Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4), 1517-1524 | ISSN:2251-6727

Are the Blood Pressure Levels Associated with the Hippocampal, Temporal and Amygdala Volumes in Sedentary Females? A Sub-Group Analysis of a Cross-Sectional Study

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(Received: 02 September 2023 Revised: 14 October Accepted: 07 November)

KEYWORDS
Sedentary Behavior, Hypertension, Females, Brain Size, AAL3, Brain Volumes, Hippocampus,

ABSTRACT:

Objective:
This study aimed to investigate the impact of sedentary behavior and hypertension on brain size, focusing on the female population, and to elucidate the subtle cerebral changes that often go unnoticed in the context of modern digital lifestyles.

Methods:
In pursuit of this objective, we conducted a retrospective analysis utilizing brain MRI data from 19 sedentary females. Magnetic resonance imaging was performed using a 1.5T GE Signa scanner, and post-processing analysis was carried out employing SPM and CAT 12 software. Brain regions were assessed with reference to the Automated Anatomical Labeling 3 (AAL3) atlas.

Results:
Our findings revealed a noteworthy relationship between hypertension and brain structure alterations. Specifically, we observed an enlargement of the hippocampal region in individuals with hypertension compared to their normotensive counterparts. The left hippocampal region, in particular, exhibited a significant increase of 0.796 mm in hypertensive females. Furthermore, when examining different stages of hypertension, we observed a gradual increment in the hippocampal region from prehypertension through stage I hypertension. However, this enlargement trend subsided as hypertension progressed to stage II.

Conclusion:
In summary, this study underscores the subtle yet consequential cerebral changes associated with hypertension, particularly in the hippocampal region. The findings suggest that hypertension may have a variable impact on brain structure, with initial enlargement in the early stages, followed by stabilization or potential atrophy in more advanced stages. These results emphasize the importance of monitoring hypertension, even in the absence of overt physical symptoms, as it may silently affect cognitive health, especially in individuals with sedentary lifestyles. Recognizing and addressing these brain changes early on could be crucial in developing strategies for the prevention and

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www.jchr.org
JCHR (2023) 13(4), 1517-1524 | ISSN:2251-6727

management of cognitive decline in hypertensive individuals, particularly among females. Further research is warranted to delve deeper into the underlying mechanisms and clinical implications of these cerebral alterations.

1. Introduction

With the increase in the digital lifestyle era, the need to use the latent energy inside the human body has declined. The adult lifestyle is moving towards faster results and sophisticated workloads. In contrast, the digital world has brought the need for physical work to a sluggish speed, fastening the mental and physically inactive work pressure rate.

The thought of sedentism was first seen in humans 12,000 years ago when we decided to cut down on wandering for food and shelter; instead, we started living in groups, settled down in a good place, and resided by growing food and building shelters [1]. The same evolution has been established as a lifestyle or behavior in which a lot of sitting or lying in the most comfortable position with the least to no exercise or physical activity can use up the energy stored within us.

Approximately 28% of adults are estimated to be physically inactive globally, and one in four adults leads a sedentary lifestyle, according to 2018 WHO reports[2]. Post covid, this number has increased due to the feasibility of digital accessibility and worldwide lockdown, pushing people to look for ways to get the work done at their fingertips.

According to the WHO 2021 reports, hypertension cases have increased from 650 million to 1.28 billion in the last 30 years[3]. This number could increase by many folds over the next three decades. The medical world tags hypertension with an increased risk for the heart, brain, and kidneys[4]. However, few studies have investigated the effects of hypertension on the brain.

The brain is one of the most complex organs with a complicated network system and organized functioning capacity[5]. With any change in the rest of the body, the brain starts to feel the effects, but the visible symptoms are presented at later ages. This makes it very important to understand the brain in multiple aspects so that an avoidable decline in brain function can be detected at the earliest. Recent studies have shown a significant decrease in brain functioning when hypertension is one the sole variables, and the results are summarized as decreased brain volume, decreased cognitive functioning, decreased working memory, and so on[6–9].

Recent studies have also shown that sedentary behavior leads to a decline in cognitive functioning in healthy older adults, which gives an alarming note for understanding the structural differences in the brain in physically inactive adults[10]. The risk of developing obesity and cardiometabolic diseases, such as increased blood pressure, increased blood glucose levels, and lipidemia. So it is important to understand the effects of each risk in addition to a sedentary lifestyle, which gives us an easy path to work on the treatment ways.

