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The Effects of Cerebrovascular Aging on Sleep Quality in a Sample of Aging Adults

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THE EFFECTS OF CEREBROVASCULAR AGING ON SLEEP QUALITY IN A SAMPLE OF AGING ADULTS

by

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Abstract

Cerebrovascular burden (CVB) is a significant factor among the aging population. Age-related cognitive decline is an important social and economic issue, and understanding the mechanisms has clinical implications, both in selecting potential therapies and in choosing specific modifiers for their evaluation. In summary, past work suggests that high CVB is one source of variance in neurovascular functioning among older adults. High CVB and associated brain-changes have been identified as causes of age-related changes and it may be that high CVB is a correlate of age-related changes in sleep quality. The primary hypothesis to be tested is that cerebrovascular burden measured using an index variable reflecting blood pressure, resting heart rate, and blood oxygen saturation, will predict subjective sleep quality in a sample of adults over age 70. Sleep quality was measured using the Pittsburgh Sleep Quality Index. A sample of 8 dementia-free, community dwelling participants over the age of 70 completed the study. Though individual cerebrovascular risk factors (blood pressure, resting heart rate) had moderate but non-significant correlations with sleep quality, only the CVB index variable significantly related (1-tailed) to sleep quality. Findings support the hypothesized relationship. Future research should seek to replicate these findings with a larger sample, and to identify mechanisms by which this relationship may function.

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Introduction/Background:

Demographics and sleep patterns

Sleep impairment is widespread among older adults worldwide. While we know little about causes of age-related sleep change, the damaging effects of sleep impairment, such as impaired cognition are well established (Cameron et al., 2014). Meanwhile, older adults represent the fastest growing sector of the U.S population. According to the most recent estimates for the world, the number of persons aged over 60 years will double from the present number, 756 to 1400 million by 2030 (De Luca d'Alessandro, Bonacci, & Giraldi, 2011). Aging brings the threat of a subsequent increase in chronic illness and disability among other challenges to quality of life. By examining prospective correlates of sleep deprivation among older adults, including cerebrovascular risk and cerebral blood flow, a process model of age-related sleep change may emerge. Such models may suggest novel interventional targets for primary interventions preventing onset of sleep impairment among older adults, and thus improving health outcomes among the rapidly growing population of older adults.

Sleep

A common but significant change related to aging is disruption to the daily sleep-wake cycle. Poor sleep results in an increased risk of morbidity and mortality (Crowley, 2011). Inadequate sleep in older adults has been linked to poorer cognition, such as an impairment in executive functioning (Crowley, 2011). It has been approximated that as many as half of the population of older adults complain about difficulty initiating or maintaining sleep (Crowley,

2011). In addition to these challenges, older adults tend to report more sleep-related complaints, including decreased total sleep time, increased nocturnal wakefulness, earlier awakenings, and excessive daytime sleepiness (Crowley, 2011). Little attention has been given to identifying predictors of variability in age-related sleep change. A few studies have shown that the movement of cerebrospinal fluid differs during wakefulness and sleep (Eugene & Masiak, 2015). Cerebrospinal fluid serves to provide substantial nutrients to the brain and cushion the brain and its corresponding structures. Although the brain has a high metabolic rate and its neurons are susceptible to damage by toxic waste products, it lacks a systematic lymphatic system. Instead, studies have indicated that the cortical interstitial space increases by more than 60% during sleep, resulting in the clearance of proteins and compounds while recirculating cerebrospinal fluid (Xie et al., 2013). Thus, sleep serves to clear the products of neural activity that accumulate during wakefulness (Xie et al., 2013).

There are two types of alternating sleep, which include: non-rapid eye-movement sleep (NREM) and rapid eye-movement (REM) sleep. Normal sleep begins with the four stages of non-rapid-eye movement sleep followed by rapid eye movement sleep and concludes with an alternating cycle of NREM and REM sleep throughout the remaining sleep duration (Institute of Medicine Committee on Sleep & Research, 2006). Stage one of NREM sleep begins the sleep cycle and alpha waves are associated with this stage. Brain activity on an EEG in stage two show mixed-frequency activity which is characterized by the presence of sleep spindles and K-complexes (Institute of Medicine Committee on Sleep & Research, 2006). It is hypothesized that sleep spindles are important for memory consolidation. Research studies have reported that individuals who learn a new task have a significantly higher density of sleep spindles than those

in the control group. NREM sleep stages 3 and 4 are referred to as slow-wave sleep. In stage three, the EEG shows increased high-voltage activity and slow-wave activity. In the last stage of NREM sleep, stage four, the arousal threshold is the highest with increased amounts of high-voltage and slow-wave activity on the EEG(Institute of Medicine Committee on Sleep & Research, 2006). In the next phase of the sleep cycle, Rapid-eye movement (REM) sleep is defined by the presence of low-voltage, mixed-frequency brain wave activity, and bursts of rapid eye movements. There are numerous physiological implications in NREM and REM sleep. NREM sleep is associated with significant reductions in cerebral blood flow and metabolism. An increase in metabolism and blood flow increase in certain brain regions during REM sleep. Physiological changes within these sleep cycles can result in poor subjective sleep quality in adults (Madsen et al., 1991). Research has also indicated that because arousal thresholds are highest during slow wave sleep, and because slow wave sleep consequently declines with age, older adults experience more frequent awakenings during a sleep episode (Institute of Medicine Committee on Sleep & Research, 2006). In summary, cerebrovascular health may play an important role in the complex orchestration of cerebral activation that occurs during sleep.

