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ORIGINAL RESEARCH

ASSOCIATION BETWEEN FLAT FOOT SEVERITY AND LOW BACK PAIN RECURRENCE AMONG PRE-CLINICAL MEDICAL STUDENTS: A CROSS-SECTIONAL STUDY

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Abstract

Background: Low back pain (LBP) affects over 619 million people globally and is highly prevalent among medical students. Flat foot (pes planus), a biomechanical alteration involving the collapse of the medial longitudinal arch, may contribute to spinal stress and LBP recurrence, yet remains underexplored in young adult populations.

Methods: This cross-sectional study involved 67 pre-clinical medical students aged 19–23 years with a history of recurrent LBP in the past year. LBP frequency was assessed using the Nordic Musculoskeletal Questionnaire and Numeric Rating Scale (NRS). Foot arch structure was evaluated via Clarke's Angle, classifying flat foot severity into mild (35°–41°), moderate (30°– 34.9°), and severe (<30°). Data were analysed using Chi-square tests, with significance set at $p < 0.05$.

Results: LBP was reported by 80.6% of participants, with flat foot classified as mild in 43.3%, moderate in 37.3%, and severe in 19.4%. A significant association was found between flat foot severity and LBP recurrence ($p < 0.001$). Students with mild or moderate flat foot had a lower odd of experiencing moderate-frequency LBP compared to those with severe flat foot (OR = 0.152 95% CI: 0.048–0.483).

Discussion: These findings support the notion that structural abnormalities of the foot, particularly flat foot, may contribute to the recurrence and persistence of LBP by influencing spinal posture, altering mechanical load distribution, and affecting neuromuscular stability.

Conclusion: Flat foot severity is significantly associated with the recurrence of LBP in medical students. Early identification and foot posture assessment may help inform preventive and corrective interventions for recurrent LBP.

Keywords: Low back pain, Flat foot, Clarke's Angle, Medical students, Recurrence, Flat foot severity

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Introduction

Low back pain (LBP) is defined as pain or discomfort located below the costal margin and above the inferior gluteal folds, with or without leg symptoms, and is often associated with limited mobility and functional impairment[1]. Globally, LBP remains the leading cause of years lived

with disability (YLDs), affecting over 619 million individuals as of 2020, with the number projected to reach 843 million by 2050[2,3]. In Indonesia, the situation is similarly concerning. A large-scale study reported a 12-month prevalence of LBP of 44.29% among middle-aged adults, making it one of the most common musculoskeletal complaints[4].

Among university students, especially those in medical education, the burden of LBP is particularly notable. The prevalence of LBP among medical students ranges from 46.9% to 82% in various studies[5–7]. A study conducted at the Faculty of Medicine, Universitas Pelita Harapan, reported a prevalence of 76% among pre-clinical students, highlighting the significance of this condition in young, sedentary, and academically burdened populations[8].

LBP in students can lead to absenteeism, decreased academic performance, poor sleep quality, and early-onset musculoskeletal dysfunctions. While known risk factors such as aging, obesity, poor ergonomics, inactivity or sedentary lifestyle, and work overload are well-established[9–12]. However, flat foot remains an underexplored biomechanical contributor. Pes planus is characterized by the flattening of the medial longitudinal arch, causing altered lower limb alignment and increased lumbar stress[13]. Previous studies by Lulupoy et al. and Kosashvili et al. reported a significant association between flat foot and increased LBP risk[14,15].

Flat foot can be objectively assessed using Clarke's Angle, a non-invasive and reliable method based on static footprint analysis. This approach provides a simple yet validated means to classify foot arch collapse[16]. Despite its clinical utility, limited research has examined flat foot severity as a potential risk for frequent or repeated episodes of LBP among medical students. Most existing data originate from clinical or geriatric populations, and therefore may not be generalizable to young, active adults[14,15]. This study addresses that gap by investigating the relationship between flat foot severity and the recurrence of LBP among pre-clinical medical students. The findings are expected to provide insight into underrecognized biomechanical contributors and support targeted preventive strategies for musculoskeletal health in student populations.

Methods

This cross-sectional analytical study involved 67 pre-clinical medical students from the Faculty of Medicine, Universitas Pelita Harapan, and was conducted between February and April 2025. Participants were selected using purposive sampling based on inclusion criteria: age between 19 and 23 years and a history of recurrent LBP within the past twelve months. Exclusion criteria included obesity (BMI ≥ 30 kg/m²), scoliosis, spinal trauma or surgery, congenital spinal abnormalities, and neurologic conditions that could affect spinal or gait biomechanics.

After obtaining written informed consent, participants completed a structured questionnaire capturing demographic characteristics (age, sex) and clinical data related to LBP, using the Standardized Nordic Musculoskeletal Questionnaire (NMQ). This instrument has been validated by Chareani et al.,

demonstrated excellent reliability (Cronbach's Alpha > 0.945) and 100% construct validity agreement, with specificity exceeding 85% in the lower back, neck, and shoulder regions, making it a valid and reliable tool for assessing musculoskeletal complaints in Indonesian populations[17]. LBP recurrence was categorized into three groups: low-frequency recurrence (<1 episode/month), moderate-frequency recurrence (approximately 1 episode/month), and high-frequency recurrence (>1 episode/month). Pain intensity was assessed using the Numeric Rating Scale (NRS) and classified as mild (1–3), moderate (4–6), or severe (7–10). Ratings were recorded both at rest and during forward trunk flexion. Participants also reported additional symptoms, such as radiation of pain to the lower extremities.

Assessment of foot arch structure was performed using Clarke's Angle (CA), obtained through static footprint analysis. Each participant was instructed to step onto a water-soluble ink pad and then place their foot firmly on a labelled sheet of drawing paper for approximately ten seconds. This process was repeated until a clear and complete footprint was obtained. Using a ruler, pen, and a stainless-steel protractor, the Clarke's Angle was measured as the angle formed between a line drawn along the medial border of the footprint and a second line connecting the deepest point of the medial longitudinal arch to the medial forefoot. Based on this angle, foot arch type was categorized into: mild pes planus (35°–41°), moderate pes planus (30°–34.9°), and severe pes planus (<30°)[18].

Statistical Analysis

IBM's Statistical Package for the Social Sciences (SPSS) version 26 was used to manage and analyze all collected data. Descriptive analysis was conducted for demographic variables and clinical characteristics, including gender, age, flat foot severity (based on Clarke's Angle), recurrence frequency, and pain intensity. Bivariate analysis was performed to examine the association between flat foot severity and the recurrence of LBP.

Categorical variables, including LBP recurrence frequency and pain severity, were analyzed using the Chi-square test or continuity correction test, depending on expected cell counts. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the strength and precision of associations. All statistical tests were two-tailed, and results were considered statistically significant at $p < 0.05$.

Ethical Statement

This study was declared to have passed the ethical review by the Faculty of Medicine, Universitas Pelita Harapan, by obtaining ethics number 125/K-LKJ/ETIK/II/2025. All participants provided written informed consent prior to enrollment, following a clear explanation of the study's objectives, procedures, and potential benefits. Participation was entirely voluntary and based on full understanding of the research purpose.

Results

A total of 120 pre-clinical medical students from the Faculty of Medicine,

Universitas Pelita Harapan were initially recruited for this study. Following the screening process, 22 students were excluded due to obesity (BMI ≥ 30 kg/m²), 15 due to a history of spinal disorders such as scoliosis, lordosis, or spondylitis, and 16 due to a prior history of back trauma. As a result, 67 participants met the inclusion criteria and were included in the final analysis.

Table 1 summarizes the univariable characteristics of the study population. Most participants were female (73.1%) and predominantly aged 20–21 years (71.6%). Based on Clarke's Angle, 43.3% had mild flat foot, 37.3% had moderate, and 19.4% had severe flat foot. The prevalence of LBP was high, with 80.6% of respondents reporting pain in the past year. Low- frequency LBP was reported by 59.7% of participants, while 40.3% experienced moderate frequency, and none reported high-frequency episodes. Among those with LBP, the majority experienced moderate pain intensity (68.5%), and 44.4% reported radiation of pain to the lower limbs.

Table 2 shows the association between flat foot severity, measured using Clarke's Angle, and the frequency of LBP recurrence among pre-clinical medical students. Among those with mild flat foot (35°–41°), 35.8% experienced low-frequency recurrence (<1 episode/month), while only 7.5% reported moderate-frequency recurrence (≈1 episode/month). Conversely, in the moderate- to-severe flat foot group (≤34.9°), 32.8% experienced moderate-frequency recurrence, and 23.9% reported low-frequency recurrence. Statistical analysis revealed a significant association between flat foot severity and LBP recurrence frequency ($p < 0.001$), with an odds ratio of 0.152 (95% CI: 0.048–0.483), indicating that students with mild flat foot had significantly lower odds of experiencing moderate-frequency LBP compared to those with more severe deformities.

Table 1. Univariable Characteristics of Pre-Clinical Medical Students (n = 67)

Characteristic	Categories	n (%)
Age Group (years)	19	12 (17.9)
	20	27 (40.3)
	21	21 (31.3)
	≥ 22	7 (10.5)
Gender	Male	18 (26.9)
	Female	49 (73.1)
Flat Foot Severity (Clarke's Angle)	Mild (35°–41°)	29 (43.3)
	Moderate (30°-34,9°)	25 (37.3)
	Severe (<30°)	13 (19.4)
Reported Low Back Pain (LBP)	Yes	54 (80.6)
	No	13 (19.4)
LBP Intensity (Numeric Rating Scale)	Mild (1 – 3)	17 (31.5)
	Moderate (4 – 6)	37 (68.5)
	Severe (7 – 10)	0 (0.0)
	Low-Frequency (<1x/month)	40 (59.7)
	Moderate-Frequency (~1x/month)	27 (40.3)
	High-Frequency (>1x/month)	0 (0.0)
Pain Radiation to Lower Limbs	Yes	24 (44.4)
	No	30 (55.6)

Table 2. Association Between Flat Foot Severity and Frequency of Low Back Pain Recurrence in Pre-Clinical Medical Students

Subject characteristics	LBP Recurrence		P value	OR [95% CI]
	Low-frequency (<1x/month)	Moderate-frequency (<1x/month)		
Flat Foot Severity (Clarkes's Angle)				
Mild (35°–41°)	24 (35.8%)	5 (7.5%)	<0.001	0.152
Moderate – Severe (≤34,9°)	16 (23.9%)	22 (32.8%)		(0.048–0.483)

Discussion

LBP constitutes a substantial contributor to the global burden of musculoskeletal disorders, particularly

among university populations[19,20]. Medical students are uniquely predisposed to LBP due to prolonged sedentary behaviors, academic stress, disrupted sleep cycles, and insufficient ergonomic awareness during pre-clinical training years. Multiple studies have reported LBP prevalence rates exceeding 70% in this demographic[6–8,12].

In the present study, we observed that 80.6% of pre-clinical medical students experienced LBP within the preceding year. Univariable analysis revealed a predominantly female cohort (73.1%), with most participants aged between 20–21 years (71.6%). This sex disparity is consistent with prior literature, as reported by Vujcic et al., who found that both lifetime and 12- month prevalence rates of LBP were significantly higher among female medical students, with contributing factors including mental stress, prolonged sitting, fatigue, and poor posture[21]**.** Similarly, Smith et al. observed that female students reported LBP 1.8 times more frequently than their male counterparts, underscoring the influence of sex-related biomechanical and psychosocial variables[21]. Notably, this pattern of increased prevalence in females has also been observed in younger populations; a large cross-sectional study by Yao et al. involving over 2000 Chinese schoolchildren aged 10–18 years revealed a significantly higher 3-month LBP prevalence among girls (33.1%) compared to boys (24.7%), with greater frequency, radiating symptoms, and functional impact, thereby suggesting that sex-based differences in LBP manifestation may emerge early and persist into adulthood[22].

