulthood (60 years or older), most evident for men with controlled hypertension. This association seemed not only sex-specific, but also specific for status of hypertension awareness and of control of hypertension. Decreases in SBP were seen to be related to higher cognitive scores for men that were aware of their hypertension and especially for those that were medically controlled (BP < 140/90 mmHg). The association between changes in BP and cognition seemed however very specific. Specifically, this applied for clinically relevant values, we found than medically controlled hypertensive men, with reductions of 10 mmHg in SBP had 0.4 points higher mean score in MMSE than medically controlled hypertensive men with no change in SBP; and that medically controlled hypertensive men with reductions of 5 mmHg in DBP had 0.7 points lower mean score in MMSE than medically controlled hypertensive men with no change in DBP. The medically controlled hypertensive men in our population had SBP changes ranging from –50 mmHg to 35 mmHg, and DBP changes ranging from –31 mmHg to 21 mmHg. If we apply these values to our estimates, we get that those male participants with decreases of 50 mmHg in SBP have a mean score 2.2 points over those without changes in SBP. Whereas participants with decreases of 30 mmHg in DBP, have a mean score 4 points below those without changes in DBP. Although the BP change is clinically significant, the corresponding MMSE score difference is modest. Several other studies have shown similar effects

of BP changes on MMSE scores. The study from Piguet, *et al.*[5] showed that hypertensive participants had after 6-years of follow-up a 1.2 points lower MMSE score than their normotensive co-participants. More recently, it has been showed that hypertensive participants treated but poorly controlled had 0.6 points less in MMSE than those hypertensive participants treated and controlled.[17]

It is difficult to interpret the wide literature regarding BP and cognitive function because of many methodological differences among studies. There are differences in sample sizes, attrition rates, confounders taken into account (i.e., age, sex, education years…), exposure measurement (BP values *vs.* hypertension diagnosis) or even outcome definition (measures of cognitive function *vs.* diagnosis of dementia). Nevertheless, midlife higher SBP has been repeatedly associated with increased risk in late-life cognitive impairment in several populations.[18–22] Several cross-sectional and longitudinal studies have shown that the use of antihypertensive medication is associated with preservation of cognitive function.[22–24] Other longitudinal studies with participants older than 75 years have demonstrated that higher blood pressure is associated with lower incidence of dementia and cognitive impairment.[25–27] Therefore, it is possible that pharmacologic measures to lower blood pressure only in midlife may help preserve function. On the other hand, randomized clinical trials have shown conflicting results: neither the Systolic Hypertension in the Elderly Program nor the Systolic Hypertension in Europe Study found differences in cognitive scores measured with MMSE between treated and untreated hypertensive participants.[28,29] There might be several reasons for this discrepancy in the current literature. One could be due to the differential effects of mid-life and late-life hypertension on cognition; where mid-life BP is more predictive of cognition that late-life BP.[1] A second reason is that MMSE might be not the adequate tool to detect cognitive function differences after 4-years of follow-up, as suggested by studies with a more thorough neuropsychological assessment which show associations between BP and cognitive functioning.[30–32]

It is also likely that the effect of high BP on the brain varies dramatically between individuals. Those at high risk of hypertension-related cognitive decline would benefit the most from accurate control of their hypertension. The biological pathways linking midlife and late-life hypertension with late-life cognitive impairment are thought to be atherosclerotic and haemodynamic mechanisms.[16] Severe atherosclerosis in turn results in high SBP and low DBP and may induce cerebral hypoperfusion, ischaemia and hypoxia. Antihypertensive medication started in midlife can reduce the risk for cognitive impairment by lowering BP and thus

delaying the atherosclerotic process.[33] Our results support this proposed pathway in two ways: first, only for successfully treated men, lowering the SBP was associated with higher cognitive scores and second, successfully treated men with decreases in DBP had lower cognitive scores, whereas those with increases in DBP had higher cognitive scores.

There are several alternative explanations of our results. First, those participants cognitively fitter are those who intended to get their hypertension controlled. Our results however, showed that this was not the case, fully-adjusted mean MMSE score was not different among men or women with medically controlled hypertension or not [27.2 (SD = 2.4) *vs.* 27.4 (SD = 1.9) for men and 27.2 (SD = 1.9) *vs.* 27.0 (SD = 2.3) for women]. Additionally, it has been previously shown that women irrespective of cognitive status are more concerned about health issues than men,[34] whereas men suffer at an earlier age from cognitive impairment.[35] A second explanation could be that high BP is a prodrome of cognitive impairment. However, other research has shown that long-standing high blood pressure, particularly if untreated, may give rise to cognitive impairment in later life.[16]

This study draws its strength from the fact that it is a population-based sample, with well-defined health outcomes. Nevertheless, our conclusions are limited by several factors. The measurement of cognitive status was done with the MMSE test. This is an unspecific screening test. Yet MMSE has been established as the preferred instrument for monitoring cognitive function in hypertension studies[36] and prevalence of cognitive impairment.[37] The use of this instrument was guided by the consideration that it would assist comparisons between our data and the results of other studies. Additionally, the baseline cognitive level could influence the treatment behaviour of the participants. Unfortunately, we do not have information about baseline cognitive level in our population. Also, we cannot be certain that the subgroups that showed significant relationships between BP changes and MMSE scores at follow-up did not have different MMSE scores at baseline. Our sample consisted of adults with a broad age range (60−87 years), however most were young (mean = 67.2 years), therefore the generalizability of the findings to individuals over 75 years of age is unknown. Also, this population had high mean SBP levels at baseline, indicator of untreated and/or inadequately treated hypertension. Thus, the generalizability of these results to other community-based samples is restricted. Finally, the CARLA study was not powered for this question; therefore some estimates are very imprecise.

In conclusion, BP at baseline or follow-up was not sig-

nificantly associated with cognitive status for men or for women. However, decreases in SBP were associated with higher cognitive scores in men that were aware of their hypertension and especially for those that were medically controlled.

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