Based on this information, we conducted a sub-group analysis of a previous cross-sectional study to observe brain size changes in adults with a sedentary lifestyle and in adults who were not sedentary [19].

2. Materials and Methods

This study was conducted from March 2021 to Sept 2022 at Kasturba Medical Hospital, Manipal, under the supervision of the Department of Radiodiagnosis and Imaging. We used a 1.5T GE Signa MRI machine with 8 channel head coil. T1 weighted BRAVO (fast-spoiled gradient echo FSPGR) sequence was used for better brain structural information. We focused on attaining maximum constant values and one variable, hypertension.

To achieve this, we concentrated on female subjects who had a low IPAQ score[11], an education level lower than 12^{th} grade, and no diabetes history. We collected data from 44 female adults who were advised to undergo an MRI scan. Of these, 24 females were included in this study. To simplify the data analysis, we divided the participants into four age groups namely 18-29, 30-39, 40-49 and 50-59. Due to the non-availability of hypertensive adults in the age groups between 18-40, we excluded the samples and were left with 9 samples in the age group between 40-49 and 10 samples from age group 50-59.

The MRI brain images were further analyzed using MATLAB-based post-processing software, such as CAT 12 (computational anatomical toolbox, version 12.8) and SPM12 (statistical parametric mapping, version 12). We assessed the structural brain dimensions and volume using the AAL3 atlas (automated anatomical labelling), and the sizes of different aspects of the brain, such as the hippocampus and cingulate gyrus, in both hemispheres [12]. The volumes of the gray matter, white matter, and total CSF were also measured. The abbreviations of the AAL3 atlas and the regions explored are marked in the table 1

Abbreviations	Full form
HIP	Hippocampus
PCC	Posterior cingulate gyrus

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AMYG	Amygdala
STG	Superior temporal gyrus
MTG	Middle temporal gyrus
ITG	Inferior temporal gyrus
FFG	Fusiform gyrus
PHG	Parahippocampal gyrus
LING	Lingual gyrus

Table 1: AAL3 abbreviations and its full form

3. Results

Our subgroup analysis included 44 female participants with an educational qualification lower than 12th grade and were non-full-time homemakers. Of these, 20 were excluded because of moderate IPAQ scores. Five more data points were excluded because no hypertensive female data was available for the 18-39 age group. The remaining 19 data points were categorized into two age groups namely 40-49 years and 50-59 years.

Based on the data collected, our analysis included five non-hypertensive adults, whose average brain size is summarized in Table 2. We used AAL3 (automated anatomical labelling - 3) to measure the brain volumes of different regions and performed total volumetric analysis of gray matter (GMV), white matter (WMV), cerebrospinal fluid (CSF), and total intracranial volume (TIV). Because our samples were right-hand dominant, we tabulated the left hemisphere regional values for simplified results.

Table 3 depicts the left hemisphere regional values of prehypertensive adults (N=9), stage I hypertension (N = 3), and stage II hypertension (N = 2). In Table 4, we can observe an increase in brain size in the prehypertension stage and stage I hypertension, where there is a decrease in size compared to the other two stages are easily differentiated.

Volume analysis of the four groups, namely, non-hypertension, prehypertension, stage I, and stage II, showed slight differences in the total intracranial volume (TIV), GMV, and WMV, except that the CSF values were not significantly different. The values are tabulated in the table 4

If we observe the progression in the brain size, Table 5 depicts the changes in the size of the left hippocampus arranged based on the increasing systolic blood pressure in the 40-49 years age group and 50 -59 years.

Owing to statistical errors, we assessed statistical significance based on normotensive and hypertensive data. The hypertensive group is clubbed information of all stages of hypertension mentioned above. Based on the collective data, we found that the left hippocampal region had statistically significant data ($p < 0.05$). The left hippocampal region was 0.796 mm larger in the hypertensive group, the right hippocampal region was 0.385 mm, and the left and right posterior cingulate measured 0.167 mm and 0.098 mm, respectively, larger than that in normotensive adults.