Additionally, the severity of flat foot based on Clarke's Angle showed a notable distribution: 43.3% had mild flat foot, 37.3% moderate, and 19.4% severe. The link between flat foot and LBP can be explained biomechanically. A decreased medial longitudinal arch alters the biomechanics of the lower extremities, leading to excessive foot pronation and internal tibial rotation. These changes may cause compensatory pelvic tilt, lumbar hyperlordosis, and increased axial loading on spinal structures. Over time, such postural adaptations can result in paraspinal muscle fatigue, facet joint irritation, and intervertebral disc stress—factors that contribute to recurrent episodes of LBP[23–25].

Our bivariate analysis demonstrated a robust and statistically significant association between increased severity of flat foot and higher frequency of LBP recurrence ($p < 0.001$). Specifically, among participants with mild flat foot (Clarke's angle 35°–41°), only 7.5% reported moderate-frequency recurrence (approximately once per month), compared to 32.8% of those with moderate to severe deformity (≤34.9°). The calculated odds ratio of 0.152 (95% CI: 0.048–0.483) indicates that students with mild flat foot were approximately seven times less likely to experience recurrent LBP than their counterparts with more pronounced arch collapse.

These findings are in accordance with previous studies which have implicated flat foot as a modifiable extrinsic risk factor for spinal discomfort and dysfunction. Godaria et al. further substantiated this association, demonstrating that foot posture, along with working posture, significantly correlated with LBP among workers engaged in prolonged standing

occupations, whereas other factors such as repetition, core strength, and flexibility showed no significant relationship[26]. In a large-scale epidemiological study, Almutairi et al. reported that individuals with flat feet had markedly higher prevalence of both acute (51.6%) and chronic LBP (48.4%), with flat foot increasing the odds of acute and chronic LBP by 3.28 and 4.5 times, respectively[27]. Amoozadeh et al., using the navicular drop test in a case-control design, identified a significant relationship between decreased medial longitudinal arch and the presence of chronic mechanical LBP, highlighting the role of altered foot mechanics in disrupting postural alignment and gait stability, thereby contributing to spinal loading and discomfort[28]. Moezy et al. conducted a case- control study involving 242 subjects, using the Helbing sign and Navicular Drop Test to assess foot overpronation, and found significant associations with LBP intensity, duration, and reduced ankle dorsiflexion ($p = 0.001$)[29]. These results support the kinetic chain theory linking foot posture to spinal load. Likewise, Lulupoy et al. used Clarke's angle (≤30°) in a case-control design and showed that flat foot increased the risk of mechanical LBP by over six times (OR: 6.29; $p < 0.001$)[14]. Cumulatively, the evidence supports the notion that structural abnormalities of the foot, particularly flat foot, may contribute to the recurrence and persistence of LBP by influencing spinal posture, altering mechanical load distribution, and affecting the stability of neuromuscular function.

While our study offers valuable insight into a relatively underexplored etiological factor among medical students, several methodological limitations must be acknowledged. The cross-sectional design precludes causal inference and limits temporal analysis. Self-reported measures of LBP frequency may also be subject to recall or reporting bias. Additionally, Clarke's Angle, while widely used, may not fully capture the dynamic aspects of foot biomechanics. Future studies should incorporate gait analysis and longer follow-up to assess the impact of flat foot correction (e.g., orthotics) on LBP outcomes.

Conclusion

In conclusion, this study demonstrates a significant association between the severity of flat foot and increased recurrence of LBP among pre-clinical medical students. Biomechanical alterations due to arch collapse likely contribute to compensatory postural changes and spinal stress, reinforcing the relevance of foot posture in musculoskeletal health. Despite methodological limitations, these findings highlight flat foot as a potentially modifiable risk factor for recurrent LBP in young adults.

Conflict of Interest

The authors declared no conflict of interest.

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ORIGINAL RESEARCH

ADDICTION TO ONLINE GAMES AFFECTS THE ATTENTION LEVELS OF MEDICAL STUDENTS OF PELITA HARAPAN UNIVERSITY

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Abstract

Background: Epidemiologically, the incidence of online games addiction in students in Indonesia in 2013 is estimated to be around 10.15%. Addiction to online games is one of the factors that might affect a person's level of attention. Previous studies had shown that there are positive and negative effects of attention function. There are also several studies that have reviewed the relationship between online games addiction and cognitive function but only a few studies focus on the level of attention. The study was conducted to determine the relationship of online games addiction with the level of attention to students.

Methods: This study uses a cross-sectional method. A sample of 158 peoples, who are students of the Faculty of Medicine at the University of Pelita Harapan in 2017 and were selected using a purposive technique. Data was collected from February to March 2020. The results were processed with Chi Square using SPSS version 25.0 software.

Results: Of the 158 samples needed, only 97 samples were collected due to COVID-19 and power by 56%. Of the 93 samples that met the inclusion criteria, 22.6% were addicted to games. In the game's addiction group, it was found that 23.8% experienced a decrease in forward attention and 57.1% experienced a decrease in backward attention. (forward: p value = 0,000, backward: p value = 0,001).

Conclusion: In conclusion, a significant relationship was found between online game addiction and decreased attention levels.

Keywords: Online games addiction, attention levels

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Introduction

The advancement of the internet in Indonesia is increasing expeditiously. Based on the APJII (Asosiasi Penyelenggara Jasa Internet Indonesia) survey in 2018, internet users in Indonesia were at 64,8%, which is 171.1 million people out of a total of 264.16 million people in Indonesia. From 100% internet users, there were 5.7% (ranked 6th as the main reason for using the internet) use the internet as the main reason for playing online games, and 7.8% of internet users (ranked 5th as the second reason for using the internet) use the internet as the second reason for playing online games.[1]

The addiction towards online games has now been officiated by the World Health Organizations (WHO) as the mental health disease in International Classification of Disease 11th Revision (ICD-11).[2] Online games addiction with the presence of clinical disorders can be categorized as the Internet Gaming Disorder in DSM V (Diagnostic and Statistical Manual of Mental disorders) by American Psychiatric Association in 2013.[3]

In 2013, according to Jab et al., it was estimated there were 10.15% Indonesian students addicted to online games.[4] Online games addiction had similar neural processes as drug addiction and other addictive behaviors, such as pathological gambling.[5] Online games addiction also led to several problems, such as problems with verbal memory, poor academic achievement, sleep disorders (insomnia and low sleep quality), difficulty in social adjustment, anxiety, and stress.[6,7] In 2014, Sara et al. found a relationship between playing video games and attention problems and several conceptually related abilities, and games that had violent elements were associated with greater attention problems.[8] In 2017, Peracchia et al. stated that playing video games was also often done at night which might affect sleep time, thereby, reducing sleep time. On the other hand, games addiction is also reported to have positive impacts on cognitive abilities, emotions, and social habits.[9] In 2018, Zahra et al. had shown that gamers had better concentration levels than non-gamers.[10]

The poor quality of sleep is also associated with reduced abilities of maintaining attention and focus on tasks.[11] Less than 6 hours of sleep during nighttime is considered as partial lack of sleep and might cause attention deficit continuously.[12] In 2017, Peracchia et al. had shown that hard gamers (playing almost 4-6 hours daily) had better sleep quality and efficiency than casual gamers (playing less than 1 hour), this might be due to larger physiological activity on the hard gamers, therefore causing the better and deeper sleep quality.[9]

From this description, the researcher is finally intrigued in examining whether there is an influence between online games addiction and the level of attention among respondents. Therefore, this study is conducted to determine whether there is an influence and physiological and psychological impact produced by online games addiction with a person's level of attention.

Methods

The study design in this research was a cross-sectional study design. This study was an unpaired categorical study. The Chi Square method was the method used for data analysis. This research was conducted at the Faculty of Medicine, Pelita Harapan University using the questionnaire method, digit span forward test, digit span backward test, Depression Anxiety Stress Scales 21 (DASS 21) test and will be described in the variables and research methods. This research was conducted during February - March 2020.

The target population was students of the Faculty of Medicine, Pelita Harapan University, class of 2017. The research sample is students of the Faculty of Medicine, Pelita Harapan University, batch

2017 with inclusion and exclusion criteria. The inclusion criteria were students that were part of the students of Pelita Harapan University (Batch 2017), agreeing to participate in the research, playing video games on any devices, such as smartphone, PlayStation, computer, laptop, and other game consoles, playing video games for 12 months, without 1 full month without playing video games. The exclusion criteria are the students that were training for video games competition, interested in becoming an e-sport athlete, needed time to play video games for certain purposes, DASS score for depression ≥ 9, DASS score for anxiety ≥ 8. The data obtained were processed and statistically tested using the SPSS 25.0 program with the Chi Square method.

Results

Based on the research that was conducted in February–March 2020 at the Faculty of Medicine, Pelita Harapan University, 97 research samples were obtained, which was less than the required number of respondents, which was 158. A total of 93 respondents met the inclusion criteria, while 4 respondents met the exclusion criteria because their DASS scores was 21, which met the criteria for depression or anxiety. The respondents were the preclinical medical students at the Faculty of Medicine, Pelita Harapan University, batch 2017, who voluntarily participated in this study, which involved completing a questionnaire and attention test, and met the inclusion and exclusion criteria.

Based on the respondents who met the criteria, 52 (55.9%) were female and 41 (44.1%) were male. The age range of respondents was between 18 and 30 years, with a mean of 20.24 ± 1.2.

From the collected data, 21 people (22.6%) were classified as addicted to games, and 72 people (77.4%) were not classified as addicted to games, according to the Internet Gaming Disorder (IGD) questionnaire. All respondents met the inclusion criteria, namely being a Medical Students of Pelita Harapan University, batch 2017, agreeing to participate in this study, and meeting the criteria for completing the IGD questionnaire, with always playing for 12 months, without any 31 full days without playing games, and from the data collected from respondents, none suffered from attention deficit hyperactivity disorder (ADHD) or autism as confounding variables (Table 1).

The level of attention of the respondents was measured using two types of attention tests; forward and backward, with a cut-off score of 4.

Table 1. Subjects Characteristics

Variable	n	Percentage (%)	Mean
Gender			
Male	41	44,1	
Female	52	55,9	
Mean Age ± SD, Year			20,24 ± 1,2
Online Games Addict (IGD)			
Yes	21	22,6	
No	72	77,4	
Forward Attention			
Decreased	5	5,4	4,48 ± 1,36
Normal	88	94,6	5,93 ± 1,09
Backward Attention			
Decreased	24	25,8	3.62 ± 0,92
Normal	69	74,2	4,33 ± 0,85

In the gaming addiction group, the results for the forward attention test, there were 5 respondents that had deficit of attention level and 16 had normal

attention level with mean or average score of 4,48 ± 1,36. Meanwhile, in the non-addiction group, there was no deficit of attention level based on the forward digit span, and the mean or average score of 5,93 ± 1,09. The mean forward digit span attention of all samples, both addicted and non-addicted to games, was 5.60 ± 1.303, and for backward digit span was 4.09 ± 0.905.

For the level of attention of the game addiction group with backward digit span, 12 respondents experienced decreased attention and 9 respondents had normal attention, with a mean or average score of 3.62 ± 0.92. For the group that did not experience game addiction, from the results of digit span backward, 12 respondents experienced decreased attention and 60 respondents had normal attention levels, with a mean or average of 4.33 ± 0.85 (Table 2).

The results of the statistical test using chi-square obtained a p-value using Fisher's exact test due to the Expected value of less than 5, amounting to 0.000, so it can be concluded that there is a statistically significant relationship between game addiction and attention level (forward).[40] The odd ratio value for this data cannot be calculated due to the value of 0 (Table 3).

The results of the statistical test using chi-square obtained a p-value of 0.001 (p <0.05) so it can be concluded that there is a statistically significant relationship between game addiction and attention level (backward).[40] The results of the odd ratio value in this study were 6.667 (OR> 1) and 95% CI of 2.302 - 19.31.40 (Table 4).

