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APOE-epsilon 4 polymorphism and cognitive function in Bengkulu obese individuals

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ABSTRACT

Background: While obesity and apolipoprotein E (APOE) are both important risk factors for dementia, the exact role of their interrelationship in influencing dementia risk, particularly across different ethnicities, remains unclear. This study aims to examine the correlations between APOE and the risk of dementia in obese adults from Bengkulu.

Methods: Seventy- two participants from Bengkulu, comprising obese and normal individuals (Mean age = 39.44 years; Mean BMI = 25.64 kg/m²; 33.3% APOE- ε4 carriers; 69.4% female), underwent anthropometric assessments, blood sampling for APOE genotyping, and cognitive evaluation using the MoCA- Ina test. The Chi- square analysis was conducted to investigate the association between APOE and the risk of dementia in obese adults from Bengkulu.

Results: Statistical analyses revealed significant differences between obese and non-obese groups regarding age (41.28 ± 6.76 vs 37.61 ± 7.19; *P* = .011), sex (80.6% women and 19.4% men vs 58.3% women and 41.7% men; *P* = .041), BMI (28.64 ± 3.98 vs 22.63 ± 1.86; *P* < .001), weight (69.01 ± 12.24 vs 57.94 ± 7.97; *P* < .001), and MoCA-Ina score (19.4% vs 61.1%; *P* < .001). This study found no significant differences in cognitive decline between APOE-ε4 carriers in both obese (OR: 3.67, 95% CI: 0.39 to 34.65, *P* = .384) and non-obese groups (OR: 0.584, 95% CI: 0.12 to 2.78, *P* = .706) among individuals from Bengkulu.

Conclusion: We found no evidence of neurodegenerative risk associated with APOE-ε4 in obese individuals from Bengkulu. Further research is required to investigate potential characteristics.

INTRODUCTION

Obesity is a worldwide health concern that ranks sixth among global health issues [1]. In 2016, almost 13% of the global population, or around 650 million individuals, were identified as obese, representing a three-fold rise since 1975 [1,2]. Conversely, the global population afflicted with dementia was 57.4 million in 2019, projected to increase by about 2.5 times by 2050 [3]. The incidence of obesity in Indonesia increased markedly from 10.5% in 2007 to 21.8% in 2018 [4]. Obesity is characterized by abnormal or excessive fat accumulation, which can adversely affect health [2]. Obesity is a risk factor for numerous cardiovascular and cerebrovascular illnesses [5]. Dementia is a syndrome characterized by a decline in cognitive function that exceeds the typical expectations of normal biological aging [6]. It impairs independence in daily activities, necessitating assistance for complex instrumental tasks [7]. The impact of obesity on cognitive deterioration and the onset of dementia has been documented and analysed in prior studies [8-12]. Midlife obesity has been related to the development of vascular damage and cerebral atrophy, as well as the onset of dementia in later life [8,9]. Conversely, late-life obesity decreased the risk of dementia in comparison to individuals with a normal body mass index (BMI) [10,11]. A meta-analysis indicated a favourable correlation between midlife obesity and subsequent dementia, but the reverse was observed in late life [10]. An examination of data from 1.3 million individuals found that a higher BMI has a detrimental effect in long-term follow-up and a protective effect in short-term follow-up before dementia diagnosis [11]. Conversely, an additional systematic literature analysis and another research did not substantiate the advantageous effects of obesity in later life on the onset of dementia [12], indicating that the notion of the obesity paradox in dementia remains contentious. Currently, research on obesity and Alzheimer's Disease (AD) has advanced significantly to some degree. Nonetheless, numerous arguments and questions persist concerning the likelihood of obesity-inducing AD and the impact of various obesity types on AD, characterized by inconsistencies in research findings and underlying mechanisms.