Cerebrovascular health and Aging

A continuous supply of oxygen in the blood is critical to the cerebrovascular health of the brain. Oxygen storage is not a function of the brain, as a result, any disruption or discontinuation in supply would quickly result in tissue oxygen depletion and metabolic stress as the brain under anaerobic glycolysis would not be able to produce sufficient energy to maintain normal cell function (Boas & Franceschini, 2011). Additionally, the brain relies on a constant perfusion of oxygen to fulfill its energetic demands especially during neuronal activity.

It has been shown that neurovascular coupling is associated with cognitive performance and white matter integrity (Sorond, Hurwitz, Salat, Greve, & Fisher, 2013). Among older adults, high cerebrovascular burden is also associated with white matter disease in the central nervous system (Raz & Rodrigue, 2006) . White matter consists of nerve fibers that lie deep within the tissues of the cortex which connects gray matter of the brain together allowing for communication. White matter also carries nerve impulses between neurons. The nerve fibers of the white matter are extensions of neurons which are covered by a myelin sheath, giving the matter its "white" color. White matter disease results from vascular blockages termed ischemia or other disruption of small blood vessels deep inside the white matter in the brain. As a result, blood flow to specific areas becomes restricted. Intact white matter is vital for the processing and integration of information generated by neural networks. The consequent loss of integrity of white matter pathways is thought to be the cause of the loss of cortical connectivity (O'Sullivan et al., 2001).

There are a few structures of the brain that are affected due to aging. One of the structures in the brain that aging impacts, is the pineal gland. The pineal gland is a small endocrine gland that is located in the brain is responsible for producing melatonin- a hormone that regulates sleep patterns (Touitou, 2001). Research findings have also shown that as a result of aging, the Pineal gland calcifies. These deposits are made up of mainly calcium and phosphorus (Touitou, 2001). These calcified deposits are called "brain sand" (Vigh et al., 1998). With imaging techniques the degree of calcification provides a useful landmark for the orientation in the diagnosis of various intracranial diseases. Although calcification of the pineal gland is not indicative of any particular pathological state, the degree of calcification has been associated with various diseases (Vigh et

al., 1998). Calcification of the pineal gland is common with aging and its deposits increase in both number and size with age.

Cerebrovascular burden and neurological functioning

As previously mentioned, the brain loses volume as it ages due to atrophy. Studies have also shown that lesser volumes of the brain regions are thought to underlie and support varying aspects of cognition and have been linked to poorer performance in those regions (Raz & Rodrigue, 2006). While the exact mechanisms of the cause are unknown, vascular risk and disease are one likely cause (Raz, Rodrigue, & Haacke, 2007). One common source of cerebrovascular burden is hypertension, which is defined as an excess of 160 mmHg in systolic pressure and greater than 90 mmHg in diastolic pressure (Iadecola & Davisson, 2008). Hypertension affects a large number of older adults and corresponds to changes in the vascular system. Additionally, hypertension may hasten the effects of aging on the structure of the brain (Raz & Rodrigue, 2006). It has been broadly demonstrated that changes brain structure widely impact neurological functions. Over time, older adults with hypertension and various other sources of vascular risk show decline in regions that are generally stable in normal aging (Raz & Rodrigue, 2006). Past work suggests that high CVB and associated white matter hyperintensities in the prefrontal cortex predict dysregulation of mood (Sneed, Rindskopf, Steffens, Krishnan, & Roose, 2008). It is possible that high CVB similarly leads to disrupted sleep through a similar pathway; however, little is known about how neurovascular changes in the prefrontal cortex relate to sleep.

The phenomenon of sleep has much in common with mood regulation, and the research on mood and CVB may be informative to our understanding of sleep problems in later life. Like

sleep, variation in mood over time is normal, and it is influenced to a considerable degree by individual decision-making. Mood regulation and sleep regulation are also similar in that both processes recruit disparate areas of the cerebral cortex which are connected by white mater projections (Gruber & Cassoff, 2014). The vascular depression hypothesis argues that high CVB adversely affects prefrontal white mater projections underlying regulation of mood (Alexopoulos et al., 1997). Vascular depression theory has been supported by findings relating the number of cerebrovascular risk factors (hypertension, for instance) to the endorsement of depressive symptoms (Mast, Neufeld, MacNeill, & Lichtenberg, 2004). It is possible that a similar relationship exists between CVB and sleep disruption.