Table 2. Attention Test Results

Variable	Game Addiction	Non Game Addiction	n	%
Forward Attention				
Decreased (< 4)	5	0	5	5,4
Normal	16	72	88	94,6
Mean forward attention	4,48 ± 1,36	5,93 ± 1,09		
Overall Mean Forward Attention	5,60 ± 1,303			
Backward Attention				
Decreased (< 4)	12	12	24	25,8
Normal	9	60	69	74,2
Mean Backward Attention	3.62 ± 0,92	4,33 ± 0,85		
Overall Mean Backward Attention	4,09 ± 0,905			

Table 3. Statistical Analysis of Game Addiction with Attention Level (Forward)

Game Addiction	Attention (Forward)				Total	P Value
	Decreased		Normal			
Yes	5	23,8%	16	76,2%	21	0,000
No	0	0,0%	72	100%	72	
Total	5	5,4%	88	94,6%	93	

Table 4. Statistical Analysis of Game Addiction with Attention Level (Backward)

Game Addiction	Attention (Backward)				Total	OR (95% CI)	P Value
	Decreased		Normal				
Yes	12	57,1%	9	42,9%	21	6,667	
No	12	16,7%	60	83,3%	72	(2,302-19,311)	0,000
Total	24	25,8%	69	74,2%	93		

The respondents needed for this study were 158 respondents, and the number of accumulated respondents was 97 respondents, in which 4 respondents met the exclusion criteria, therefore, the data that could be processed was 93 respondents. As a result of the lack of accumulated respondents from the required number, the power calculation

was carried out. From the power calculation, the result was 56%.

Discussion

The results from the collected data in this study were still less than expected, there were 158 respondents, therefore, a power calculation was done, and the results obtained were 56%. The results of the analysis of this study found a relationship between addiction to online video games and the level of attention among Pelita Harapan University Medical Students batch 2017, with a p-value for forward attention using the fisher's exact test of 0.000 ($p < 0.05$) due to an expected value of less than 5, and for backward attention of 0.000 ($p < 0.05$). The odds ratio value for forward attention was not obtained due to the value of 0 in the table analyzing the level of attention (forward) with addiction to games in table 5.3, and for backward attention the value was 6.667 (OR> 1, 95% CI 2.302-19.311), therefore, the chances of someone who is addicted to online video games are 6.6 times greater to have a decreased level of attention than those who do not suffer from addiction to online video games.

In theory, playing games can be explained through a dual processing model where there is a reactive and reflective system, in people addicted to games, the reactive system (dopamine pathway) will remain because of the repeated pleasure of playing games so that the reactive system ("go" network) will strengthen and the reflective system ("stop" network) will weaken because of the strengthening of the reactive system, which causes decreased attention is the weakening of the reflective system, because the reflective system is a part area related to attention and impulse control.[3,25]

For the forward and backward attention tests, each has a different level of sensitivity and specificity, for sensitivity, digit span backward has a higher level of sensitivity, namely 77% and for forward it is 22%, so from this level of sensitivity, digit span forward allows it to miss more samples or respondents who may have attention disorders or decreased attention, while for digit span backward, it has a higher percentage level than forward so that there is less chance of this digit span backward to miss samples who have attention disorders, so the possibility of people addicted to games who have low attention is higher in sensitivity to digit span backward.[41] For specificity, digit span forward has a higher specificity level of 100% and digit span backward is 57%, so in digit span forward the possibility of people who are not addicted to games has normal attention with higher specificity than digit span backward.[42]

The results of this study are not in line with the results of research by Zahara A et al. which showed protective results, that gamers have a better level of concentration (attention in a long period) than people who are not gamers. In the results of Zahara's study, the prevalence of gamers was 34 (33%) out of 103 respondents. The incidence of game addiction or gamers in Zahara's study was higher than the study conducted. The difference in the results of this study with the study conducted by Zahara, could occur because of the genre and duration of playing games, where in Zahara's study it focused on DOTA 2 games

and specifically how long the duration of playing games was.[10]

The results of this study are in line with the research of Sara Prot et al. and Sri L.[3.8] Research conducted by Sara Prot concluded that increased time playing video games increases attention problems.[8] For confounding variables, namely autism and ADHD, it could not be done because there were no respondents who experienced these disorders.

The similarity of this study with that conducted by Zahara and Sara Prot, this study was conducted on a sample with an age range of 17-25 years and the same research design as Zahara, namely cross-sectional.

Some weaknesses in this study are that it has a number of respondents less than required. The lack of samples in this study meant that researchers were unable to further examine the relationship between online video game addiction and attention levels. In this study, researchers failed to check the number of remaining respondents needed so that the number of respondents or samples was less than required, this lack of samples was due to the COVID-19 pandemic which caused the research time to be cut short and the researcher's time constraints, for online data collection solutions were not carried out due to connection limitations that could cause the attention test not to run properly so that it could cause the results to be biased. The attention test conducted by the researcher also could not be conducted in a crowded place, because of the bottleneck model theory that limits a person's attention to something, so that if the attention test is conducted in a crowded or noisy place, it can reduce a person's level of attention to this attention test, which produces biased data.[23] In addition, the time for conducting the attention test is also limited, because a quiet room and sufficient time are needed so that the attention test can be conducted properly and without interference or distraction. Finally, the researcher did not examine the duration of playing online video games and the genre played, which are factors that are also related to attention.[8]

Conclusion

In this study, it was found that online game addiction affects the attention levels among students of the Pelita Harapan University Medical Students batch 2017, and changes in attention levels in the online game addiction group were a decrease in attention levels.

Conflict of Interest

The authors declared no conflict of interest.

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ORIGINAL RESEARCH

ASSOCIATION BETWEEN DAILY TEA CONSUMPTION AND SLEEP QUALITY: A CROSS-SECTIONAL ANALYTICAL STUDY

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Abstract

Background: Sleep quality is a critical determinant of physical and mental health, and dietary factors such as caffeine intake from tea may influence sleep patterns. Evidence on this association in the Indonesian population remains limited despite the high prevalence of both tea consumption and poor sleep quality. This study aimed to investigate the relationship between daily tea consumption and sleep quality among Indonesian adults.

Methods: A cross-sectional correlational study was conducted from January to March 2022 using an online survey. A total of 104 adults aged 18–64 years with low stress levels (Perceived Stress Scale score ≤13) were included. Tea consumption was assessed by frequency and quantity (cups/day), while sleep quality was measured using the Pittsburgh Sleep Quality Index (PSQI). A global PSQI score >5 indicated poor sleep quality. Data were analyzed using Spearman's rank correlation, with significance set at $p < 0.05$.

Results: Most participants were female (61.5%), aged 20–49 years, with 40.4% consuming ≥3 cups of tea daily. Poor sleep quality was reported by 72.1% of respondents. A significant positive correlation was found between daily tea consumption and PSQI score ($r_s = 0.528$, $p < 0.001$), indicating that higher tea intake was moderately associated with poorer sleep quality.

Conclusions: Higher daily tea consumption is significantly associated with poorer sleep quality among Indonesian adults. These findings underscore the need for public health initiatives to raise awareness about caffeine-containing beverages and their potential effects on sleep.

Keywords: tea consumption, sleep quality, caffeine, Pittsburgh Sleep Quality Index, Indonesian adults

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Introduction

Sleep is a fundamental physiological necessity that profoundly influences physical, emotional, and cognitive health.[1] Inadequate sleep disrupts immune function, increases the risk of chronic conditions such as cardiovascular disease, diabetes, and obesity, and impairs

cognitive functions, mood regulation, and motor coordination. Moreover, chronic sleep disturbances are associated with higher rates of depression, anxiety, and decreased productivity, particularly among working-age adults and the elderly.[2–5] Among vulnerable populations such as older adults, shift workers, and individuals with comorbidities, poor sleep quality exacerbates existing health burdens and compromises quality of life.

Globally, the burden of sleep disturbances has intensified over recent years, particularly among older adults. A comprehensive systematic review by Du et al. , which analyzed 64 studies involving 181,224 older adults during the COVID-19 pandemic, reported that 47.1% experienced poor sleep quality, 40.8% had short sleep duration, and 21.2% exhibited insomnia symptoms.[6] In Indonesia, Petzer et al. reported that among 31,432 individuals aged ≥15 years, 33.3% experienced sub-threshold insomnia and 11.0% met criteria for clinical insomnia.[7] Similarly, Alfian et al. analyzed data from 22,024 respondents, revealing that 42.9% reported sleep disturbances, including 3.0% severe, 16.5% moderate, and 23.3% mild cases.[8]

Despite the growing prevalence of sleep disturbances, public awareness of modifiable lifestyle factors such as tea consumption remains limited. Tea is one of the most commonly consumed beverages in the world and contains several bioactive compounds, including caffeine, theobromine, L-theanine, and catechins.[9] Caffeine, a known stimulant, acts as an adenosine receptor antagonist and may delay sleep onset and reduce total sleep time.[10] In contrast, L-theanine, an amino acid found predominantly in green tea, has been shown to promote relaxation and improve subjective sleep quality in some studies.[11,12]

Due to the combination of these compounds with differing mechanisms of action, the effects of tea consumption on sleep remain highly variable and, in some cases, controversial. A study by Yong Tian et al. demonstrated that habitual tea consumption, particularly daily intake (6–7 days per week) in small amounts (<10 g per day) was significantly associated with improved sleep quality among Chinese adults.[13] Conversely, other studies have suggested potential adverse associations. For instance, Kleiser et al. reported that short sleep duration was correlated with higher intake of black tea, highlighting a possible negative relationship between certain types or amounts of tea and sleep quality.[14] Despite these contradictory findings, most existing studies have been conducted in East Asian or Western populations, with limited evidence from Southeast Asia, particularly Indonesia, where tea consumption is deeply embedded in cultural practices and the prevalence of poor sleep is high. Understanding this relationship in the Indonesian context is crucial for developing culturally relevant public health recommendations. Therefore, this study aimed to investigate the association between habitual tea consumption and sleep quality among Indonesian adults.

Methods

This study employed a cross-sectional correlational design to investigate the

relationship between tea consumption and sleep quality among Indonesian adults. The research was conducted from January to March 2022 through an online survey using Google Forms.

Participants were selected using purposive sampling, with a total of 104 adults aged between 18 and 64 years included in the final analysis. Participants were selected based on clearly defined inclusion and exclusion criteria. The inclusion criteria were adults (both male and female) aged 18 to 64 years who had consumed tea at least once in the past week. Exclusion criteria included individuals with moderate or high stress levels, as measured by the Indonesian version of the Perceived Stress Scale (PSS), and those who consumed more than two cups of coffee daily. Stress levels were classified according to the PSS-10 scoring: low (0–13), moderate (14–26), and high (27–40).[15,16] Only participants with low stress levels (≤13) were included in the final analysis to minimize psychological confounding.

Data collection involved a structured questionnaire divided into four main sections: demographic information, tea consumption patterns, sleep quality, and stress levels. Tea consumption was assessed based on frequency (e.g., 1–3 times per week, 4–5 times per week, daily) and quantity (number of cups per day: 1, 2, or ≥3 cups, where one cup equaled approximately 250–350 mL). Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI), a validated instrument that measures subjective sleep quality, latency, duration, efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the past month. A global PSQI score greater than 5 was categorized as poor sleep quality.[17,18] Stress levels were assessed using the 10-item PSS, a validated tool to measure perceived psychological stress in the past month.

Statistical Analysis

All collected data were tabulated using Microsoft Excel and analyzed using SPSS version 23.0. Descriptive statistics were used to summarize demographic characteristics, tea consumption, and sleep quality data. Normality of distribution was tested, and due to non-normal data, the Spearman rank correlation test was used to assess the relationship between daily tea consumption and PSQI scores. A p-value less than 0.05 was considered statistically significant.

Results

Table 1 presents the demographic characteristics of the 104 adult respondents included in the study. The majority of participants were female (61.5%), and most were within the 20–49-year age range. Regarding tea consumption habits, 40.4% reported consuming three or more cups of tea per day, while 35.6% consumed one cup daily. Sleep quality, measured using the Pittsburgh Sleep Quality Index (PSQI), revealed that 72.1% of respondents had poor sleep quality.

Prior to correlation analysis, a normality test was performed using the Shapiro–Wilk method, which showed that both tea consumption scores and PSQI scores were not normally distributed ($p < 0.05$). Therefore, a Spearman's rank correlation

test was applied. As shown in Table 2, a statistically significant positive correlation was found between daily tea consumption and PSQI score (r_s = 0.528, p < 0.001), suggesting that higher tea intake was moderately associated with poorer sleep quality among Indonesian adults.