Apolipoprotein E (APOE) represents the most significant hereditary risk factor for Alzheimer's disease. Alzheimer's disease (AD) is a prevalent neurodegenerative disorder among the elderly and the leading cause of dementia [13]. The mechanisms behind this hereditary risk, however, are not well comprehended. The structural variations among apolipoprotein E (ApoE) isoforms encoded by the APOE ε2, ε3, and ε4 alleles are associated with distinct binding affinities of ApoE to lipoprotein receptors and amyloid-β (Aβ) [14,15]. Apolipoprotein (APOE) ε4 is the predominant and extensively researched genetic risk factor for late-onset AD and overall cognitive deterioration in the elderly [16]. The influence of the APOE genotype on AD risk differs according to ethnicity, sex, age, and geographic region. African Americans are 1.4 times more likely than European Americans to have the APOE-ε4 allele [16], but it has less of an effect on how AD gets worse in African American populations [17,18]. The frequency of the ε4 allele was greater among Laotian minorities compared to the Laotian majority in Laos [19]. Recent study indicates that environmental or health factors, such as obesity, may alter the impact of APOE-ε4 in some racial and ethnic groups [18]. So far, no research has investigated the relationships between obesity and AD through APOE-ε4 in older adults from Bengkulu.

Therefore, the objective of this study was to investigate: (1) the impact of obesity on cognitive decline as assessed by the Indonesian version of the Montreal Cognitive Assessment questionnaire (MoCA-Ina); and (2) the interaction between BMI and APOE-ε4 in obese individuals from Bengkulu. We hypothesized that an association exists between BMI and APOE-ε4 regarding cognitive deterioration among people in Bengkulu Province, Indonesia.

METHODS

Study Participants

This case-control study involved participants selected from Community Health Service (Puskesmas) across nine districts in the city of Bengkulu, conducted from January to March 2023. Participants were required to meet the following criteria: (1) residency in Bengkulu for a minimum of one year; (2) age between 30 and 60 years; (3) a BMI ≥ or greater than 25 kg/m² for the obese group; and (4) a BMI lower than 25 kg/m² for the control group. The exclusion criteria included: (1) individuals diagnosed with HIV and severe liver disorders; (2) those who experienced a heart attack or pregnancy within the past two months; (3) participants involved in a weight loss program or taking lipid-lowering medication; (4) individuals suffering from other metabolic disorders, such as diabetes or hypertension; and (5) subjects who are illiterate, or have hearing impairments. Seventy-two participants met the inclusion criteria for the analyses.

Participants were categorized into two groups: the control group, comprising healthy individuals with a normal BMI, and the case group, consisting of obese individuals with a higher BMI. All participants submitted written informed consent upon enrolment. Ethical approval was obtained from the Faculty of Medicine and Health Sciences institutional review board, reference number 257/UN30.14.8/LT/2022.

Procedure

Medical records of participants were screened to establish initial eligibility. Individuals who were potentially eligible attended an in- person screening conducted door- to- door. Following the provision of informed consent, participants who met the inclusion criteria undergo a comprehensive assessment that includes cognitive evaluations, anthropometric measurements, and total cholesterol analysis. Participants submitted a blood sample for APOE genotyping analysis.

Measures

Body Mass Index and Total Cholesterol

Body mass index (BMI) serves as an estimate of body fat, calculated by dividing weight (in kilograms, kg) by height (in meters, m). Participants were classified into two groups according to the Indonesian Minister of Health. Obesity is defined as a Body Mass Index (BMI) ≥ 25 kg/m², while normal weight is defined as a BMI < 25 kg/m². Total cholesterol levels are assessed using the CHOD- PAP method with the Indiko™ Clinical Chemistry Analyzer and associated digital application (Thermo Scientific, Finland). Blood serum undergoes centrifugation at 3,000 RPM for a duration of 15 minutes. The sample is then placed into a coded sample cup, inserted into the machine's rack, and the program is initiated. The machine will execute the CHOD-PAP method automatically, and the examination results will be presented via the computer application.

