ANKARA MEDICAL JOURNAL

Research Article

Ankara Med J, 2025;(3):245-259 // 10.5505/amj.2025.26125

EXPLORING THE RELATIONSHIP BETWEEN METABOLIC SYNDROME AND DEMENTIA IN A POST-COVID CLINICAL POPULATION

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Submitted: 23.03.2025 // Accepted: 30.08.2025

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ANKARA MEDICAL JOURNAL

Abstract

Objectives: This study aimed to assess the cognitive functions and dementia risk among individuals with and without metabolic syndrome who had previously contracted COVID-19, using Mini-Mental State Examination (MMSE) scores. It also aimed to support early and effective interventions for those at risk of dementia or metabolic syndrome in accordance with clinical guidelines.

Materials and Methods: This descriptive cross-sectional study included 375 participants aged 18 years and older who visited the COVID-19 follow-up clinic. During the clinic visit, the MMSE was administered, and participants underwent blood pressure measurement, anthropometric assessment, and laboratory testing.

Results: A statistically significant association was found between dementia frequency and factors such as age, education level, and female gender in the post-COVID population (95% CI; OR=1.039, p=0.001; OR=2.937, p=0.004; OR=1.793, p=0.038, respectively). Although dementia was more common among individuals with metabolic syndrome compared to those without, this relationship was not statistically significant (OR=1.347, p=0.266).

Conclusion: In line with the principles of family medicine, which emphasize early recognition and community health responsibility, we recommend cognitive screening for at-risk individuals. Tools such as the MMSE, which offer valuable insights into cognitive decline, should be used proactively to improve public health outcomes.

Keywords: Metabolic Syndrome, dementia, mini-mental state examination.

Introduction

Metabolic syndrome is characterized by a cluster of metabolic disorders, including high blood pressure, hyperglycemia, central obesity, and dyslipidemia. [1,2] Metabolic syndrome is thought to be a risk factor for coronary heart disease, other cardiovascular diseases, stroke, and type 2 diabetes. [3,4] Approximately 25% of the Western population shows some characteristics of insulin resistance syndrome. [5] In a study conducted to determine the prevalence of metabolic syndrome in Turkey, metabolic syndrome was detected in one-fourth of men and one-third of women. [6]

The incidence of metabolic syndrome generally parallels the incidence of obesity and type 2 diabetes. As a result of the global obesity study conducted in 195 countries in 2015, obesity was found in 604 million adults and 108 million children. Since 1980, the prevalence of obesity has doubled in 73 countries, and increases have been observed in many other countries. Of even greater concern is the rate of growth in childhood obesity, which is even higher. [7]

The importance of examining insulin resistance alongside the more easily measured features of the syndrome is unknown. In addition, although no formal definition of metabolic syndrome includes glycated hemoglobin (A1c), abnormal A1c (5.7 to 6.4 percent) is increasingly considered appropriate and is used to characterize impaired glycemia in patients with metabolic syndrome. [8]

Dementia is an acquired disorder characterized by a decline in cognition involving one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition). [9,10] These must represent a decline from the previous level of function and be severe enough to interfere with daily function and independence. As the global population ages, the prevalence of dementia is expected to increase significantly over the next few decades, particularly in low- and middle-income countries. [11]

The Lancet Commission estimates that around 35% of dementia cases are attributable to a combination of nine potentially modifiable risk factors: Low education level, midlife hypertension, midlife obesity, hearing loss, senile depression, diabetes, physical inactivity, smoking, and social isolation. [12]

Age remains the most important risk factor for dementia, especially Alzheimer's disease. The incidence of Alzheimer's disease approximately doubles with each decade after age 60. Overall, about 85% of dementia cases occur in adults aged 75 and older. [13,14]

This study aims to examine the relationship between metabolic syndrome and dementia in patients attending a post-COVID follow-up clinic.