Table 1. Demographic Characteristics of Respondents (n = 104)

Subject characteristics	n = 104
Age Group (years)	
19	2 (1.9%)
20-29	32 (30.8%)
30-39	26 (25.0%)
40-49	30 (28.9%)
50-59	13 (12.5%)
60-64	1 (0.9%)
Gender	
Male	40 (38.5%)
Female	64 (61.5%)
Daily Tea Consumption	
1 cup	37 (35.6%)
2 cups	25 (24.0%)
≥3 cups	42 (40.4%)
Sleep Quality	
Good (PSQI ≤ 5)	29 (27.9%)
Poor (PSQI > 5)	75 (72.1%)

Table 2. Spearman's Rank Correlation between Tea Consumption and Sleep Quality (PSQI Score)

Variable	n	r (Spearman)	p-value
Tea consumption	104	0.528	<0.001

Discussion

The primary objective of this study was to investigate the relationship between the amount of tea consumption and sleep quality among adults aged 18–64 years in Indonesia, given that sleep quality is essential for both physical and mental health, and dietary habits, particularly caffeine intake from tea, represent modifiable factors influencing sleep patterns.

Our study found a significant positive correlation between the amount of tea consumed and poorer sleep quality, with r_s = 0.528 (p < 0.001), indicating a strong positive relationship. Among the 104 respondents analyzed, 40.38% consumed three or more cups of tea daily, and 72.12% reported poor sleep quality. These findings are consistent with studies by Tseng et al. who documented a negative impact of tea drinking habit on sleep quality among university students in Taiwan, and Watson et al. who reported that caffeine consumption adversely affects sleep quality in Australian adults.[19,20] The role of tea's caffeine content in sleep disruption is further supported by Hindmarch et al., who found that while tea improved cognitive alertness during the day, repeated consumption into the evening was associated with delayed sleep onset, shorter sleep duration, and reduced sleep quality.[21] In contrast, Choi et al. reported no significant relationship between tea consumption and sleep quality among Korean college students.[22] Further illustrating the diversity of beverage effects on sleep, Hieu et al. conducted a systematic review and meta-analysis on chamomile, finding that although one RCT reported no significant reduction in insomnia severity, chamomile administration significantly improved sleep quality.[23]

The association between tea consumption and poorer sleep quality in this study may be explained by its caffeine content and neurochemical effects. Carrier et al. reported that caffeine can influence

the circadian rhythm, delaying the onset of melatonin secretion and shifting sleep timing, which can impair overall sleep quality.[24] As tea contains caffeine, it is plausible that similar circadian disruptions occur with high tea intake. Camfield et al. demonstrated that caffeine increases cognitive performance and alertness, effects that, while beneficial during the day, may hinder the ability to initiate and maintain sleep when consumption occurs later in the day.[25] Mechanistically, caffeine enhances levels of acetylcholine and dopamine in the brain and acts as an adenosine (A1 and A2A) receptor antagonist, reducing sleep pressure and increasing wakefulness.[26,27] Additionally, caffeine has been shown to suppress melatonin secretion, the hormone responsible for regulating sleep–wake cycles, thereby further contributing to delayed sleep onset and reduced sleep efficiency.[28]

This study has several limitations. Its cross-sectional design prevents determining causality between tea consumption and sleep quality, and reverse causation is possible. Tea intake and sleep quality were self-reported, which may lead to recall bias and mismatch with objective measures. Details on tea type, brewing strength, caffeine content, and timing of consumption were not recorded, limiting interpretation of the physiological effects. Other lifestyle and health factors that may influence sleep were not fully controlled, and the relatively small, single-population sample limits generalizability. Future research should employ longitudinal designs, incorporate objective sleep measurements (e.g. polysomnography or actigraphy), and include detailed assessments of tea type, caffeine content, and timing of consumption to better clarify the causal pathways.

Conclusion

This study demonstrates a significant positive correlation between daily tea consumption and poorer sleep quality among Indonesian adults, suggesting that higher tea intake may adversely affect sleep. The findings highlight the potential impact of caffeine-containing beverages on circadian rhythm regulation and sleep efficiency, particularly when consumed in larger amounts.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

The authors declared no acknowledgment.

Ethical Statement

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Pelita Harapan, with ethical clearance number 167/K-LKJ/ETIK/II/2022. All participants provided electronic informed consent after receiving a clear explanation of the study's objectives, procedures, and data confidentiality. Participation was entirely voluntary, and no personally identifiable information was collected.

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ORIGINAL RESEARCH

THE RELATIONSHIP BETWEEN BODY MASS INDEX AND THE DEGREE OF DEMENTIA IN ELDERLY PATIENTS WITH MEMORY IMPAIRMENT AT MEMORY CLINIC SILOAM HOSPITALS LIPPO VILLAGE

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Abstract

Introduction: Body mass index (BMI) can describe the level of nutrition and vitality of a person. Monitoring BMI values prevents elderlies from various risks of disease, one of which is dementia. The development of neuropathological lesions in the olfactory bulb has been proposed to cause symptoms which affect dementia patients' appetite and thus resulting in weight loss.

Methods: A cross-sectional study was conducted among 55 memory impairment patients from ages ≥65 years at Siloam Hospitals Lippo Village Memory Clinic. Data was obtained using Montreal Cognitive Assessment – Indonesian Version (MoCA-INA) and Clinical Dementia Rating Scale (CDRS) and BMI was measured using Seca 703 instrument.

Results: A significant relationship was found between body mass index and the degree of dementia with a value of p = 0.046 for MoCA examination and p = 0.039 for CDRS examination. The results of the analysis shows that underweight-normal (BMI <23kg/m^2) patients have 3.8 times (95% CI 1.2-12.5) and 4.6 times (95% CI 1.2-17.0) the risk of having a moderate-severe degree respectively compared to overweight-obese (BMI ≥23kg/m^2) patients.

Conclusions: Lower late life BMI is related to higher degree of dementia

Keywords: Body mass index, Dementia degree, MoCA-INA, CDRS

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Introduction

Dementia is a progressive condition that affects memory, cognition, behavior, and social functioning, ultimately interfering with daily activities. The most common cause is Alzheimer's disease, followed by vascular dementia, Lewy body dementia, and frontotemporal dementia. Clinical manifestations include cognitive impairment and neuropsychiatric symptoms, collectively known as

behavioral and psychological symptoms of dementia (BPSD).

Globally, dementia ranks among the top ten most burdensome conditions in the elderly and is the seventh leading cause of death. In 2015, there were approximately 46.8 million individuals living with dementia worldwide, and this number is projected to double every 20 years. In Indonesia, the number of people with dementia is expected to rise from 1.2 million to 3.9 million by 2050. The disease also imposes significant physical, psychological, and economic burdens on caregivers.

Body Mass Index (BMI) reflects the nutritional status of older adults and has been associated with cognitive function. A high BMI during midlife increases the risk of developing dementia, whereas obesity in late life appears to have a protective effect, possibly due to reverse causation. Conversely, being underweight has consistently been linked to a higher risk of dementia.

However, the association between BMI and the severity of dementia remains unclear, particularly in the Indonesian population. This study aims to examine the relationship between body mass index and cognitive impairment in elderly at the Memory Clinic of Siloam Hospitals Lippo Village.

Materials and Methods

This study was a cross-sectional, unpaired categorical analytic study. Primary data, including BMI measurements, were collected using the Seca 703 scale. Secondary data on cognitive impairment and dementia severity were obtained from medical records based on MoCA-INA and CDR-S scores. Participants were recruited from the Memory Clinic at Siloam Hospitals Lippo Village according to inclusion criteria.

Data collection involved structured questionnaires and direct assessments. Collected data were tabulated using Microsoft Excel and analyzed using SPSS version 25.0. The Chi-square test was employed for statistical analysis. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Medicine, Pelita Harapan University prior to study implementation.

Results

Subject characteristic

Based on the demographic data presented in Table 1, a total of 55 patients were included in the study, consisting of 30 males (54.5%) and 25 females (45.5%). The patients' ages ranged from 65 to 90 years, with a mean age of 73 years. Body Mass Index (BMI) was categorized according to the Asia-Pacific classification: underweight (9.1%, n=5), normal (38.2%, n=21), overweight (25.5%, n=14), and obese (27.3%, n=15). Cognitive status based on MoCA scores showed that 6 patients (10.9%) were within the normal range, 30 (54.5%) had mild impairment, 12

(21.8%) had moderate impairment, and 7 (12.7%) had severe impairment. In addition to MoCA, the Clinical Dementia Rating Scale (CDRS), considered a more accurate indicator of dementia severity, classified patients as follows: questionable (45.5%, n=25), mild (27.3%, n=15), moderate (16.4%, n=9), and severe (10.9%, n=6).

Body Mass Index and Dementia Severity All data obtained were collected and analyzed using a bivariate analytical model with the chi-square method. The analysis was conducted to examine the relationship between Body Mass Index (BMI) and the degree of dementia in elderly patients at the Memory Clinic of Siloam Hospitals Lippo Village.

Table 1. Subject Characteristics

Variable	n	Percentage
Sex		
Males	30	54,5%
Females	25	45.5%
Age	Range 65-90	Mean 73
Body Mass Index		
Underweight	5	9,1%
Normal	21	38,2%
Overweight	14	25,5%
Obese	15	27,3%
MoCA		
Normal	6	10,9%
Mild	30	54,5%
Moderate	12	21,8%
Severe	7	12,7%
CDRS		
Questionable	25	45,5%
Mild	15	27,3%
Moderate	9	16,4%
Severe	6	10,9%

Table 2 shows the data results, which indicate a significant relationship between body mass index and the degree of dementia, based on MoCA (Montreal Cognitive Assessment) examination indicators, with a P-value of 0.046. In the underweight-normal BMI group, 13 patients (50%) showed moderate-severe results, while 13 patients also showed normal-mild results.

Meanwhile, in the overweight-obese BMI group, there was a substantial difference in examination results, with 23 patients (79.3%) showing normal-mild results and 6 patients (20.7%) showing moderate-severe results. Additionally, the obtained odds ratio was 3.833 (95% CI = 1.175–12.506). From the odds ratio, it can be interpreted that patients with an underweight-normal BMI are 3.833 times more likely to have a moderate-severe degree of dementia compared to patients with an overweight-obese BMI.

Another indicator used is the CDRS (Clinical Dementia Rating Scale), which is considered more effective in assessing the severity of dementia. Based on the analysis results in Table 3, a significant relationship was again found between body mass index (BMI) and the degree of dementia, with a P-value of 0.039. A greater difference in percentages was again observed between patients with an overweight-obese BMI, with 25 patients (86.2%) showing normal-mild results and 4 patients (13.8%) showing moderate-severe results.

In the underweight-normal BMI group, 11 patients (42.3%) had moderate-severe results and 15 patients (57.7%) had normal-mild results, out of a total of 26 patients. The analysis yielded an odds ratio of 4.583 (95% CI = 1.235–17.008).

Table 2. The Association Between Body Mass Index and Dementia Severity (MoCA).

BMI	MoCA				Total	OR (95%CI)	P-Value
	Normal-Mild		Moderate-Severe				
	n	%	n	%			
Overweight-Obese	23	79,3	6	20,7	29	3,833 (1,175-12,506)	0,046
Underweight-Normal	13	50	13	50	26		
Total	36	65,5	19	34,5	55		

Table 3. The Association Between Body Mass Index and Dementia Severity (CDRS)

BMI	CDRS				Total	OR (95%CI)	P-Value
	Normal-Mild		Moderate-Severe				
	n	%	n	%			
Overweight-Obese	25	86,2	4	13,8	29	3,583 (1,235 - 17,008)	0,039
Underweight-Normal	15	57,7	11	42,3	26		
Total	40	72,7	15	27,3	55		

Discussion

Research on BMI and dementia shows conflicting results. A 2015 study by Nawab Qizilbash et al. found that being underweight was linked to a 34% higher dementia risk, while the Whitehall II study showed that obesity at age 50 increased risk, but this link weakened at older ages. Given the limited research in Indonesia, our study provides new evidence. Our findings show a significant link between BMI and dementia severity in elderly Indonesian patients. A low BMI appears to increase dementia risk, while a higher BMI may be protective, especially in older age. This aligns with findings from other countries and highlights the importance of maintaining a healthy BMI to help manage dementia progression.