APOE genotyping

The DNA extraction from blood samples was performed using the Promega ReliaPrep™ Blood gDNA Miniprep System A5081, USA. Prior to data analysis, blood samples were stored in a secure laboratory storage room. Genomic DNA was subjected to polymerase chain reaction (PCR) with primers specific for APOE isoforms (Forward Primer-1; CGG ACA TGG AGG ACG TGT for APOE-112cys, and Reverse Primer-2; CTG GTA CAC TGC CAG GCG for APOE-158arg, Reverse Primer-3; CTG GTA CAC TGC CAG GCA for APOE-158cys, Forward Primer-4; CGG ACA TGG AGG ACG TGC for APOE-112arg), these primers were developed and validated previously [20], and curently it is suitable for APOE genotyping in a general population [21]. Combinations of two-allele-specific sequence-specific primers were used to determine each APOE haplotype: primers F1 and R3 for E2, primers F1 and R2 for E3 and primers R2 and F4 for E4 haplotypes [21]. Forward Primer; TGC CAA GTG GAG CAC CCA A and Reverse Primer; GCA TCT TGC TCT GTG CAG AT were used as common primers.

The PCR mix consists of two specific primers, each at a volume of 0.4 µl, combined with 5 µl of GoTaq Green Master Mix (Promega, USA). The DNA isolation result of 5 µl was added into the mixture, accompanied by the common primer, each at a volume of 0.2 µl. The PCR protocol consists of sequential temperature steps. The procedure commences with an initial denaturation phase at 95°C for 3 minutes. A denaturation step occurs at 95°C for 30 seconds. An annealing step was conducted at 60°C for 30 seconds. Following annealing, an elongation phase was conducted at 72°C for a duration of 1 minute. A concluding elongation step was performed at 72°C for 10 minutes. This PCR protocol aims to amplify targeted regions of the gene of interest, facilitating the identification of various alleles (E2, E3, and E4) using specific primers. The APOE genotype status was categorized into three groups: APOE2 carriers (ε2/ ε2 or ε2/ ε3), APOE3 homozygotes (ε3/ ε3), and APOE4 carriers (ε3/ ε4 or ε4/ ε4). Participants possessing the APOE ε2/ ε4 genotype (n=2) were excluded because of the mutually exclusive influences of APOE2 and APOE4 on cognitive decline with aging. After genotyping, participants were classified as either APOE- ε4 non- carriers or APOE- ε4 carriers, irrespective of heterozygosity or homozygosity, as previously outlined [22].

Cognitive Assessment

Cognitive function was evaluated using the Indonesian version of the Montreal Cognitive Assessment (MoCA-Ina). Most items of the MoCA-Ina test were translated literally from the original version without modification [23]. The test is a validated and widely utilized instrument for assessing cognitive function, comprising several questions categorized into seven domains: orientation, short-term memory, visuospatial skills, executive function, attention and concentration, language, and orientation. The test duration was approximately 10 to 15 minutes. The subjects were made comfortable, and scoring for each question was conducted immediately upon its presentation in an orderly manner. The MoCA-Ina score ranges from 0 to 30, where higher scores indicate superior cognitive performance. A score of 25 or lower is indicative of mild cognitive impairment [24].

Statistical analysis

Descriptive techniques, including count and percent for categorical variables, or mean and standard deviation for continuous variables, were employed to summarize demographic characteristics and cognitive test performance, stratified by obese and normal groups. *p-values* in Table 2 were employed to assess the probability that differences in these features between obese and non-obese groups exist in the broader population, based on the null hypothesis of no actual difference. Age, weight, BMI, and waist circumference were compared using the Mann–Whitney U test due to non-normal distribution, whereas height and total cholesterol were analyzed using the independent t-test. Categorical variables (sex, education level, ethnicity, blood type, smoking status, APOE genotype, and MoCA-Ina score) were analyzed using the chi-square test, while employment status was assessed using Fisher's exact test because >20% of expected cell counts were <5. All analyses evaluated associations with obesity status. The Odds Ratio was calculated to evaluate the strength of the relationship. A *p-value* of less than 0.05 was considered statistically significant. Statistical analyses were performed utilizing Statistical Package for Social Sciences (SPSS) version 26 (IBM, USA).

RESULTS

Characteristics of the study participants

The characteristics of the study participants were summarized as shown in Table 1. Among the seventy-two participants, the mean age was 39.44 years (SD = 7.17), with 69.4% identifying as women and 62.5% as Bengkulu ethnicity. Of the participants, 50% possessed the APOE e2 allele, while 30.6 possessed the APOE e4 allele. The obese and non-obese groups showed no significant differences in mean height, waist circumference, and total cholesterol, or in the distribution of blood types, ethnicity, employment, education categories, smoking habits, and APOE genotypes (all comparisons, P >.05). Significant differences were observed between obese and non-obese groups regarding age, weight, sex, BMI, and MoCA-Ina score (all comparisons, P < .05).