In summary, past work consistently suggests that high CVB is one source of variance in neurovascular functioning among older adults. High CVB and associated brain-changes have been identified as causes of age-related changes in executive functioning and mood regulation, and thus, CVB is suggested as one potential source of age-related change in sleep quality. The primary goal of this research study is to examine the relationships between sleep and cerebrovascular burden in a sample of community-dwelling older adults over the age of 70. A second goal of this study is to examine the utility of an index variable over individual cerebrovascular variables in the prediction of sleep deficits.

Method

Sample

The research study recruited 8 participants 70 years of age and above from the Learning Institute for Elders (L.I.F.E) group at UCF. Research participants were also recruited from the community using advertisements in the local newspaper. The sample included participants who speak English as their first language and those with corrected to normal vision. The sample participants were screened for moderate to severe dementia, severe mental illness, cognitive impairments and the history of a cerebrovascular event(s).

Measures

Demographic Variables

Demographic and idiographic variables were collected via phone calls or face-to-face interviews. The following demographic variables were obtained: Race/ ethnicity, age, gender, and level of education. … Ethnicity was collected using the question "How do you describe yourself ethnically?" Response options include, "White/Caucasian," "Black/African American," "Hispanic/Latino," "Pacific Islander," "Native American," "Asian," and "Other."

Physiological Variables

Cerebrovascular burden was measured using a combination of indices. Pulse Oximetry, a Sphygmomanometer, resting heart rate, participant endorsement(Bush, Miller, Golden, & Hale, 1989) of diabetes, cardiac disease, and high cholesterol.

Pulse Oximetry is the direct measurement of the oxygen levels in the blood. This noninvasive procedure measured the oxygen saturation level of arterial blood, which is an indicator of oxygen supply. This system uses a pulse oximeter which consists of a sensor attached to the patient's finger, a cable, and a monitor providing a readout of the patient's pulse rate and oxygen saturation levels (Ali, Breed, Novak, & Kiani, 2004; Ammar Al Ali, 2004) .

A Sphygmomanometer, also known colloquially as a blood pressure cuff was used to measure the patient's blood pressure to determine if hypertension is a factor in the patient's medical history. This non-invasive procedure measures the patient's blood pressure by using a cuff and a stethoscope. The cuff was placed on the upper right arm above the brachial artery and inflated to measure both systolic and diastolic blood pressures. Systolic pressure is the peak pressure in the arteries during the cardiac cycle and diastolic pressure is the lowest pressure or the resting phase of the cardiac cycle (Banet, 2005).

Cognitive Screener

The Telephone Interview for Cognitive Status (TICS) was used to screen for mild cognitive impairment or dementia. This tool is a cognitive screening test administered over the phone. The instrument consists of 35 measures and it is administered verbally with a high test-retest reliability (r=0.965) (Brandt, Spencer, & Folstein, 1988).

Sleep Quality

The Pittsburgh sleep Quality Index (PSQI) is a questionnaire that assessed sleep quality and patterns in older adults over a period of time. The PSQI is a 24-item scale that measures

sleep disturbances along 7 dimensions: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). Daytime dysfunction was omitted from the calculation of sleep quality score. Scores from the remaining six areas were added together into a global score. Responses are based on the majority of days and nights of the previous month. The psychometric properties of this questionnaire indicate a high test-retest reliability (r = 0.82) for global scores and (r = 0.45 - 0.84) for component scores (Carpenter & Andrykowski, 1998).

Procedure

Recruitment

As previously stated, 8 research participants were recruited from the Learning Institute for Elders (LIFE) group at UCF and from the local community using a newspaper advertisement. Prospective participants were 70 years of age and over. The Telephone Interview for Cognitive Status (TICS) measure was used to assess moderate to severe dementia in prospective research participants which is a screening tool for cognitive disorders. This screening tool includes a number of indices ranging from orientation, concentration, short-term memory, mathematical skills, praxis and language (Paulson, Bowen, & Lichtenberg, 2011). The TICS measure is scored from 0-35 points with higher scores indicating better functioning (Paulson et al., 2011). This instrument has a Cronbach's alpha of.69 and a high test-retest reliability (38, 40–42) (Paulson et al., 2011). Prospective participants who scored below 11 on this verbally-administered 35-point measure (Langa et al., 2008) were excluded from participation. After specific inclusion and exclusion criteria for the research study were met, participants were scheduled for participation.

Data Collection

Prospective data for the research study were composed of self-reports, questionnaires, and physiological measurements. Data was received, collected and managed exclusively by the principal investigator and authorized research assistants. A study ID number was given to each research participant who provided consent and reached all specific inclusion and exclusion criteria. A physical linking file was recorded on paper, listing both participant name and study ID number.

An extensive battery of physiological (including blood pressure, resting heart rate, and pulse oximetry), psychomotor, cognitive, and subjective response (including the PSQI) measures, among others, were administered. The current thesis represents one part of a larger study. The majority of these measures are beyond the scope of this thesis and their administration will not be described herein.

When the data collection is complete, the linking file will be destroyed making it impossible to associate any participant identifying information with their research data. Physical data will remain in a secure and locked file cabinet that is accessible only by the principal investigator and authorized personnel. Research data was entered into an SPSS database by a research associate. The database includes the participant's assigned Study ID number, demographic information provided, measured medical data and other research data such as scores on the described measures; however the date did not include name, address, phone number, SSN, or other identifying information. Self-reports and other questionnaires were checked for completion before participants left the research appointment.