However, the study has limitations. Its cross-sectional design prevented us from studying the effects of weight changes. Physical activity was an uncontrolled factor, and a purposive sampling method created potential for bias due to a limited sample size and timeframe. For future studies, we recommend using a longitudinal design to track weight changes over time. Researchers should also use a larger sample size, control for confounders like physical activity, and use more specific variable categories to obtain more robust results. This will help doctors and patients use BMI monitoring as a tool to improve the quality of life for those with dementia.

Conclusion

The findings highlight the importance of maintaining a healthy BMI, particularly in the elderly, as a potential strategy for mitigating the progression of dementia. Further research is encouraged to examine the relationship with weight gain or loss, explore the underlying mechanisms, and to confirm these findings in other populations.

Conflict of Interest

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META-ANALYSIS

COMPARATIVE EFFICACY OF ANTIHYPERTENSIVE DRUGS FOR PRIMARY STROKE PREVENTION – A NETWORK META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Introduction: Hypertension is a major modifiable risk factor for stroke, making antihypertensive therapy essential for primary stroke prevention. However, the comparative efficacy of different antihypertensive drug classes remains uncertain. This study aims to evaluate the comparative efficacy of various antihypertensive drug classes in reducing the risk of stroke in patients with hypertension through a network meta-analysis of randomized controlled trials (RCTs).

Methods: A search was conducted using various online databases, including PubMed, Google Scholar, Scopus, and ScienceDirect, to identify RCTs which were written in English and published before January 2025. A network meta-analysis was performed to compare the effectiveness of different drug classes, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, and diuretics in stroke primary prevention. Independently, two reviewers (D.N. and L.D.P.), extracted the data and assess the quality of studies using Cochrane RoB 2.0.

Results: This analysis included 43 RCTs involving 255299 participants with hypertension. Among the evaluated drug classes, non-dihydropyridine CCB demonstrated the highest efficacy in stroke prevention (RR 0.61; 95%CI 0.48 – 0.77), followed by dihydropyridine CCB (RR 0.62; 95%CI 0.54 – 0.72). Most of the studies had decent quality assessment with moderate heterogeneity across them with I^2 = 39%. Egger's test showed nonsignificant results (p= 0.16), suggesting the absence of publication bias in the included trials.

Conclusion: This meta-analysis showed that calcium channel blocker emerges as the most effective option for reducing stroke risk, but considerations of adverse effects and individual patient profiles remain critical in treatment selection.

Keywords: *antihypertensive drugs; stroke; primary prevention*

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Introduction

Epidemiological research conducted over the past several decades has firmly established hypertension as the primary risk factor for stroke, whether ischemic or hemorrhagic stroke. The incidence of this debilitating cerebrovascular event is directly proportional to the degree of elevated blood pressure.[1–3] However, the incidence of stroke could be significantly lowered with effective blood pressure management through antihypertensive medications.[4,5]

Despite the availability of various antihypertensive medications, their comparative efficacy in preventing stroke has yet to be conclusively determined. This uncertainty is particularly evident when considering the distinct pharmacological mechanisms of different antihypertensive drug classes, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers, and diuretics.[6,7]

Given the importance of optimizing treatment for stroke prevention in hypertensive patients, it is essential to compare the relative effectiveness of these drug classes. A network meta-analysis (NMA) of randomized controlled trials (RCTs) offers a robust method to evaluate and compare multiple treatments simultaneously, providing valuable insights into the best therapeutic options for reducing stroke risk. This study aims to systematically assess the comparative efficacy of various antihypertensive drugs in primary stroke prevention, using a network meta-analysis approach to synthesize data from existing RCTs.

Materials and Methods

The study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance.[8]

Literature search strategy

We conducted a search across several databases, including PubMed, Google Scholar, Scopus, and ScienceDirect, to identify RCTs which were written in English and published before January 2025.

We utilized search terms such as (“stroke” OR “cerebrovascular accident” OR “CVA”) AND (“antihypertensive agents” OR “antihypertensive drugs” OR “blood pressure-lowering” OR “blood-pressure lowering” OR “diuretics” OR “Angiotensin-converting enzyme inhibitors” OR “Angiotensin receptor blocker” OR “Angiotensin receptor antagonists” OR “calcium channel blockers” OR “beta blockers” OR “ACEI” OR “ARB” OR “CCB”). In addition, we performed a manual search of the reference lists of all included studies and relevant reviews to find any other potentially eligible trials.

Study selection criteria

Studies were considered eligible if they met all of the following criteria: 1) they were randomized controlled trials; 2) they compared an antihypertensive agent with another antihypertensive agent, placebo, or control; and 3) they reported outcomes related to stroke both ischemic and hemorrhagic stroke. Trials with a follow-up duration of less than 3 months were excluded. In cases of duplicate trials, the trial with the longest follow-up period was included.

Outcomes assessments

The outcomes we focused on were stroke, both ischemic and hemorrhagic stroke including both fatal and non-fatal events.

Data extraction

Two independent reviewers (D.N. and L.D.P.) assessed the publications and extracted the data. In cases of disagreement, a third investigator (A.A.) would review the data. The following information was extracted: first author, year of publication, sample size, treatment class, duration of interventions, and outcomes of interest.

Study quality assessment

We evaluated the risk of bias in the included randomized trials using the updated version of the Cochrane "Risk of Bias" tool (RoB 2.0). Each trial was classified as having a "low risk of bias," "some concerns," or "high risk of bias".[9]

Statistical analysis

We conducted a frequentist network meta-analysis using R Software Studio version 4.2. We calculated treatment estimates as relative risks (RRs) with their 95% confidence intervals (CIs). We used Eager test and plotted comparison-adjusted funnel plots for each outcome to make visual assessments of possible publication bias.

Results

Search results and study characteristics

A total of 930 entries were identified from the preliminary database search. A total of 873 records were removed for multiple reasons during the title and abstract screening (duplicate and irrelevance to the analysis). The complete texts of the remaining 57 papers were meticulously examined. Subsequently, 14 papers were removed for the following reasons: not full text, not in English, not RCT, and had different outcomes. A total of 43 randomized controlled trials involving 255,299 patients were incorporated into the network meta-analysis.

The selecting process is illustrated in Figure 1. The characteristics of the studies included are presented in Table 1. The quality evaluations of the 43 RCTs are presented in Table 2. The diagram of the network structure is presented in Figure 2. Network structure diagrams are utilized to illustrate the direct relationships among several antihypertensive regimens, with the thickness of the lines indicating the quantity of direct comparisons between two regimens.

Network meta-analysis results

Figure 2 displays the network plot that represents comparisons among the hypertensive patients. This network meta-analysis evaluated the effect of 7 interventions for primary prevention of stroke for the hypertensive patients including angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), beta blocker (BB), dihydropyridine calcium channel blocker (DH-CCB), non-dihydropyridine calcium channel blocker (non-DH-CCB), diuretic, and placebo.

Our study included a total of 43 trials involving 255299 participants to analyse stroke incidence in the overall population.

Compared to placebo, all antihypertensive drugs showed efficacy in preventing stroke. In addition, among the evaluated drug classes, non-dihydropyridine CCB demonstrated the highest efficacy in stroke prevention (RR 0.61; 95%CI 0.48 – 0.77), followed by dihydropyridine CCB (RR 0.62; 95%CI 0.54 – 0.72). Furthermore, beta blocker showed the lowest efficacy in stroke prevention (RR 0.75; 95%CI 0.64 – 0.88) (Figure 3).

Publication bias

The comparison-adjusted funnel plots are presented in Figure 4, all of which appear visually symmetrical, indicating the absence of publication bias.

Discussion

This meta-analysis utilized an enhanced categorization of antihypertensive drugs to evaluate the comparative efficacy of all existing treatments in stroke prevention both ischemic and hemorrhagic stroke. Through a comprehensive systematic review and network meta-analysis, the study offers valuable insights to guide the optimal choice of antihypertensive therapy for individuals with hypertension.

The Renin-Angiotensin System (RAS) plays a pivotal role in the pathophysiology of hypertension. Consequently, RAS inhibitor was common therapeutic approach for controlling hypertension.[10] In 2018, Chen et al. carried out a meta-analysis to assess the effectiveness and safety of RAS inhibitors relative to other classes of antihypertensive medications in patients with hypertension. Their findings indicated that first-line use of thiazide diuretics and calcium channel blockers (CCBs) was associated with a reduced incidence of stroke compared to RAS inhibitors. Additionally, RAS inhibitors demonstrated greater efficacy in stroke prevention than beta-blockers (BBs) when used as first-line therapy; however, the analysis did not differentiate between angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).[54] A separate meta-analysis conducted by Thomopoulos et al. reviewed 50 clinical trials comprising 247,006 individuals, with a hypertension prevalence exceeding 40%. The analysis revealed that RAS inhibitors were more effective than both placebo and beta-blockers in stroke prevention, yet they were outperformed by diuretics and calcium channel blockers (CCBs). Specifically, ACE inhibitors (ACEIs) showed greater efficacy than placebo but were less effective compared to CCBs and other antihypertensive drug classes. In contrast, angiotensin receptor blockers (ARBs) demonstrated superior stroke prevention benefits relative to placebo and beta-blockers.[55] Likewise, our findings demonstrated that both ARBs and ACEIs outperformed placebos but were less effective than diuretics and calcium channel blockers in reducing the incidence of stroke in the general population.

Table 1. Characteristic of Studies

Author	Study	Treatment Class	Treatment Drugs	Duration	Age	N	Stroke	
							n	%
ALLHAT, 2022[11]	ALLHAT	Diuretic DH – CCB ACE Inhibitor	Chlorthalidone Amlodipine Lisinopril	4.9 years	66.9 ± 7.7	15255 9048 9054	675 377 457	4.4 4.2 5.0
Baba, 2001[12]	J-MIND	DH-CCB ACE Inhibitor	Nifedipine Enalapril	2 years	60.2 ± 8.9 59.9 ± 8.6	228 208	2 5	2.2 3.8
Beckett, 2014[13]	HYVET	ACE Inhibitor Placebo	Perindopril Placebo	2.1 years	83.6 ± 3.2 83.5 ± 3.1	1933 1912	51 69	2.6 3.6
Black, 2003[14]	CONVINCE	Non-DH-CCB Conventional Therapy	Verapamil Atenolol or HCT	3 years	65.6 ± 7.4	8179 8297	133 118	1.6 1.4
Borhani, 1996[15]	MIDAS	DH-CCB Diuretic	Isradipine HCT	3 years	58.2 ± 8.3 58.7 ± 8.7	442 441	6 3	1.35 0.68
Brown, 2000[16]	INSIGHT	DH-CCB Diuretic	Nifedipine HCT + amiloride	4 years	65 ± 6.5	3157 3164	67 74	2.1 2.3
Dahlof, 1991[17]	STOP - Hypertension	Conventional Therapy Placebo	Atenolol / HCT / amiloride Placebo	65 months	70 – 84	812 815	29 53	3.6 6.5
Dahlof, 2002[18]	LIFE	ARB Beta Blocker	Losartan Atenolol	4 years	66.9 ± 7.0 66.9 ± 7.0	4605 4588	369 359	8.0 8.0
Dahlof, 2005[19]	ASCOT-BPLA	DH-CCB Beta Blocker	Amlodipine Atenolol	5.5 years	63 ± 8.5 63 ± 8.5	9639 9618	327 422	3.0 4.0
Estacio, 1998[20]	ABCD	DH-CCB ACE Inhibitor	Nisoldipine Enalapril	5 years	57.2 ± 8.2 57.7 ± 8.4	235 235	11 7	4.7 3.0
Hannson, 1993[21]	STOP – Hypertension-2	ACE Inhibitor DH-CCB	Enalapril / Lisinopril Felodipine / Isradipine	4 years	76.1 75.9	2205 2196	50 46	4.5 4.2
Hansson, 1999[22]	CAPPP	ACE Inhibitor Conventional Therapy	Captopril Atenolol / HCT	5.5 years	52.4 ± 8.3 52.7 ± 8.4	5492 5493	193 149	3.5 2.7
Hansson, 2000[23]	NORDIL	Non-DH-CCB Conventional Therapy	Diltiazem Atenolol / HCT	5 years	60.5 ± 6.5 60.3 ± 6.5	5410 5471	159 196	2.9 3.6
Julius, 2004[24]	VALUE	ARB	Valsartan	3.2 years	66.9 ± 8.3	3263	108	3.3