Association of obesity with cognitive function

In the non-obese group, the mean BMI was comparable between participants with MoCA-Ina score < 25 and those with MoCA-Ina score 25 (22.57 1.95 vs. 22.73 1.78 kg/m², respectively). Similarly, the mean waist circumference was slightly higher among participants with MoCA-Ina score < 25 (80.41 5.86 cm) compared to those with MoCA-Ina score 25 (77.39 11.39 cm), although the difference appeared modest. In the obese group, participants with MoCA-Ina score < 25 had a higher mean BMI compared to those with MoCA-Ina score 25 (30.44 5.39 vs. 28.21 3.55 kg/m²). A similar pattern was observed for waist circumference, with higher mean values among participants with MoCA-Ina score < 25 (95.57 ± 12.31 cm) than those with MoCA-Ina score 25 (91.03 9.73 cm). Overall, mean BMI and waist circumference tended to be higher among participants with MoCA-Ina score < 25 in the obese group, whereas differences were less pronounced in the non-obese group.

Associations of APOE genotyping with cognitive function

The associations between APOE genotyping and MoCA-Ina Score are summarized in Table 3. After genotyping, participants were classified as either APOE-ε4 non-carriers or APOE-ε4 carriers, irrespective of heterozygosity or homozygosity, as previously detailed [22]. The presence of the APOE e4 allele did not show a significant association with the MoCA-Ina score

in either the obese (OR: 3.67, 95% CI: 0.39 to 34.65, *P* = .384) or non-obese groups (OR: 0.584, 95% CI: 0.12 to 2.78, *P* = .706).

Tables

Demographic Characteristics	Total (n=72) [a]	Obese (n=36) [b]	Non-Obese (n=34) [b]	*P*-value
Age, years, mean ± SD	39.44 ± 7.17	41.28 ± 6.76	37.61 ± 7.19	.011*
Weight, Kg, mean ± SD	63.48 ± 11.68	69.01 ± 12.24	57.94 ± 7.97	<.001**
Height, cm, mean ± SD	157.17 ± 8.38	155.1 ± 7.46	159.3 ± 8.80	.182
BMI, kg/m², mean ± SD	25.64 ± 4.32	28.64 ± 3.98	22.63 ± 1.86	<.001**
Waist circumference, cm, mean ± SD	85.58 ± 11.29	91.92 ± 10.25	79.24 ± 8.43	.185
Total Cholesterol, mg/dl, mean ± SD	185.28 ± 39.51	187.47 ± 33	185.08 ± 45.47	.321
Sex				.041*
Men, n (%)	22 (30.6)	7 (19.4)	15 (41.7)	
Women, n (%)	50 (69.4)	29 (80.6)	21 (58.3)	
Education categories				.147
Up to Middle School, (n, %)	11 (15.3)	6 (16.7)	5 (13.9)	
Up to High School, (n, %)	36 (50.0)	14 (38.9)	22 (61.1)	
College or more, (n, %)	25 (34.7)	16 (44.4)	9 (25.0)	
Employment				.478
Government Employees, n (%)	9 (12.5)	3 (8.3)	6 (16.7)	
Non-Government Employees, n (%)	63 (87.5)	33 (91.7)	30 (83.3)	
Ethnicity				.224
Non-Bengkulu, n (%)	27 (37.5)	11 (30.6)	16 (44.4)	
Bengkulu, n (%)	45 (62.5)	25 (69.4)	20 (55.6)	
Blood types				.989
A, n (%)	26 (36.1)	13 (36.1)	13 (36.1)	
B, n (%)	19 (26.4)	9 (25.0)	10 (27.8)	
AB, n (%)	12 (16.7)	6 (16.7)	6 (16.7)	
O, n (%)	15 (20.8)	8 (22.2)	7 (19.4)	
Smoking				.814
No smoking, (n, %)	37 (51.4)	17 (47.2)	18 (50)	
Current smoking, (n, %)	35 (48.6)	19 (52.8)	18 (50)	
APOE Genotype, (n, %)				.792
APOE2+ carriers (ε2/ε2 or ε2/ε3) (n, %)	36 (50.0)	18 (50)	18 (50)	
APOE3 homozygotes (n, %)	14 (19.4)	6 (16.7)	8 (22.2)	
APOE4+ carriers (ε3/ε4 or ε4/ε4) (n, %)	22 (30.6)	12 (33.3)	10 (27.8)	
MoCA-Ina score				<.001**
< 25, (n, %)	29 (40.3)	7 (19.4)	22 (61.1)	
⩾ 25, (n, %)	43 (59.7)	29 (80.6)	14 (38.9)	