Cognitive and behavioral assessments are designed to distinguish between normal and abnormal performance in several conditions. The Mini-Mental State Examination is the most commonly used screening test for dementia. [15]

Although there is some evidence linking metabolic syndrome and dementia, longitudinal cohort studies have yielded different results. In the French Three-City study, metabolic syndrome was associated with a modest increase in the risk of cognitive decline. [16] In the Honolulu-Asian Aging Study, metabolic syndrome was weakly associated with vascular dementia but not Alzheimer's. [17] In the Italian longitudinal study on aging, several individual components of the metabolic syndrome were associated with the risk of developing dementia and mild cognitive impairment. [18]

Although the study was conducted among individuals who had previously contracted COVID-19, it did not directly evaluate the impact of the infection on metabolic syndrome or dementia. Instead, the focus of the study was the post-COVID status of patients. This study aims to explore the association between metabolic syndrome and dementia among post-COVID patients. The innovative contribution of this study lies in its focus on a clinical population in Türkiye recovering from COVID-19, addressing the long-term cognitive implications that have received limited attention in the existing literature. However, this population may experience lingering inflammatory responses, chronic metabolic changes, and cognitive dysfunction that persist after the acute phase of infection.

Materials and Methods

Data source and study population

It consists of patients aged 18 and over who applied to the COVID-19 follow-up clinic within the department of family medicine of a university hospital in Türkiye between 03.01.2022, when patient admissions started, and 01.05.2023. In the G power analysis, the power of the study was determined as 94% and the sufficient sample size was defined as 370 people with α=0.05, X parm π=0.2, critical z=1.95 values , and 95% confidence interval.

The Ethics Committee of Recep Tayyip Erdogan University, with decision number 2022/189, deemed our study scientifically and ethically appropriate during a meeting held on October 27, 2022.

Rize Provincial Health Directorate's Scientific Research Application Review Commission approved our study's conduct in a letter dated May 27, 2022, numbered E-64247179-799.

The Scientific Research Platform of the Ministry of Health (Türkiye) evaluated our conduct of this study as appropriate in its letter dated April 28, 2022.

All patients were informed about the study, and written consent was obtained. The study adhered to the ethical principles of the Declaration of Helsinki.

The assessments, particularly the administration and scoring of the Mini-Mental State Examination, were conducted by trained professionals who were blinded to the participants' metabolic syndrome status to minimize assessment bias.

Inclusion Criteria

• Having a positive Covid-19 PCR test result

• COVID-19 follow-up clinics have been opened in certain centers across the country by the Republic of Turkey Ministry of Health to follow up on patients who had COVID-19. In our hospital, the task of managing this polyclinic has been undertaken by our department. Other units were also informed and asked to refer patients who had Covid-19 to our polyclinic for follow-up. Patients who have attended the COVID-19 follow-up clinic, since it is the unit where we can collect the data of patients who had COVID-19 and apply it to our hospital most comprehensively.

• Being 18 years of age or older

Exclusion Criteria

• Individuals diagnosed with dementia or Alzheimer's

• Pregnants

• Individuals without the requested laboratory tests

The study was completed with 375 patients, considering the inclusion and exclusion criteria, and the data were analyzed.

In our descriptive cross-sectional study, the Mini-Mental State Test, standardized according to the patients' education levels, was administered face-to-face during the examination, and all sections in the Public Health Management System COVID-19 Tracking Module were filled out. The MMSE was administered only to patients who met the inclusion criteria and were eligible for cognitive assessment. The choice of MMSE version was adjusted according to each participant's education level to ensure accuracy. Specifically, lower-educated patients received a simplified MMSE version, while higher-educated patients received the full version. This ensured the cognitive load was appropriate for each participant.

The Mini-Mental State Test, which measures mental status, is a scale that evaluates cognitive functions in five different parts (orientation, recall, attention and calculation, and language). The total score is 30. Those with scores of 24 and below ought to be examined for dementia. [19,20]

It has been reported to be highly correlated with similar screening tests, including the standardized and more comprehensive Wechsler Adult Intelligence Scale (WAIS) and the Modified Blessed Test, which assess cognitive functions. [21,22]

In our study, the Mini-Mental State Test was administered to individuals with five years or more of education, and the Mini-Mental State Test, designed for the uneducated, was administered to individuals with less than five years of education. 24-30 points are normal, 18-23 points are compatible with mild dementia, and 17 points and below are compatible with severe dementia.

Following the algorithm of the Republic of Turkey Ministry of Health for patients applying to the COVID-19 follow-up Polyclinic, fasting blood sugar, urea, creatinine, eGFR, uric acid, total cholesterol, triglyceride, HDL, LDL, non-HDL, VLDL, alt, ast, sodium, potassium, calcium, iron, iron-binding, magnesium, phosphorus, total iron binding capacity, CRP, HbA1c, hemogram, free T4, TSH, ferritin, vitamin B12, folate, aPTT, PT, INR, fibrinogen, d-dimer, chest X-ray and electrocardiography tests were performed on the patients.