		DH-CCB	Amlodipine		66.8 ± 8.2	3817	127	3.3
Kaplan, 2003[25]	ANBP2	ACE Inhibitor Diuretic	Enalapril HCT	4.1 years	72 71.9	3044 3039	112 107	3.7 3.5
Kasanuki, 2009[26]	HIJ – CREATE	ARB Non-RAASI	Candesartan Non-ARB	4.2 years	64.5 ± 9.4 65 ± 8.9	1024 1025	45 49	4.4 4.8
Kjeldsen, 2008[27]	ACCOMPLISH	DH-CCB Diuretic	Amlodipine HCT	3 years	68.5 ± 6.9 68.2 ± 6.7	5744 5762	112 133	1.9 2.3
Lithell, 2003[28]	SCOPE	ARB Placebo	Candesartan Placebo	3 – 5 years	76.2 ± 4.4 76.5 ± 4.6	1253 845	31 27	2.5 3.2
Liu, 1998[29]	Syst – CHINA	DH-CCB Placebo	Nitrendipine Placebo	2 years	≥ 60	1253 1141	45 59	3.6 5.2
Liu, 2005[30]	FEVER	DH-CCB Placebo	Felodipine Placebo	40 months	61.5 ± 7.1 61.5 ± 7.2	4841 4870	177 251	3.7 5.2
Malacco, 2003[31]	SHELL	Diuretic DH-CCB	Chlorthalidone Lacidipine	32 months	72.4 ± 7.6 72.3 ± 7.5	940 942	38 37	4.0 3.9
Matsuoka, 1995[32]	GLANT	ACE Inhibitor CCB	Delapril CCB	12 months	60 ± 10 60 ± 9	980 956	5 11	0.5 1.2
Matsuzaki, 2011[33]	COPE	ARB Beta Blocker Diuretic	ARB Beta Blocker Thiazide	3.6 years	63 ± 10.6 63.2 ± 10.8 63.1 ± 10.8	1110 1089 1094	17 27 12	1.5 2.5 1.1
MRC, 1992[34]	MRC-2	Beta Blocker Diuretic	Atenolol HCT	5.8 years	70.3 ± 5.6 70.2 ± 5.6	1102 1081	56 45	5.1 4.2
Muramatsu, 2012[35]	NHS	ARB DH-CCB	Valsartan Amlodipine	3.2 years	63 ± 8 63 ± 8	575 575	13 16	2.3 2.8
Narumi, 2016[36]	VART	ARB DH-CCB	Valsartan Amlodipine	3.4 years	60 ± 12 60 ± 11	510 511	10 10	2.0 2.0
NICS-EH, 1999[37]	NICS-EH	DH-CCB Diuretic	Nicardipine Trichlormethiazide	5 years	≥ 60	204 210	1 0	0.5 0.0
Ogawa, 2012[38]	OSCAR	ARB CCB	Olmesartan Amlodipine / Azelnidipine	3 years	73.6 ± 5.3 73.6 ± 5.5	578 586	111 96	19.2 16.4
Ogihara, 2011[39]	PATE-Hypertension	ACE Inhibitor DH-CCB	Delapril Manidipine	3 years	70 ± 7 69 ± 7	699 1049	14 23	2.0 2.2
Ogihara, 2014[40]	COLM	CCB Diuretic	Amlodipine / Azelnidipine HCT / Indapamide	3 years	73.6 ± 5.3 73.6 ± 5.4	2568 2573	63 66	2.5 2.6

Pepine, 2003[41]	INVEST	Non-DH-CCB Beta Blocker	Verapamil Atenolol	2.7 years	66 ± 9.7 66.1 ± 9.8	11267 11309	176 201	1.6 1.8
Rosei, 1997[42]	VHAS	Non-DH-CCB Diuretic	Verapamil Chlorthalidone	2 years	54.5 ± 6.9 53.9 ± 7.0	707 707	3 4	0.4 0.6
Ruggenenti, 2011[43]	BENEDICT-B	Non-DH-CCB ACE Inhibitor	Verapamil Trandolapril	4.5 years	62.3 ± 8.5 62.4 ± 8.2	138 143	1 0	0.7 0.0
Schrader, 2005[44]	MOSES	ARB DH-CCB	Eprosartan Nitrendipine	2.5 years	67.7 ± 10.4 68.1 ± 9.5	681 671	102 134	15.0 20.0
SHEP, 1991[45]	SHEP	Beta Blocker Placebo	Atenolol Placebo	4.5 years	≥ 60	2365 2371	106 163	4.5 6.9
Staessen, 1997[46]	Syst-EUR	Conventional Therapy Placebo	Enalapril / Nitrendipine / HCT Placebo	2 years	70.3 ± 6.7 70.2 ± 6.7	2398 2297	16 21	2.7 3.7
Suzuki, 2005[47]	E-COST	ARB Non-RAASI	Candesartan Non-ARB	3.1 years	35 – 79	1053 995	47 77	4.5 7.7
Tatti, 1998[48]	FACET	ACE Inhibitor DH-CCB	Fosinopril Amlodipine	3.5 years	62.8 ± 0.5 63.3 + 0.4	189 191	4 10	0.7 1.9
UKPDS, 1998[49]	UKPDS 38	Conventional Therapy Placebo	Captopril / Atenolol Placebo	8.4 years	56.4 ± 8.1 56.5 ± 8.1	758 390	38 34	5.0 8.7
UKPDS, 1999[50]	UKPDS 39	ACE Inhibitor Beta Blocker	Captopril Atenolol	9 years	56.3 ± 8.1 56 ± 8.2	400 358	21 17	5.2 4.7
Wikstrand, 1991[51]	MAPHY	Beta Blocker Diuretic	Metoprolol Thiazide	5 years	40 – 64	1609 1625	2 7	0.3 0.9
Yui, 2004[52]	JMIC-B	DH-CCB ACE Inhibitor	Nifedipine Retard Enalapril / Lisinopril / Imidapril	3 years	65 ± 8 64 ± 9	828 822	16 16	1.9 1.9
Zanchetti, 2002[53]	ELSA	Beta Blocker DH-CCB	Atenolol Lacidipine	3.75 years	55.9 ± 7.5 56.1 ± 7.5	1157 1177	14 9	1.2 0.8

Calcium ions are implicated in tissue injury affecting the heart and various organs, contributing to conditions such as stroke and myocardial infarction. Calcium channel blockers (CCBs) are commonly prescribed for managing angina and hypertension. Numerous meta-analyses have examined the influence of CCBs on cardiovascular and cerebrovascular outcomes. In a 2009 meta-analysis, Costanzo et al. assessed the comparative effectiveness of CCBs against other antihypertensive agents. Their findings demonstrated that CCBs were associated with a lower risk of stroke both hemorrhagic and non-hemorrhagic stroke compared to ACE inhibitors, without elevating the risk of cardiovascular mortality, myocardial infarction, or major cardiovascular events.[56] The meta-analysis by Thomopoulos et al., which included 247,006 participants with a hypertension prevalence exceeding 40%, revealed that calcium channel blockers (CCBs) were more effective in stroke prevention than placebos, beta-blockers (BBs), ACE inhibitors (ACEIs), RAS inhibitors, and all other antihypertensive drug classes combined.[55]