Table 1: Demographic characteristics. a Summary statistics for the Bengkulu samples are unweighted. b Total number of observations for subsamples and number of observations in each cell of categories for Bengkulu are unweighted. Age, weight, BMI, and waist circumference were compared using the Mann–Whitney U test due to non-normal distribution, whereas height and total cholesterol were analyzed using the independent t-test. Categorical variables (sex, education level, ethnicity, blood type, smoking status, APOE genotype, and MoCA-Ina score) were analyzed using the chi-square test, while employment status was assessed using Fisher's exact test because >20% of expected cell counts were <5. All analyses evaluated associations with obesity status. All P-values for differences across groups were significant at .05. Abbreviations: APOE, apolipoprotein E; SD, standard deviation.

Subject	MoCa-Ina category	N (%)	BMI (kg/m²) (Mean ± SD)	Waist Circumference (cm) (Mean ± SD)	Adjusted OR (95% CI)	*P*-values
Obese	-	36	-	-	-	-
	< 25	7	30.44 ± 5.39	95.57 ± 12.31	0.77 (0.48 - 1.25)[a]	0.296
	≥ 25	29	28.21 ± 3.55	91.03 ± 9.73	1.08 (0.96 - 1.22)[b]	0.185
Non-obese	-	36	-	-	-	-
	< 25	22	22.57 ± 1.95	80.41 ± 5.86	1.16 (0.77 - 1.72)[a]	0.480
	≥ 25	14	22.73 ± 1.78	77.39 ± 11.39	0.99 (0.84 - 1.16)[b]	0.885

Table 2: Anthropometric characteristics and its association with cognitive function among obese and non-obese groups.

Subject	Allele	MoCA-Ina (<25) [a], n (%)	MoCA-Ina (≥25) [a], n (%)	*P*-value	OR (95% CI)
Obese	APOE e4 carriers	1 (8.3)	11 (81.7)	.384	3.67 (.39-34.65)
	APOE e4 non-carriers	6 (25)	18 (75)		
Non-Obese	APOE e4 carriers	7 (70)	3 (30)	.706	0.584 (0.12-2.78)
	APOE e4 non-carriers	15 (57.7)	11 (42.3)		

Table 3: Associations of APOE genotyping with MoCA-Ina score. a Number of observations with APOE in each cell for Bengkulu subsamples are unweighted. Categorical variables were analysed using Chi-Square tests and the Odds Ratio was calculated. All p-values for differences across groups were significant at .05. Abbreviations: APOE, apolipoprotein E; MoCA-Ina, the Indonesian version of the Montreal Cognitive Assessment; OR, odds ratio.

DISCUSSION

This study aimed to examine the relationship between APOE polymorphism and cognitive decline as a risk factor for dementia in obese adults in Bengkulu. Our findings indicate that sex is independently linked to obesity. The study demonstrated that women exhibited a 2.96-fold increased risk of obesity (OR: 2.96; CI 95% 1.03 - 8.53) relative to men, aligning with prior research that indicates a higher obesity risk among women [25]. Research indicates that the prevalence of obesity in women is affected by socio-cultural and environmental factors, as well as physiological differences [26]. Women exhibit a higher susceptibility to obesity as a result of the interaction among gonadal hormones, the insulin/insulin-like growth factor-1 axis, and their effects on adipokines [25]. The variation in fat and adipose distribution influenced by gonadal hormones results in women experiencing weight gain during pre- menopause and post-menopause, attributed to a decline in estrogen hormone levels [26].