Research Compensation

Following recruitment and consent, research participants took a series of questionnaires and assessment measurements. Research participants received $30 in cash upon successful completion of the described research protocol.

Statistical Methodology

Cerebrovascular indicators such as blood pressure, blood oxygen saturation (scores on this metric were inverted by multiplying by -1), and resting heart rate were standardized and transformed to z-scores based on means and standard deviations for the sample. Z- Scores were calculated to determine how many standard deviations a particular variable is away from the sample mean. These scores were then summed to create an index score reflecting degree of CVB. A Higher CVB index scores reflect greater burden and predict subjective sleep impairment.

Results

The final sample included 8 participants. Their demographic information is summarized in Table 1. The average age of participants was 76.5 years old (SD=0.5). The majority of the sample was female (62.5%), all of the participants reported to be White or Caucasian, and participants had some form of college education. The sample had a blood oxygen saturation average of 97.8 (SD= 1.7), a systolic blood pressure average of 135.9 (SD=9.3), and a diastolic blood pressure average of 74.1 (SD=9.3). The average of the resting heart rate in the sample was 66.1 (SD=11.9). The CVB index variable had a mean score of 0 (SD=1.9). The mean score on the Pittsburgh Sleep Quality Index was 9.0 (SD=2.3).

The results of the correlational analysis of demographic characteristics, CVB variables, and subjective sleep quality are listed in Appendix: A, Table 2. Systolic blood pressure was positively correlated with diastolic blood pressure ($r = .75$, $p < .05$). Scores on the CVB index were positively correlated with education ($r = .72$, $p < .05$). Diastolic blood pressure was positively correlated with CVB index scores ($r = .81$, $p < .05$). Level of education was negatively correlated with Pittsburgh Sleep Quality index scores ($r = -.66$, $p < .05$). Other correlations between hypothesized variables were not statistically significant.

In addition, there was a significant correlation between scores on the CVB index and sleep quality ($r = .70$, *two-tailed* $p < .055$). The *a priori* hypothesis was directional in nature indicating a one-tailed analysis, and the corresponding adjusted p-value (p=.023) is considered to support the primary hypothesis. The large magnitude of this correlation suggests that 49% of the variability in PSQI scores are accounted for by variability in CVB. Interestingly, PSQI scores

did have moderate, but non-significant correlations with single CVB variables, diastolic blood pressure and heart rate in particular, that were examined in this study.

Lastly, scatter plots were created for significant correlations between variables which can be referenced to appendix A: Tables 3-6. Also, pictures of the pulse oximeter and blood pressure cuff, which were used to measure resting heart rate, blood oxygen saturation, and diastolic/ systolic blood pressure can be referenced to the figures in appendix B.

Discussion

The presented research study sought to examine the relationships between sleep and cerebrovascular burden in a sample of community-dwelling older adults over the age of 70. Our first finding of this study was that high CVB negatively correlates with subjective sleep impairment. The second finding of this study is summarized by the contrasting findings that the CVB index variable, reflecting multisystemic cerebrovascular load, emerged as a covariate of sleep quality whereas individual cerebrovascular risk factors were not significantly correlated with sleep quality. This finding supports the practice of modeling CVB as an integrated variable reflecting multiple facets of vascular health.

This research study utilized a correlational, cross sectional design to identify correlates of sleep quality and cerebrovascular burden. Correlation does not imply causation and the analysis should not be interpreted as supporting causal relationships between key variables. Results also suggest a positive correlation between systolic blood pressure and diastolic blood pressure, and that diastolic blood pressure was positively correlated with cerebrovascular burden index. Support for the primary hypotheses of this study suggested that poor sleep may well be an indicator of cerebrovascular aging; a finding that could aid in the development of significant interventions for the treatment of sleep deprivation. The coefficient of determination for the relationship between cerebrovascular index and sleep quality is .49. The variability in cerebrovascular burden is accounted for by the variability in sleep quality by 49%.

Cerebrovascular aging is a significant health concern among the older adults. Age-related sleep change is an important public health issue, and understanding its correlates and causes has

important clinical implications. Identification of correlates of poor sleep among older adults may help integrate sleep into theoretical models of late-life decline. Support for the primary hypothesis may eventually contribute to the identification of novel therapeutic targets for sleep disruption among older adults. Sleep impairment is widespread among older adults worldwide. Older adults represent the fastest growing sector of the U.S population and cerebrovascular burden (CVB) is a significant aspect of the aging population. With aging comes the threat of increase of mortality and morbidity including a decline in cognitive functioning. High cerebrovascular burden and associated brain-changes have been identified as causes of age-related brain changes and these results suggest that sleep impairment may be one manifestation of that progression.