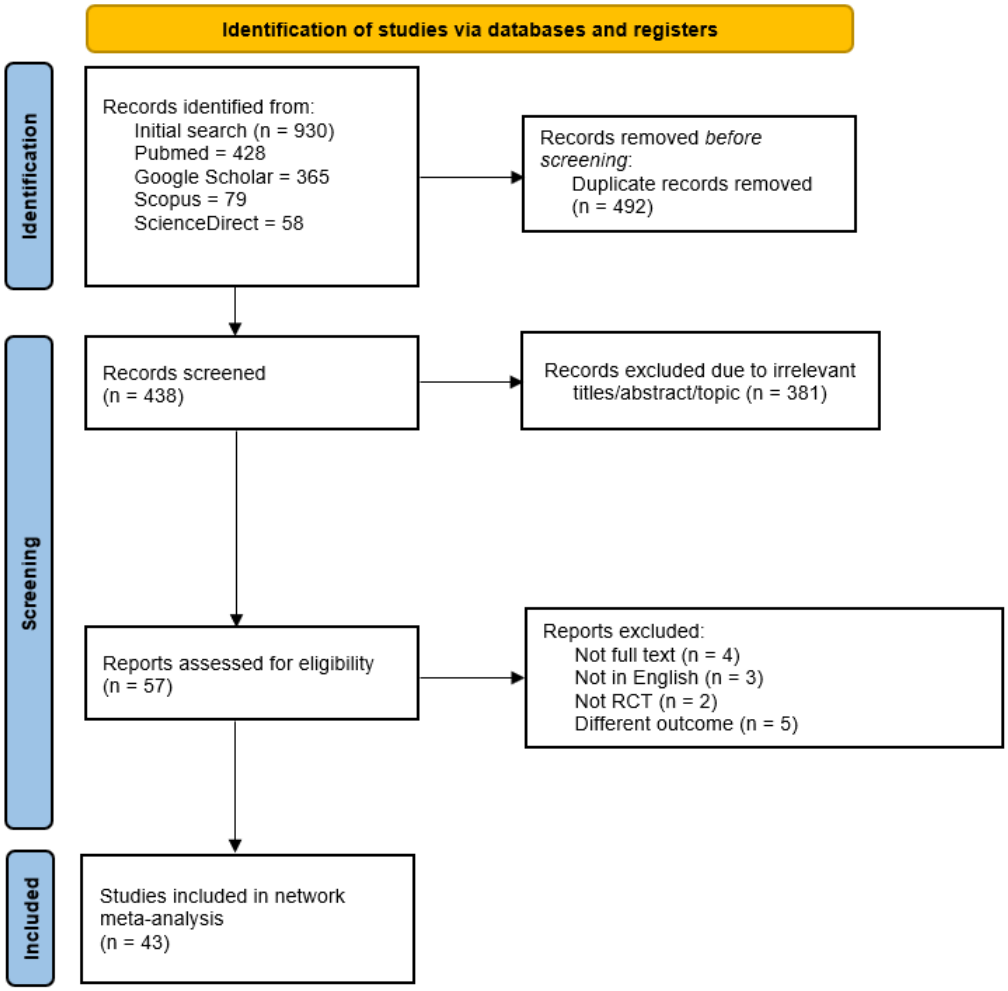

Figure 1. Flowchart of selecting process for this network meta-analysis

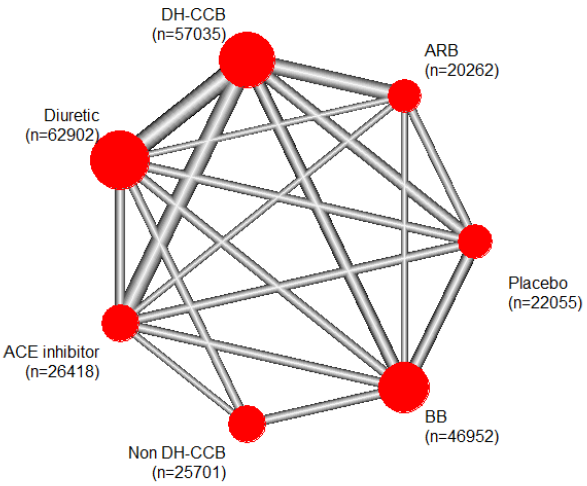

Figure 2. Network structure diagram of this network meta-analysis

Table 2. Quality appraisal of studies included

Study	D1	D2	D3	D4	D5	Overall
Liu, 2005 - FEVER	+	+	+	+	+	+
MRC, 1992	+	+	+	+	-	+
SHEP, 1991	+	+	+	-	+	+
Dahlof, 1991 - STOP	+	+	+	+	+	+
Liu, 1998 - SYST-China	+	+	+	-	-	+
Staessen, 1997 - SYST-Eur	+	+	+	+	-	+
UKPDS, 1998	+	+	+	+	+	+
UKPDS, 1999	+	+	+	+	+	+
Estacio, 1998 - ABCD	+	-	+	+	-	+
Kjeldsen, 2008 - ACCOMPLISH	+	+	-	-	-	-
ALLHAT, 2002	+	+	+	+	+	+
Dahlof, 2005 - ASCOT	+	+	+	+	+	+
Ruggenenti, 2011 - BENEDICT B	+	+	+	+	-	+
Ogihara, 2014 - COLM	+	-	+	+	+	+
Black, 2003 - CONVINCE	+	+	+	+	+	+
Zanchetti, 2002 - ELSA	+	+	+	+	+	+
Tatti, 1998 - FACET	+	+	+	-	+	+
Matsuoka, 1995 - GLANT	+	-	+	-	+	+
Brown, 2000 - INSIGHT	+	-	-	-	-	-
Pepine, 2003 - INVEST	+	+	+	+	+	+
Baba, 2001 - J-MIND	+	+	+	+	-	+
Yui, 2004 - JMIC-B	+	+	+	-	-	+
Dahlof, 2002 - LIFE	+	+	+	+	+	+
Wikstrand 1991 - MAPHY	+	-	-	-	+	-
Borhani, 1996 - MIDAS	+	+	+	-	-	+
Schrader, 2005 - MOSES	+	+	+	+	+	+
Muramatsu, 2012 - NAGOYA HEART	+	+	+	+	+	+
NICS-EH, 1999	+	-	X	-	+	X
Hansson, 2000 - NORDIL	+	-	-	X	-	X
Ogawa, 2012 - OSCAR	+	+	+	+	+	+
Ogihara, 2011 - PATE	+	+	+	+	-	+
Malacco, 2003 - SHELL	+	-	-	+	+	+
Hansson, 1999 - STOP II	+	+	+	-	+	+
Julius, 2004 - VALUE	+	+	+	+	+	+
Narumi, 2016 -VART	+	-	-	-	X	X
Rosei, 1997 - VHAS	+	+	-	+	+	+
Kaplan, 2003 - SANBPS	+	+	+	+	+	+
Matsuzaki, 2011 - CTHPCETG	+	+	+	+	+	+
Suzuki, 2005 - E-COST	+	+	+	-	-	+
Beckett, 2014 - HYVET	+	+	+	+	-	+
Hansson, 1999 - CAPPP	+	+	-	-	-	-
Lithell, 2003 - SCOPE	+	+	+	+	+	+
Kasanuki, 2009 - HIJ-CREATE	+	+	+	+	+	+

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
X High
\- Some concerns
\+ Low

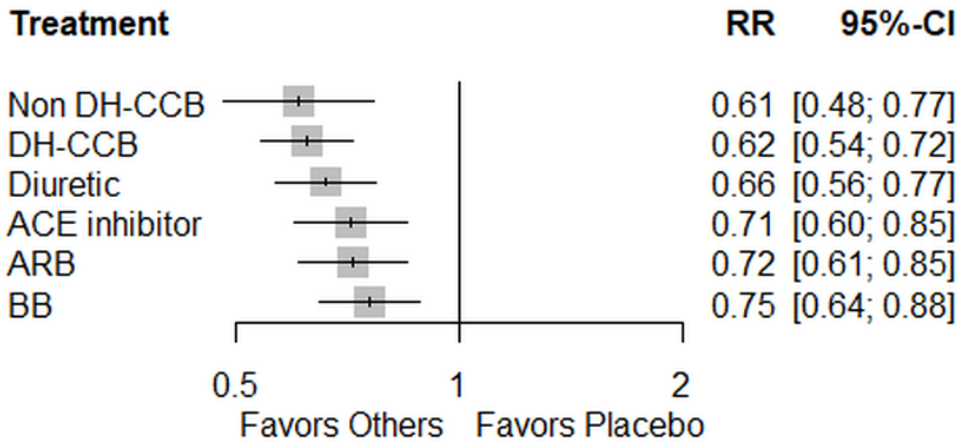

Figure 3. Forest plot of this network meta-analysis

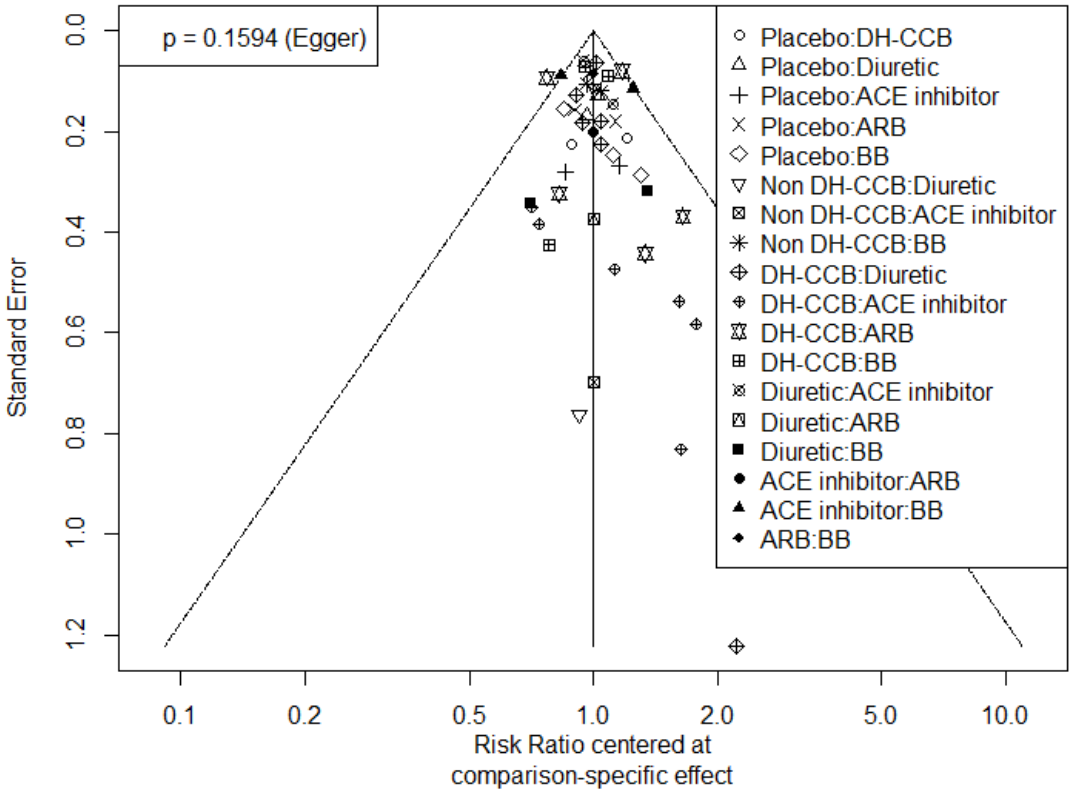

Figure 4. Funnel plot of this network meta-analysis

A meta-analysis encompassing 13 clinical trials with a total of 103,793 participants demonstrated that dihydropyridine calcium channel blockers (CCBs) significantly reduced the risk of stroke compared to non-dihydropyridine CCBs and other antihypertensive agents. Meta-regression analysis further suggested that the stroke risk reduction associated with dihydropyridine CCBs occurs independently of systolic blood pressure lowering. This benefit may partly stem from the neuroprotective properties of CCBs and their ability to slow the progression of carotid atherosclerosis. Moreover, dihydropyridine CCBs—such as benidipine—have been shown to inhibit the generation of reactive oxygen species by polymorphonuclear leukocytes in salt-loaded spontaneously hypertensive rats, likely due to their antioxidant properties and suppression of the Ca^{2+}/protein kinase C/NADPH oxidase signaling pathway.[57] Our findings also confirmed that calcium channel blockers (CCBs) were more effective than placebos, beta-blockers (BBs), ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) in reducing the incidence of stroke in the general population.

Thiazide diuretics, encompassing both thiazide-type agents (such as chlorothiazide, hydrochlorothiazide, bendroflumethiazide, trichlormethiazide, and bendrofluazide) and thiazide-like compounds (such as indapamide and chlorthalidone), have been utilized in hypertension management for over fifty years. In 2015, Chen et al. conducted a meta-analysis to evaluate the cardioprotective benefits of both thiazide-type and thiazide-like diuretics in patients with hypertension. Their analysis indicated that these diuretics were associated with lower risks of cardiovascular disease and heart failure; however, no significant difference was observed in stroke incidence when compared to the control group.[58] Thomopoulos et al.'s meta-analysis demonstrated that diuretic therapy was more effective in reducing the risk of stroke compared to both placebo and renin-angiotensin system (RAS) inhibitors.[55] Our study further validated that diuretics were more effective than placebos, beta-blockers (BBs), ACE inhibitors (ACEIs), and angiotensin receptor blockers (ARBs) in preventing stroke across the general population.

Beta-blockers (BBs) have been a mainstay in hypertension treatment for over forty years. Nonetheless, emerging evidence has questioned their suitability as a first-line option, as randomized placebo-controlled trials have not demonstrated substantial cardiovascular protective benefits. In a 2017 Cochrane systematic review by Wiysonge et al., first-line BB therapy was found to offer only a modest reduction in stroke risk among hypertensive patients, with no significant impact on overall mortality or incidence of coronary heart disease. Moreover, their effectiveness in stroke prevention was inferior compared to calcium channel blockers (CCBs) and renin-angiotensin system (RAS) inhibitors.[59] Additionally, a 2020 meta-analysis by Thomopoulos et al. found that beta-blockers (BBs) were less effective than other classes of antihypertensive agents in reducing the incidence of stroke and all-cause mortality,

both in the overall trial population and in studies focusing solely on individuals with hypertension.[60] Our findings also provide evidence that beta-blockers (BBs) were ineffective in reducing the risk of stroke, all-cause mortality, and cardiovascular mortality in both the general population and individuals with hypertension.

Limitations

This network meta-analysis has several limitations. Firstly, the management of hypertension has evolved considerably over the past three decades, reflecting shifts in clinical perspectives. Variations exist across studies in terms of the classes of antihypertensive agents used, their dosing regimens, and the therapeutic objectives for stroke prevention, particularly when comparing older trials to more recent ones. Second, due to limited available data, we were unable to conduct subgroup analyses to compare the effects of antihypertensive medications based on gender or race. Third, comparisons between patients with and without diabetes or hyperlipidemia across different drug classes could not be performed, as data for these subgroups were insufficient within each drug category. Fourth, there were no primary outcome sub-analysis whether ischemic stroke hemorrhagic stroke due to insufficient clinical outcome data.

Conclusion

In conclusion, the current evidence suggests that calcium channel blockers (CCBs) and diuretics may offer superior protection against stroke in individuals with hypertension.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgment

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CASE REPORT

CANVAS SYNDROME: A COMPREHENSIVE CASE REPORT ON RARE ATAXIA

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Abstract

Introduction: Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is characterized by cerebellum, vestibular system, and sensory pathways impairments. It progresses slowly compared to other ataxias like Friedreich's ataxia, and its genetic basis is complex and under investigation.

Case Report: A 34-year-old male presented with worsening imbalance over the past year, vertigo, slurred speech, and hand tremors. Physical examination revealed bidirectional nystagmus, dysmetria, and cerebellar atrophy on MRI. Vestibular tests were abnormal, and neuropsychological assessments showed memory and executive function deficits. Sensory nerve conduction studies were normal.

Discussion: The patient's symptoms of ataxia, vestibular areflexia, and sensory neuropathy are consistent with CANVAS. Cerebellar atrophy and Purkinje cell degeneration contribute to motor coordination deficits. Sensory neuropathy involves dorsal root ganglia degeneration. Despite supportive clinical features, genetic testing is necessary to confirm the diagnosis and exclude other genetic ataxias.

Conclusion: CANVAS is a rare ataxia syndrome with autosomal recessive inheritance affecting the cerebellum, vestibular, and sensory systems. The patient's symptoms and MRI findings suggest CANVAS, but further genetic testing is required for definitive diagnosis.