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3.2. Figures, Tables and Schemes

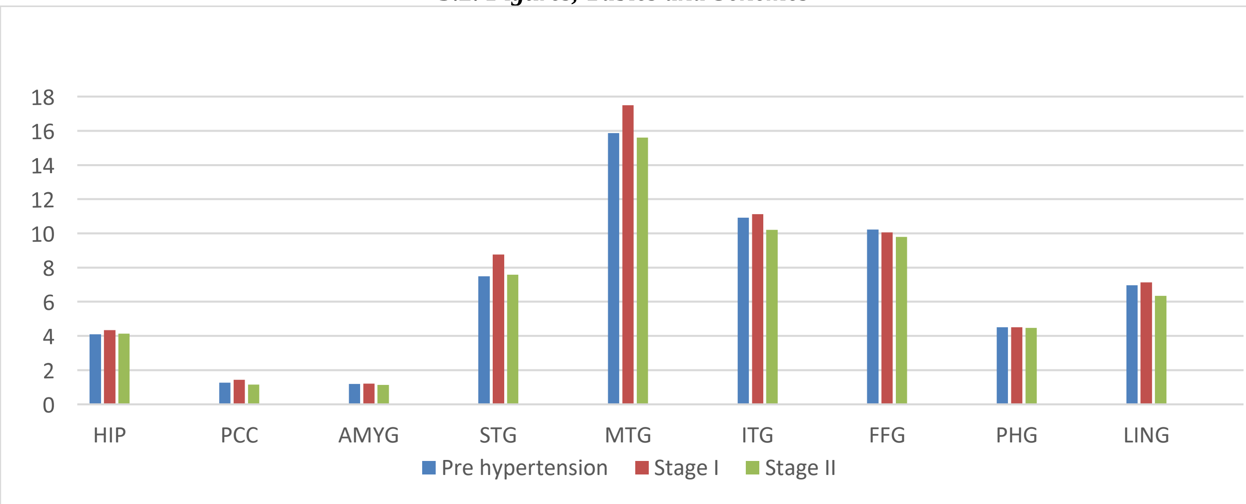


Fig 1: Graphical representation of Hypertensive Sedentary Behavior adults' brain measurements

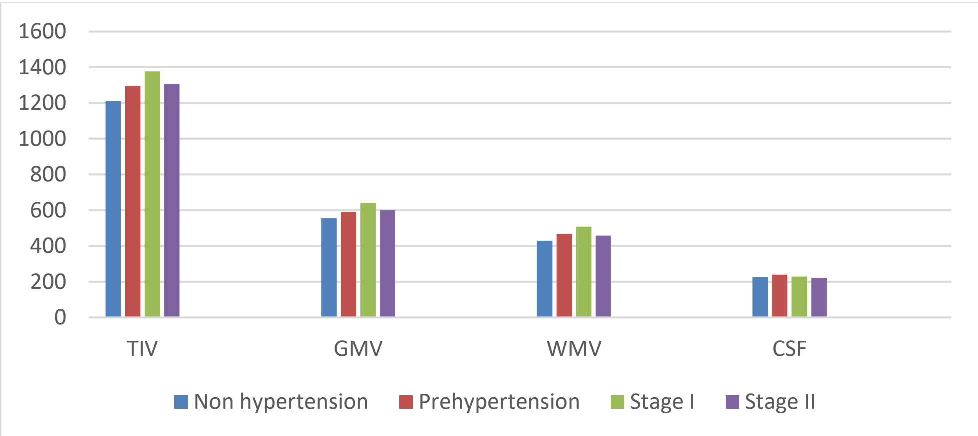
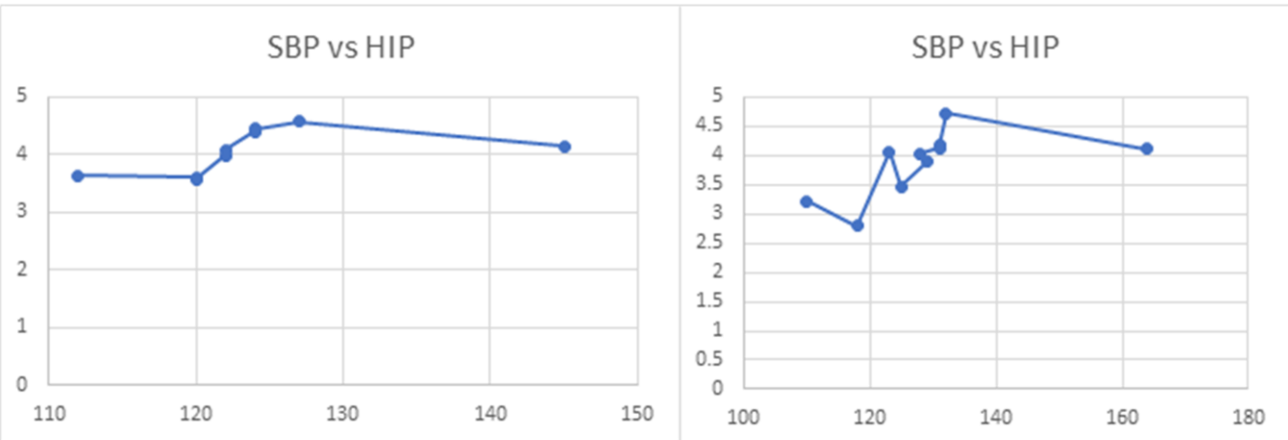