The demographic information section in the Covid Tracking Module consists of questions about the patient's marital status, educational status, whether they have children, the number of children, who they live with, body weight, and blood type. The vaccination section includes information on how many doses of which COVID-19 vaccine the patient has received. In the habits section, the patient's smoking, alcohol, drug use, and exercise status were questioned. In the physical examination section, patients' vital signs, anthropometric measurement data, and all physical examination findings were recorded.

In the chronic diseases section, we questioned the patients about their chronic diseases, medications, and surgeries before and after the COVID-19 infection and recorded the answers.

In the IDF guideline, different threshold values for central obesity were accepted for different races, unlike the WHO and NCEP-ATP III guidelines (Table 1). We used the International Diabetes Federation (IDF) guideline for the diagnosis of metabolic syndrome in our research in terms of its suitability for our country.

We obtained the HDL, fasting blood glucose, and triglyceride parameters used to evaluate the metabolic syndrome of the patients from their examinations at the COVID-19 follow-up clinic.

Participants' anthropometric and blood pressure measurements were taken by the researcher and the nurse on duty at the COVID-19 follow-up clinic during the outpatient clinic visit.

Statistical Analysis

The SPSS 25.0 program was used for statistical analyses. While evaluating the study data, descriptive statistics (mean, standard deviation, median, minimum, maximum, difference between values, frequency, proportion) as well as the Kolmogorov-Smirnov test were used to check the conformity of continuous and discrete variables, including age, BMI, and mini-mental state test to normal distribution. Variables conforming to a normal distribution are presented with mean and standard deviation. One-way ANOVA test was used to compare three or more groups of normally distributed variables, the Bonferroni test was used to determine the group causing the difference, and the Student t-test was used in evaluations according to two groups. Variables that do not conform to a normal distribution are presented with median and standard deviation. The Kruskal-Wallis test was used to compare variables that did not show normal distribution between groups, the Dunn test was used to determine the group causing the difference, and the Mann-Whitney U test was used in evaluations according to two groups. The Pearson Chi-Square test was used to compare qualitative data in evaluating the relationships between variables. In chi-square analyses, the groups were combined when the expected value in the cells was below 5. (Dementia levels such as mild/severe dementia and normal, not using alcohol, such as using/quitting alcohol). In analyses comparing more than one group, post-hoc analyses were applied for the group that revealed the difference. The significance level was determined as $p<0.05$.

Primary variables affecting dementia were determined by Logistic Regression. Primary variables related to dementia were determined by applying Logistic Regression to gender, education level, employment status, alcohol grams, age, and metabolic syndrome, which were found to be associated with dementia at the $p < 0.20$ level in one-way analyses. Age grouping was made as follows: under 30 years old, 30-49 years old, 50-64 years old, 65 years old and above.

Results

The frequency of metabolic syndrome in women was 42.6% (n=104), and in men it was 55.0% (p=0.022). According to marital status, the prevalence of metabolic syndrome was 27.4% (n=17) in singles, 50.2% (n=150) in married individuals, and 64.3% (n=9) in divorced individuals (p=0.002). The frequency of metabolic syndrome according to age groups was 15.2% in those under 30, 35.5% in the 30-49 age group, 68.9% in the 50-64 age group, and 57.7% in the 65 and over age group. (p=0.0001) (Table 1)

Table 1. Distribution of metabolic syndrome frequency according to sociodemographic characteristics

	With Metabolic Syndrome		**Without Metabolic Syndrome**		**Total**		**p**
Gender	**n**	**%**	**n**	**%**	**n**	**%**	
Female	104	42.6	140	57.4	244	100.0	**0.022**
Male	72	55.0	59	45.0	131	100.0	
Marital status							
Single	17	27.4	45	72.6	62	100.0	**0.002**
Married	150	50.2	149	49.8	299	100.0	
Divorced	9	64.3	5	35.7	14	100.0	
Age							
Under 30	7	15.2	39	84.8	46	100.0	**0.0001**
30-49	55	35.5	100	64.5	155	100.0	
50-64	84	68.9	38	31.1	122	100.0	
65 and over	30	57.7	22	42.3	52	100.0	
Total	176	46.9	199	53.1	375	100.0	