The primary limitation of this study is the small sample size. Despite this, support for the primary hypothesis was still found. However, without longitudinal data, the direction of these findings remains unclear. Indeed, some have concluded that sleep impairment engenders development of cerebrovascular risk factors among other health problems. Also, without longitudinal study, it is not possible to establish directionality in this relationship. Another limitation of the research study is the idiosyncratic administration of the Pittsburgh Sleep Quality Index, two questions reflecting daytime sleepiness were not administered. However the vast majority of studies use measures such as the Pittsburgh Sleep Quality Index to identify patterns of sleep quality. Future research may examine these relationships between cerebrovascular burden and sleep quality using an in-lab sleep study.

Appendix A: Tables

Table 1: Descriptive statistics for the sample and key variables

		Mean (SD) or %
Age		76.5(0.5)
Gender		
% Female		62.5%
% Male		37.5%
Education		
	Some College	12.5%
	Associate's Degree	12.5%
	Bachelor's Degree	37.5%
	Some Graduate School	12.5%
	Master’s Degree	25.0%
Race		
	White or Caucasian	100%
O_2Saturation		97.8 (1.7)
Systolic BP		135.9 (9.3)
Diastolic BP		74.1 (9.3)
Heart Rate		66.1 (11.9)
CVB Index		0 (1.9)
PSQI		9.0 (2.3)

Table 2: Results of correlational analysis of demographic characteristics, CVB variables, and subjective sleep quality

	Gender	Age	Education	Oxygen Saturation	Systolic BP	Diastolic BP	Heart Rate	CVB Index
Age	0.17							
Education	0.11	-0.06						
Oxygen Saturation	-0.12	0.48	-0.16					
Systolic BP	0.07	-0.50	0.52	-0.59				
Diastolic BP	-0.43	-0.57	0.67	-0.38	.75*			
Heart Rate	-0.24	0.43	0.36	-0.02	-0.06	0.20		
CVB Index	-0.37	-0.08	.72*	0.00	0.57	.81*	0.58	
PSQI	0.23	-0.46	-0.66	-0.19	-0.24	-0.44	-0.49	-0.70$^{\delta}$

*$p<.05$; $^{\delta}p=.055$

Table 3: Scatter plot of the following variables: systolic and diastolic blood pressure