Fig 2: Graphical representation of Hypertensive Sedentary Behavior adults' total brain volume measurements



(a) **(b)**

Fig 3: Graphical representation of Systolic Blood Pressure (SBP) and Hippocampal size values. (a) represents 40- 49 years (b) 50- 59 years

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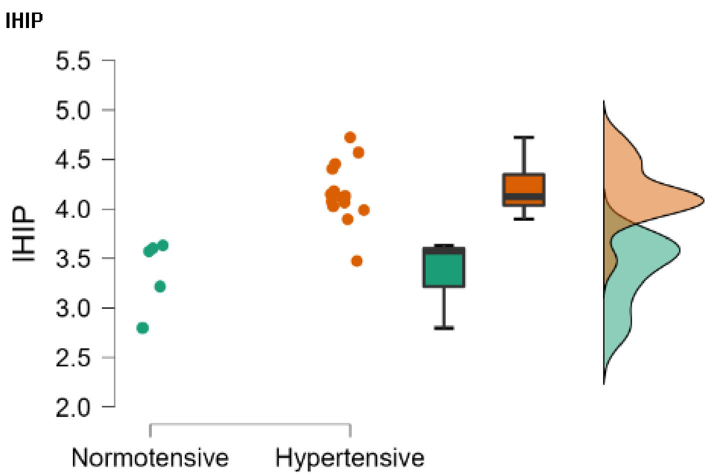

Fig 4: left hippocampus size measurement comparison between normotensive and hypertensive data

Brain regions	Left hemisphere values
HIP	3.36516
PCC	1.12006
AMYG	0.97208
STG	7.21024
MTG	14.69132
ITG	9.94874
FFG	8.87202
PHG	3.97782
LING	6.06928
TIV	1209.926
GMV	555.594
WMV	429.5
CSF	224.83

Table 2: Normotensive Sedentary Behavior adultls' brain measurements

Brain regions	Pre hypertension	Stage I	Stage II
HIP	4.106456	4.342467	4.13195
PCC	1.2638	1.438033	1.16205
AMYG	1.192333	1.206433	1.13245
STG	7.496333	8.768867	7.58425
MTG	15.86631	17.49757	15.6012
ITG	10.92534	11.13083	10.2072
FFG	10.21644	10.0482	9.8025
PHG	4.503267	4.5023	4.4799
LING	6.955533	7.140867	6.34535

Table 3: Hypertensive Sedentary Behavior adults' brain measurements

Volume	Non hypertension	Prehypertension	Stage I	Stage II
TIV	1209.926	1296.64	1377.227	1306.83
GMV	555.594	589.8544	640.9167	599.325
WMV	429.5	466.79	508.0067	458.945
CSF	224.83	239.9967	228.3	222.39

Table 4: Hypertensive Sedentary Behavior adults' total brain volume measurements

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Age Group – 40- 49		Age Group – 50- 59	
SBP	HIP	SBP	HIP
112	3.6335	110	3.2172
120	3.6041	118	2.7981
120	3.5729	123	4.0657
122	3.9892	125	3.4738
122	4.0762	129	3.8959
124	4.4054	128	4.0276
124	4.4546	131	4.1295
127	4.5697	131	4.177
145	4.1479	132	4.7209
		164	4.116

Table 5: Systolic Blood Pressure (SBP) and Hippocampal size values based on age groups

Independent Samples T-Test								
						95% CI for Mean Difference		
	t	**df**	**p**	**Mean Difference**	**SE Difference**	**Lower**	**Upper**	**Cohen's d**
lHIP	-4.757	17	< .001	-0.796	0.167	-1.148	-0.443	-2.478
rHIP	-1.638	17	0.120	-0.385	0.235	-0.880	0.111	-0.853
lPCC	-1.755	17	0.097	-0.167	0.095	-0.367	0.034	-0.914
rPCC	-2.377	17	0.029	-0.098	0.041	-0.185	-0.011	-1.239