The mean age of those with metabolic syndrome is 53.40±11.87, while it is 43.55±14.27 in those without metabolic syndrome. (p=0.0001). Table 2 shows the distribution of dementia levels by gender. The frequency of severe dementia is 5.0% in women and 0.0% in men. The frequency of mild dementia in women was 24.5%, while it was 22.5% in men (p=0.028). Severe dementia has begun to be seen in the 50 and above age group, while mild dementia has been seen in all age groups. (p=0.001) (Table 2)

Table 2. Level of dementia frequency distribution according to sociodemographic characteristics

	Severe Dementia		Mild Dementia		Normal		Total		p
Gender	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Female	12	5.0	59	24.5	170	70.5	241	100.0	**0.028**
Male	0	0.0	29	22.5	100	77.5	129	100.0	
Age									
Under 30	0	0.0	7	15.6	38	84.4	45	100.0	**0.001**
30-49	0	0.0	30	19.5	124	80.5	154	100.0	
50-64	6	5	28	23.3	86	71.7	120	100.0	
65 and over	6	11.8	23	45.1	22	43.1	51	100.0	
Total	12	3.2	88	23.8	270	73.0	370	100.0	

The frequency of dementia was 24.2% (n=15) in single, 27.2% (n=80) in married, and 35.7% (n=5) in widowed/divorced. (p=0.673). As the level of education increased, the prevalence of dementia decreased. The frequency of dementia was 68.0% (n=17) in those with no education, and 9.9% in those with university or higher education. (p=0.0001). The frequency of dementia in employees was 18.6% (n=32), while it was 34.3% (n=68) in unemployed individuals. (p=0.001) (Table 3)

Table 3. Frequency of dementia according to sociodemographic characteristics

	Dementia		Normal		Total		p
	n	**%**	**n**	**%**	**n**	**%**	
Marital status							
Single	15	24.2	47	75.8	62	100.0	
Married	80	27.2	214	72.8	294	100.0	0.673
Widow/Divorced	5	35.7	9	64.3	14	100.0	
Education							
No	17	68.0	8	32.0	25	100.0	**0.0001**
Primary/Secondary	43	27.7	112	72.3	155	100.0	
High school	30	33.7	59	66.3	89	100.0	
University/Higher	10	9.9	91	90.1	101	100.0	
Employment status							
Unemployed	68	34.3	130	65.7	198	100.0	**0.001**
Employee	32	18.6	140	81.4	172	100.0	
Total	100	23.8	270	73.0	370	100.0	

The frequency of metabolic syndrome was 56.0% in those with chronic diseases and 30.3% in those without chronic diseases. (p=0.0001). 30.9% of the participants have hypertension. The frequency of metabolic syndrome among individuals with hypertension is 68.1% and 37.5% in those without hypertension. (p=0.0001). 14.4% of participants have diabetes. The prevalence of metabolic syndrome was 88.9% among those with diabetes and 39.9% among those without diabetes. (p=0.0001). 4.8% of participants have cardiovascular disease. The frequency of metabolic syndrome among those with cardiovascular disease (83.3%) is significantly higher than the prevalence of metabolic syndrome among those without cardiovascular disease (45.1%). (p=0.002). Dementia was found in 27% of the participants. The frequency of metabolic syndrome was identified as 50% among those with dementia and 45.9% among those without dementia. (p=0.486) (Table 4)

Table 4. Frequency of metabolic syndrome according to disease status

		Metabolic Syndrome		Without Metabolic Syndrome		Total		p
		n	%	n	%	n	%	
Chronic disease								
	No	40	30.3	92	69.7	132	100.00	**0.0001**
	Yes	136	56.0	107	44.0	243	100.00	
Hypertension								
	No	97	37.5	162	62.5	259	100.00	**0.0001**
	Yes	79	68.1	37	31.9	116	100.00	
Diabetes								
	No	128	39.9	193	60.1	321	100.00	**0.0001**
	Yes	48	88.9	6	11.1	54	100.00	
Cardiovascular disease								
	No	161	45.1	196	54.9	357	100.00	**0.002**
	Yes	15	83.3	3	16.7	18	100.00	
Dementia								
	No	124	45.9	146	54.1	270	100.00	0.486
	Yes	50	50	50	50	100	100.00	
Total		176	46.9	199	53.1	375	100.00	

The severity of COVID-19 infection, hospitalization status, and symptom duration were not evaluated, which may limit interpretation regarding the impact on metabolic or cognitive status.

Although individuals with a previous diagnosis of dementia were excluded, cases of mild and severe cognitive impairment detected via the Mini-Mental State Examination during post-COVID follow-up were classified and analyzed as dementia for this study.