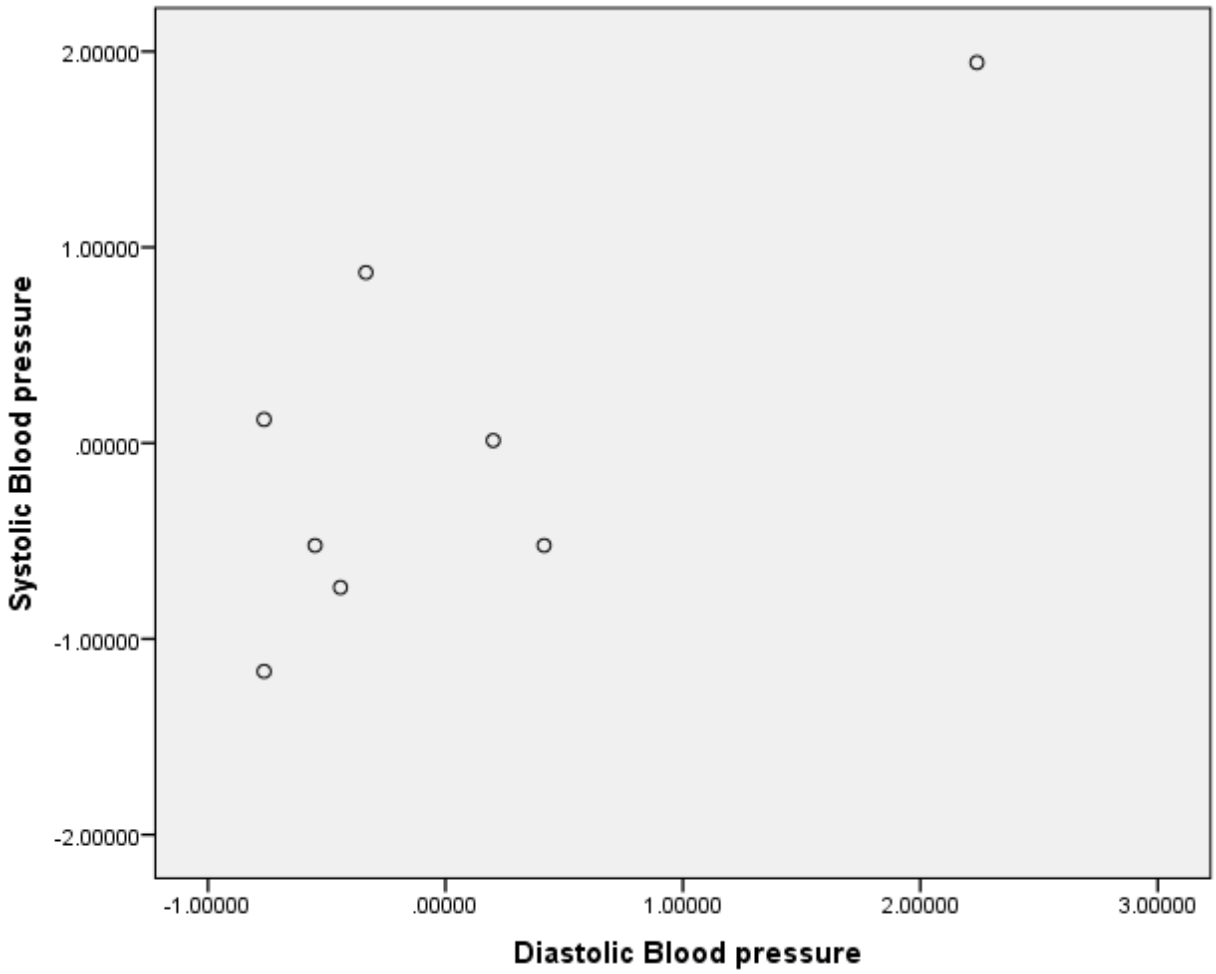


Table 4: Scatter plot of the following variables: sleep quality index and cerebrovascular burden index

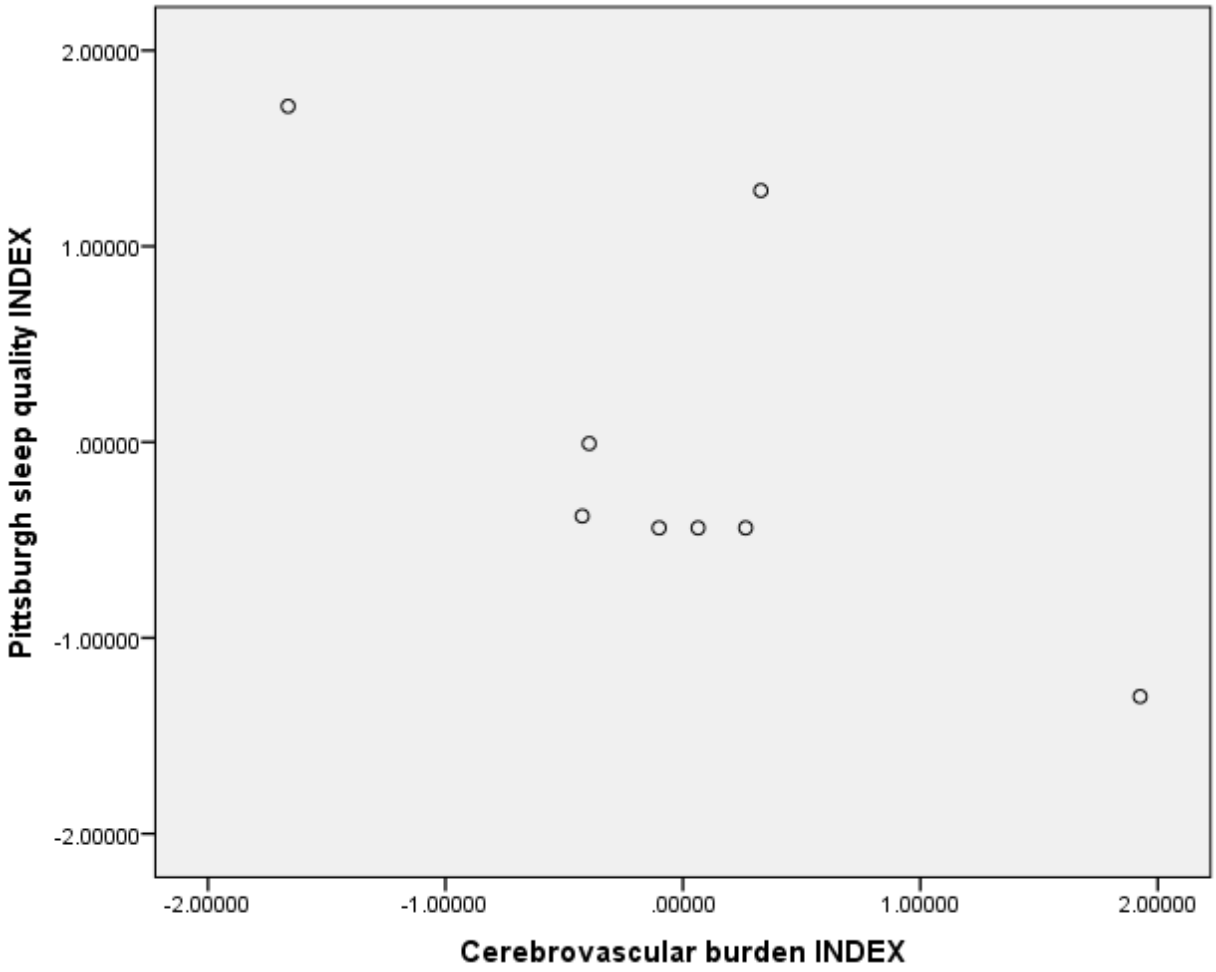


Table 5: Scatter plot of the following variables: diastolic blood pressure and cerebrovascular burden index