Keywords: CANVAS, cerebellar ataxia, cerebellar atrophy, sensory neuropathy, vestibular areflexia

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Introduction

Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is a recently recognized ataxic disorder that affects three key components of balance regulation: the cerebellum, vestibular system, and sensory pathways. This condition impairs three of the four cardinal balance components, with vision being the only unaffected modality. Compared to other ataxias, such as Friedreich's ataxia or spinocerebellar ataxia type 3, CANVAS progresses at a relatively slow rate. The underlying genetic etiology of CANVAS remains under investigation, although emerging evidence suggests that the

disorder may be associated with multiple causative genes, indicating a complex inheritance pattern. [1]

CANVAS is classified as a rare neurological disorder with an autosomal recessive inheritance pattern. There is no predictable sequence in the onset of its three cardinal features—cerebellar impairment, bilateral vestibular hypofunction, and somatic sensory deficits. Patients may present with only two of these three features for several years before fulfilling the minimum diagnostic criteria for CANVAS. Pathologically, CANVAS is characterized by neuronopathy affecting multiple cranial nerves and dorsal root ganglia, alongside a consistent pattern of cerebellar atrophy.[2]

In 2016, proposed diagnostic criteria for definitive CANVAS included the presence of an abnormal visually enhanced vestibulo-ocular reflex (VVOR) detected via video-oculography, videonystagmography, or rotational chair testing. Additionally, MRI findings demonstrating cerebellar atrophy, particularly involving the anterior and dorsal vermis as well as the lateral hemispheres (primarily affecting crus I), provide further diagnostic support. Neurophysiological evidence of neuronopathy (ganglionopathy) is also required, along with the exclusion of genetically testable ataxias, particularly spinocerebellar ataxia type 3 (SCA3) and Friedreich's ataxia.[3]

Case Report

A 34-year-old male presented with progressive imbalance over the past year. He reported difficulty maintaining balance while walking, which was absent when standing or sitting. He also experienced episodic vertigo, particularly when changing positions from lying to standing. Over the past six months, he developed slurred speech and hand tremors, especially while typing on a keyboard. He denied nausea, vomiting, hearing loss, tinnitus, facial numbness, headaches, or unilateral weakness.

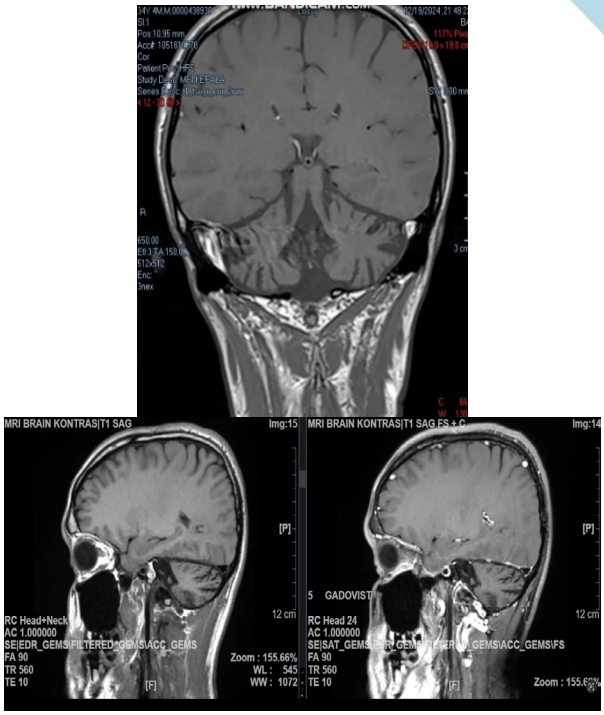
On examination, the patient was alert with a Glasgow Coma Scale (GCS) score of E4M6V5. Vital signs were stable (BP: 112/85 mmHg, HR: 85 bpm, RR: 18 breaths/min, Temp: 36.5°C). Neuro-ophthalmologic evaluation revealed corrected visual impairment and bidirectional horizontal nystagmus with rebound nystagmus. Saccadic dysmetria was observed in the left eye, while the right eye exhibited normal saccades.

Neuro-otologic examination confirmed vestibular dysfunction. Dix-Hallpike testing elicited downbeat nystagmus without latency, lasting >30 seconds, and was non-fatiguable. No spontaneous nystagmus was observed in a sitting position. Gaze-evoked nystagmus was present in horizontal but not vertical fields. Rebound nystagmus was positive bilaterally, and head-shaking testing revealed cross-coupled nystagmus. Hearing examination revealed no abnormalities. However, balance assessment showed that the patient had a stable stance with both feet together (Romberg test). When performing the sharpened Romberg test with eyes open, the patient fell.

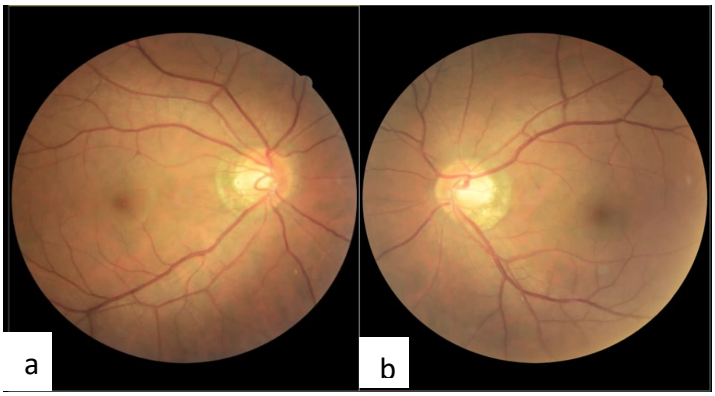
Figure 1. Gait Pattern in Cerebellar Ataxia

Tandem walking assessment revealed impairments. In the finger-to-finger coordination test, the patient exhibited positive dysmetria. The knee-to-heel test also showed disturbances. Vestibulo-ocular reflex (VOR) testing was positive on both sides, and the VOR suppression test was impaired in both right and left directions. Bilateral bradykinesia was observed, with greater severity on the left side. Visual dynamic acuity testing showed bilateral impairments.

Additional examinations, including somatosensory evoked potentials (SSEP) and nerve conduction studies (NCS), revealed no abnormalities. Higher cognitive function assessment using MMSE, MoCA-Ina, CERAD, TMT A, and TMT B indicated memory dysfunction (impairment in verbal and visual delayed recall) and executive function deficits (including difficulties in calculation and abstraction). Contrast-enhanced brain MRI revealed cerebellar atrophy, predominantly affecting the vermis. No atrophy was observed in the brainstem, cerebral cortex, or spinal cord.



Figures 2. Contrast-Enhanced Brain MRI: Coronal and Sagittal Views



Figures 3. Fundoscopy Images: (a) Right Eye, (b) Left Eye

Discussion

The clinical manifestations observed in this patient, including ataxia, vestibular areflexia, and sensory neuropathy, are highly suggestive of Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome (CANVAS). A characteristic pattern of cerebellar atrophy often precedes the full clinical presentation, manifesting as ataxia, motor coordination impairment, and nystagmus. In CANVAS, Purkinje cells in the cerebellum exhibit increased susceptibility to degeneration, which plays a crucial role in motor coordination. The progressive loss of Purkinje cells leads to cerebellar atrophy, contributing to the ataxic symptoms experienced by the patient. This condition is strongly associated with a biallelic AAGGG repeat expansion in the RFC1 gene, a mutation that results in the production of aberrant proteins, ultimately leading to neuronal dysfunction and degeneration.[4]

The patient's sensory neuropathy presents as glove-and-stocking hypesthesia, a hallmark feature of CANVAS. One of the primary neuropathological findings in CANVAS is dorsal root ganglia (DRG) degeneration, which results in axonal degeneration with secondary demyelination of the posterior columns. The progressive neural loss within the DRG supports the clinical suspicion of peripheral sensory deficits in CANVAS.[5] Similarly, the patient's vestibular areflexia manifests as impaired coordination, balance disturbances, vertigo, nystagmus, and abnormal VVOR. One of the key pathological mechanisms underlying CANVAS is vestibular ganglion neuron degeneration, which reduces vestibular input to the brain, ultimately resulting in vestibular areflexia.[5,6]

Based on the patient's symptomatology, the clinical findings strongly align with a clinically probable diagnosis of CANVAS. Supporting evidence includes abnormal VVOR and cerebellar atrophy observed on MRI. However, NCV did not reveal significant sensory abnormalities, which does not support a definite diagnosis of clinically probable CANVAS, despite the presence of glove-and-stocking hypesthesia. To establish a more definitive diagnosis, genetic testing is essential to exclude other hereditary ataxias, such as spinocerebellar ataxia type 3 (SCA3) and Friedreich's ataxia.[1]

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is the most common form of autosomal dominant spinocerebellar ataxia, caused by a CAG trinucleotide repeat expansion in the *ATXN3* gene. Clinically, it is characterized by progressive cerebellar ataxia accompanied by pyramidal signs, extrapyramidal features such as dystonia or Parkinsonism, peripheral amyotrophy with generalized areflexia, progressive external ophthalmoplegia, and action-induced facial or lingual fasciculations.[7,8] In the present case, SCA3 was considered due to the presence of progressive ataxia, vestibular dysfunction, and sensory neuropathy. However, the absence of typical features including pyramidal or extrapyramidal involvement, ophthalmoplegia, and a family history of autosomal dominant inheritance makes this diagnosis unlikely. Instead, the clinical profile of prominent vestibular areflexia and sensory neuronopathy is more

consistent with CANVAS. Nevertheless, definitive exclusion of SCA3 requires molecular confirmation of CAG repeat expansion in the *ATXN3* gene.

Friedreich's ataxia (FRDA) is a slowly progressive autosomal recessive degenerative disease involving both neural and extraneural systems, most commonly caused by GAA repeat expansion in the FXN gene. It usually manifests in childhood or adolescence with gait ataxia, dysarthria, sensory loss, and areflexia, and is frequently associated with systemic features such as hypertrophic cardiomyopathy, scoliosis, and diabetes mellitus. Neurologically, FRDA consistently involves three major systems: (1) large fiber sensory pathways, leading to proprioceptive loss and absent reflexes, (2) cerebellar coordination systems, resulting in gait ataxia, impaired limb coordination, and dysarthria, and (3) corticospinal tracts, which may cause progressive lower extremity weakness and spasticity. [9,10] In the present case, FRDA was considered as a differential diagnosis due to the presence of progressive ataxia and sensory neuropathy. However, the patient's age of onset in late adulthood, absence of cardiomyopathy, scoliosis, or diabetes, as well as the presence of vestibular areflexia, which is not characteristic of FRDA, make this diagnosis unlikely. Moreover, while clinical features can suggest the possibility of FRDA, a definitive diagnosis requires genetic confirmation of biallelic *FXN* mutations, typically GAA repeat expansion testing.[9] Genetic testing has not yet been performed in this patient and is strongly recommended to definitively rule out FRDA.

Further diagnostic assessments should be considered to refine the diagnosis. Referral to the otolaryngology (ENT) department for video head impulse testing (vHIT) could provide additional confirmation of vestibular impairment. Additionally, vestibular-evoked myogenic potentials (VEMP), sympathetic skin response (SSR), sinus rhythm (SR), and RR interval variability should be evaluated in the neurophysiology department. Moreover, transcranial magnetic stimulation (TMS) could be explored in the context of neurorestorative interventions.

Conclusion

CANVAS (Cerebellar Ataxia, Neuropathy, and Vestibular Areflexia Syndrome) is a rare neurodegenerative disorder affecting the cerebellum, vestibular, and sensory systems, following an autosomal recessive inheritance pattern. The primary clinical manifestations observed in the patient, including ataxia, motor coordination impairment, vertigo, and nystagmus, strongly support a diagnosis of CANVAS. This is further reinforced by radiological findings demonstrating cerebellar atrophy and visual-vestibular dysfunction. Although the clinical presentation is highly suggestive of CANVAS, additional diagnostic assessments are required for confirmation. Genetic testing is recommended to exclude other hereditary ataxias.

Conflict of Interest

The authors declared no conflict of interest.

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