Our research demonstrated that waist circumference is independently associated with obesity. The World Health Organization advocates for the inclusion of waist circumference measurements in the assessment of metabolic syndrome. This recommendation addresses the limitations of using body mass index (BMI) for assessing the distribution of adipose and muscle tissues, which may be affected by variables including gender, age, and personal physical activity levels [27]. Multiple studies have demonstrated a strong correlation between BMI and waist circumference, which is associated with the distribution of abdominal visceral fat [28].

The study revealed that MoCA- Ina scores were primarily below the normal level of 25, accounting for 71%, consistent with findings related to mild cognitive impairment (MCI) in other research [29]. This study represents the first attempt to describe the association between MoCA performance and body mass index (BMI) in obese individuals from Bengkulu. The findings from this study indicated significant differences in MoCA-Ina between obese and non-obese groups. Our findings align with prior research indicating an inverse relationship between higher BMI and global neurocognitive function [30-32]. The likely cause of cognitive decline observed in obese individuals may be as follows. Leptin receptor mRNA exhibits high expression levels in various brain regions, including the hippocampus, amygdala, brain stem, cerebellum, and substantia nigra. It governs the advanced functions in those areas. Leptin modulates synaptic functions and neuronal excitability in the hippocampus, thereby enhancing learning and memory [33,34].

In our study, the presence of the APOE e4 allele among participants did not correlate with the MoCA- Ina score. While certain studies from Western countries, such as those in Northern Europe, have identified a decline in cognitive function associated with APOE ε4 [35,36], a population- based investigation involving older Chinese adults did not find a significant correlation between APOE ε4 and cognitive function [37,38]. Additional research identified no significant differences between APOE ε4 carriers and non- carriers among American Indians [39]. Moreover, the association of the APOE ε4 allele did not differ between individuals with or without cognitive or memory impairment, nor across age ranges, which contrasts with findings from previous studies in other populations [40]. The ethnic differences in genetic susceptibility may partially account for the discrepancies observed in research findings across studies. The proportion of individuals carrying APOE ε4 in our study (31.4%) is comparable to that in the Nordic population, which ranges from 25% to 30%. Episodic memory and executive functioning were notably impacted by the presence of the ε4 allele [41-43]. Cognitive function, as evaluated using the MoCA-Ina, may demonstrate limited sensitivity to the effects of the APOE ε4 allele. Additional large- scale population- based studies are required to examine the relationships between various cognitive domains and the APOE ε4 allele in obese, dementia-free older adults in Bengkulu.

Strengths and Limitations

This study represents one of the initial community- based investigations of older adults in Bengkulu, focusing on the associations and genetic polymorphisms (APOE) related to cognitive performance, as evaluated using the MoCA-Ina test. The study sample was randomly recruited from the Community Health Service using medical records. Nonetheless, the limitations of this study warrant discussion. Firstly, a cross-sectional study does not allow for the determination of temporal and causal relationships, and any observed associations may be influenced by bias resulting from selective survival. The study sample is relatively small, particularly for genetic studies, which may lack sufficient power to identify a weakly to moderately strong association between the factors and the MoCA-Ina score. Additionally, we did not investigate other vascular risk factors that could be linked to genetic polymorphisms and cognitive decline in obesity. Therefore, it is important to investigate the association between vascular risk factors and genetic polymorphisms with cognitive decline in future research.

This community- based study presents evidence linking genetic polymorphism to impaired cognitive function in Bengkulu. Furthermore, our findings indicate that there is no significant association between the APOE ε4 variant and cognitive performance in obese individuals. Significant differences were observed between obese and non-obese groups regarding sex, BMI, waist circumference, and MoCA-Ina score. The findings suggest that early interventions aimed at multiple modifiable risk factors in healthy older adults may mitigate cognitive decline, potentially postponing the onset of dementia. Comprehensive community- based longitudinal studies and interventions are essential to elucidate the causal relationships and mechanisms linking various risk factors to cognitive function, as well as their interactive effects with genetic polymorphisms on cognition.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest concerning the publication of this paper.

AUTHOR CONTRIBUTIONS

All authors contributed to all aspects of this research, approved the final manuscript and agreed to be accountable for this work.

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