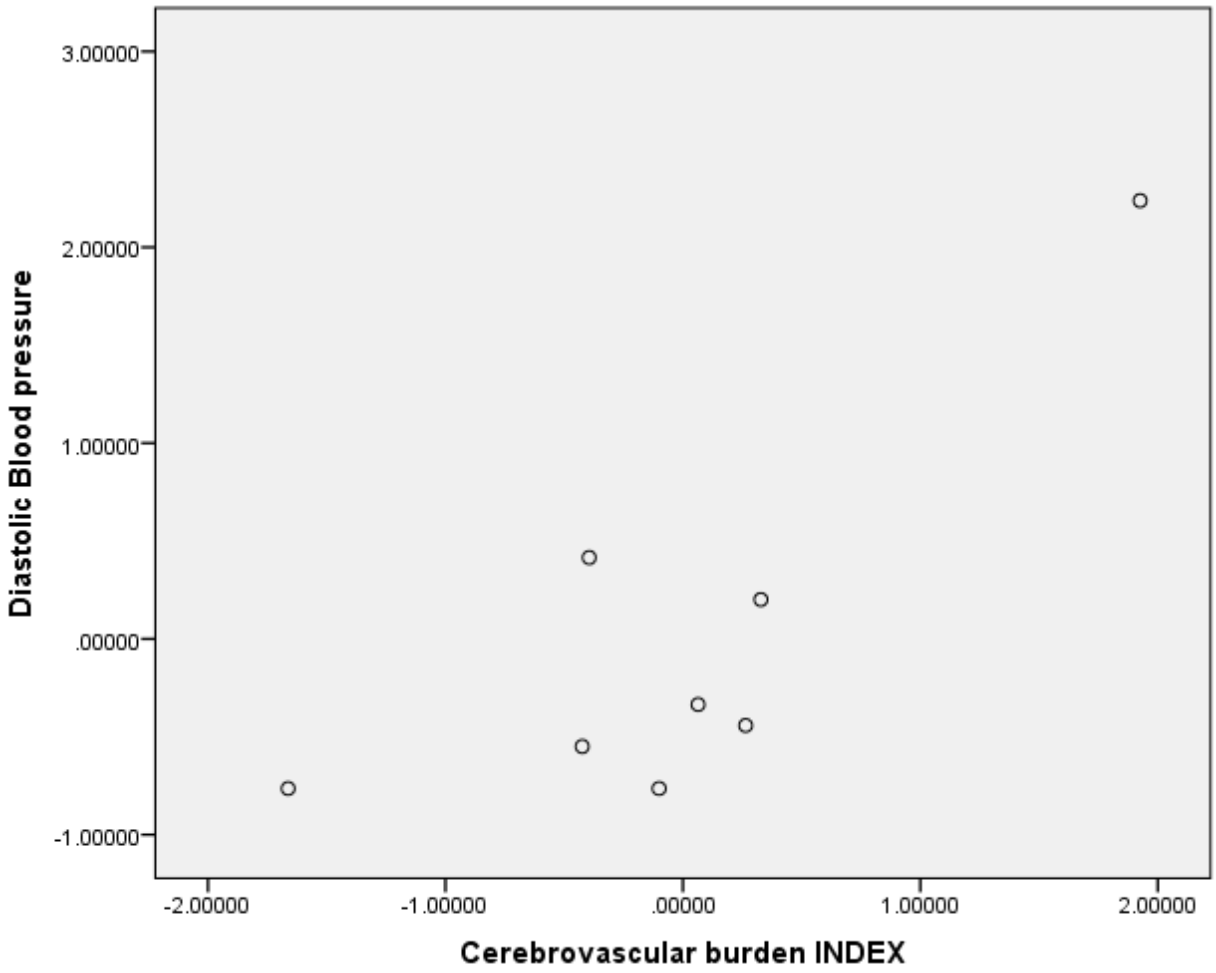
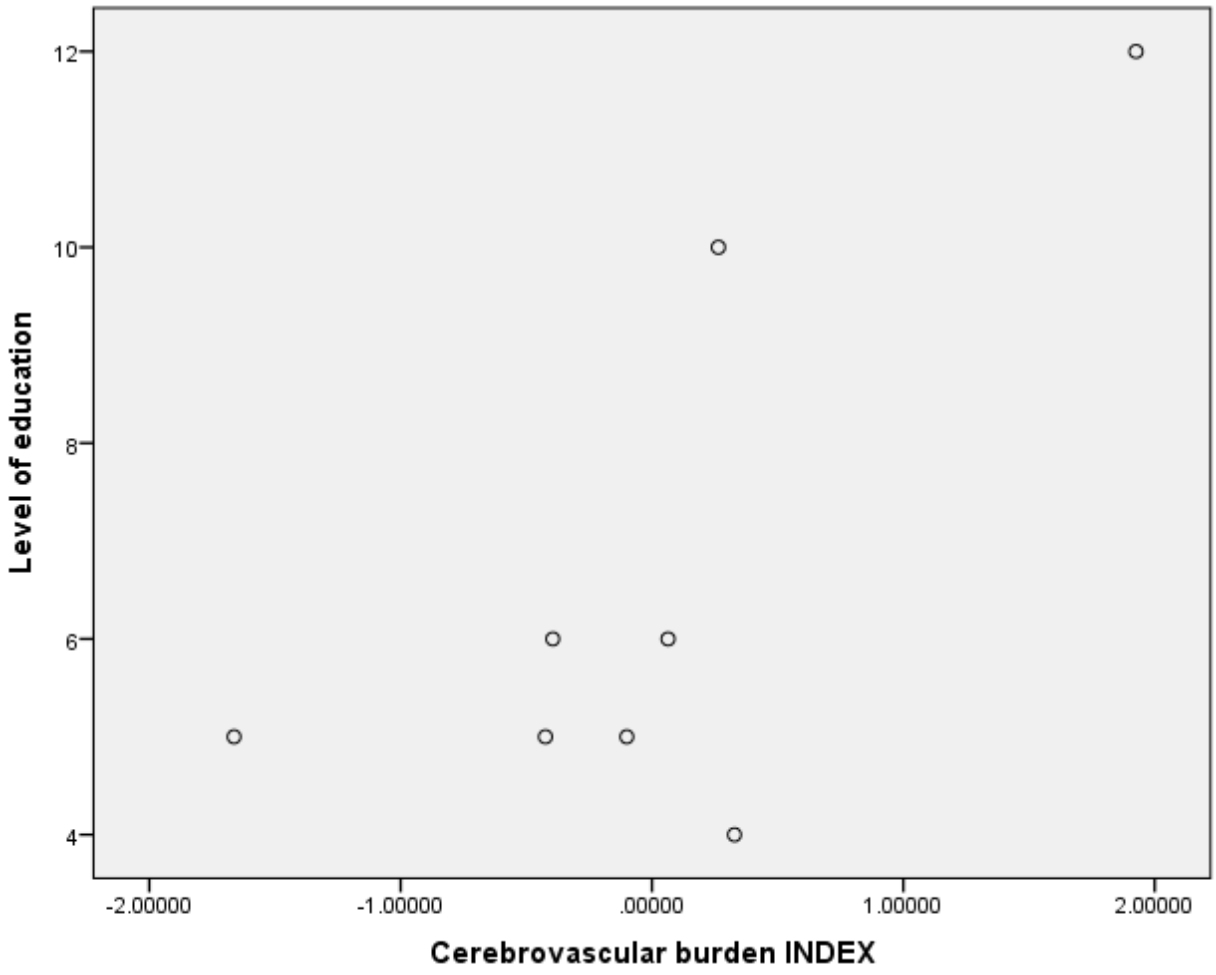