Table 6: Independent T-test results

4. Discussion

This study was conducted in the KMC Manipal to assess the prevalence of hypertension-based brain size changes. We focus on a selected population to achieve stability for the following reasons. The study population was restricted to one sex because of the controversial debate that revolves around the concept of either males or females with a larger brain. With studies depicting the difference in brain size based on sex [13,14], we confined our sub group analysis study to female adults. In 2012, a study by Noble et al. stated that hippocampal size varies across educational attainment, with a decrease in the hippocampus observed in lower educationally attained adults compared to adults with higher educational attainment over the life span[15]. With this as a stable note, we confined our sub group analysis to females with lower educational attainment, which is lower than 12th grade and non-working professional. In our study, we concentrated on the females with a lower IPAQ grade for additional stability, since studies have proven to reduce the effects of hypertension on the brain with increased physical activity[16]. All females had an IPAQ grade lower than 500 with more than 8 h of sitting time and lower than 10 min of physical activity on average. These data were collected from the study participants using IPAQ questionnaires. Since studies have shown that brain size can be altered for many reasons and conditions, we attempted to achieve maximum constants with altered blood pressure as a single variable.

The different brain region's measurement is significantly lower in our study than the normal measurements especially the hippocampal region which measures an average of 3.765 mm where we had an average of 3.365 mm which could be due to the fact that all the females were physically inactive[17]. If we observe the sizes of the brain regions in the altered blood pressure, we can see an increase in the hippocampal measurements with 4.106 mm in prehypertension, 4.342 mm in stage I, and 4.131 mm in stage II hypertension. Similar changes were observed in other regions, but the differences were not statistically significant.

A similar result was observed in whole-brain volumetric analysis. As shown in Table 5, there was a gradual increase in the total intracranial volume, gray matter, and white matter from normotensive to stage I, and a decrease in stage II. Except for the total CSF, which remained almost constant. This change was also observed in a study conducted by Melinda C Power in 2016, which explained similar changes [18].

In Table 5, we represent the left hippocampal size with an increase in systolic blood pressure. The SBP was below 120 mmHg, and the measurements were similar to the average size. However, as the SBP increased, the hippocampal size increased to a maximum based on our study up to 4.72 mm till stage I. However, these values decreased in Stage II.

The graph in the fig 4 represents the data for normotensive and hypertensive adults. Here, we can observe that the hippocampal values overlap very faintly with the peak set in both cases. There was an increased

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size of 0.796 mm in hypertensive adults compared to that in normotensive adults.

When we observed this pattern, we tried to find an answer to this effect, but found none. In a later search of the patient database, we found that the subjects who were in prehypertension and stage I hypertension were non-medicated, whereas those in Stage II were taking antihypertensive drugs. Which brought us to a question " does hypertension causes significant swelling in certain regions of brain?" , " persistent hypertension and sedentary lifestyle increases the chance of brain swelling?" "does the anti hypertension drugs restricts the swelling and preserves the brain size?" and lastly " can physically active lifestyle reduce this risk of swollen brain?"

5. Conclusions

This was a sub group analysis of a previous cross-sectional study in which our focus was to observe the changes in brain size caused by sedentary behavior with hypertension. We found a pattern where there was an increase in the hippocampal region size in the prehypertension and stage I groups compared to the non-hypertensive adults. However, the values tended to dip and reach the level of normotensive measurements in Stage II. This might provide a new perspective for assessing hypertension based on brain changes.

Limitations and recommendations

As this was a sub group analysis, we had a very small sample size. Even with this sample size, we tried to collect data across all stages of hypertension so that we could get a slighter idea to understand the effects of sedentary behavior and hypertension on the brain. We need to have a larger sample size with an equal number of samples for each stage of hypertension to provide a better comparison. We have to assess the effects on various variables such as male sex, educational level, age group, and physical activity pattern.

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Funding: No funding was provided for this study

Institutional Review Board Statement: Institutional Research Committee (IRC) was accredited by the Manipal College of Health Professions, MAHE, Manipal. Institutional Ethics Committee has approved this study [389/2021] on 13-04-2021. CTRI No: CTRI/2021/08/046624 registered on 02/09/2021

Conflicts of Interest: All the authors declare no conflict of interest.

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