Table 6: Scatter plot of the following variables: level of education and cerebrovascular burden index



Appendix B: Figures

Figure 1: Pulse oximeter: used to measure blood oxygen saturation levels

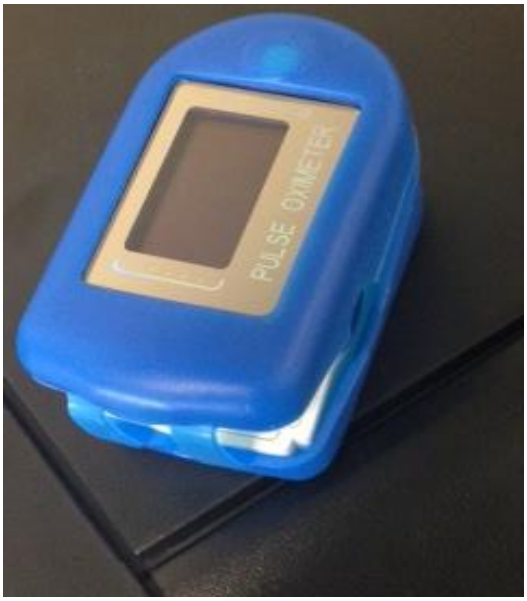
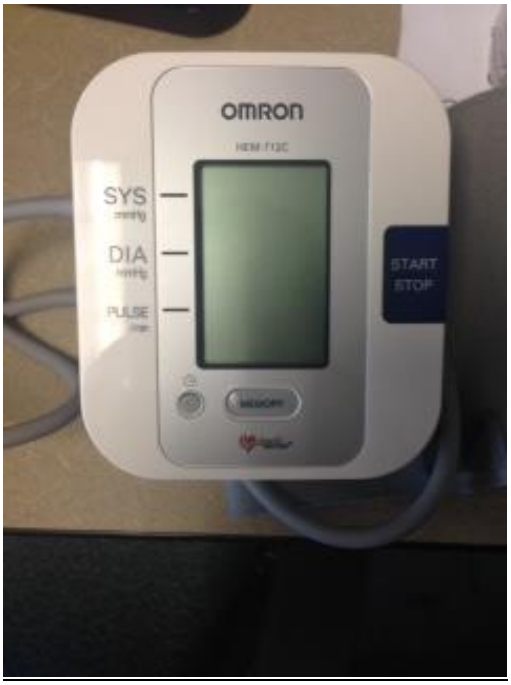


Figure 2: Blood pressure cuff: used to measure systolic/ diastolic blood pressure and resting heart rate



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