In the logistic regression analysis, the prevalence of dementia was identified as 2.9 times higher in non-university graduates. (p=0.004). Dementia is 1.8 times more common in women. (p=0.038). Each unit increase in age increases the risk of dementia by 1.039 times. (p=0.001) (Table 5)

Table 5. Primary variables associated with the presence of dementia (Logistic regression)

	B	SE	p	OR	%95 CI
Age	0.038	0.010	0.001	1.039	1.019-1.060
Not being a university graduate	1.094	0.377	0.004	2.937	1.427-6.252
Female gender	0.584	0.281	0.038	1.793	1.033-3.112
Metabolic syndrome	0.298	0.267	0.266	1.347	0.797-2.275

Discussion

We found a statistically significant relationship between age, education level, female gender, and the prevalence of dementia. (%95 CI, respectively OR:1.039; p=0.001, OR=2.937; p=0.004, OR=1.793; p=0.038).

Although the prevalence of dementia was higher in individuals with metabolic syndrome, the relationship was not statistically significant. (OR=1.347; p=0.266). Although a potential association was observed between metabolic syndrome and dementia, this finding did not reach statistical significance and should be interpreted cautiously.

In a study conducted in China with 9004 participants, the prevalence of dementia in women was identified as higher than in men, with a rate of 61.87%. (Zhou ve diğerleri, 2022).

A cohort study by the Mayo Clinic also showed that the risk of dementia was almost twice as high in women who had bilateral oophorectomy before menopause and that there was no increased risk of Alzheimer's in those who used hormone replacement therapy until at least the age of natural menopause. [23]

The reason for the higher frequency of dementia in women might be that dementia increases with age and the longer average lifespan of women, and may also be related to the hormonal decrease in estrogen after menopause. [24]

A study conducted at the University of Toronto comparing older adults aged 65 and over with younger adults aged 18 to 30 showed that older adults, especially those with higher levels of education, use the frontal cortex as an alternative pathway to aid cognition, and the higher the level of education, the more such asly they are to use the frontal cortex, resulting in better memory performance. [25]

In prospective cohort studies conducted on 1298 individuals in the United States and 1260 individuals in Spain, an increase in all dementia subtypes was observed with age. [26,27]

Because dementia is caused by diseases that damage the brain, including Alzheimer's disease or vascular diseases, it can take a long time to develop, and therefore, aging becomes a risk factor for dementia. Age also poses a risk for dementia, as older adults are more likely to have conditions including high blood pressure, damaged, twisted, or blocked brain vessels, increased risk of stroke, a weaker immune system, a slower ability to heal, and brain cells that are not as active as those of younger people. [28]

Previous studies investigating the association between metabolic syndrome and dementia have reported inconsistent results.

In a study conducted in South Korea with 84,144 individuals with 8 years of follow-up, metabolic syndrome was identified as associated with Alzheimer's (OR 11.48, 95% CI 9.03, 14.59, $p<0.0001$), but no association was found with vascular dementia (OR 1.17, %95 GA 0.94, 1.47, $p=0.158$). [29]

In the French Three-City cohort study conducted on 7807 people, it was found that metabolic syndrome increased the risk of vascular dementia ($p=0.01$) but did not increase the risk of Alzheimer's ($p=0.39$). [30]

The associations between metabolic syndrome and cognitive impairment varied according to the characteristics of the study population, the various criteria used to define metabolic syndrome, the different approaches used to assess cognitive function, and the different follow-up periods.

In conclusion, it should also be remembered that metabolic syndrome, which has turned into a global epidemic, may increase the prevalence of dementia. According to the principles of family medicine of assuming responsibility for the community and seeing problems at early/undifferentiated stages, we consider and recommend that necessary measurements be made in every patient applying to the outpatient clinic and that tests including the mini-mental status test, which could be performed in a short time but which can also reveal the risk of disease to a significant extent, be applied to patients to improve the health of the community and to provide material and moral benefits for the public good. As the level of education increases, the prevalence of both metabolic syndrome and dementia decreases. This indicates that raising an educated society can significantly reduce the burden on the health system. In this regard, the importance of providing at least an individual health and awareness education to society and practices aimed at increasing the level of general education is clearly felt.

Limitations

A major limitation of this study is the absence of detailed information regarding the severity of the participants' COVID-19 infections. Factors such as symptom duration, hospitalization, and treatment were not systematically recorded and could have influenced the outcomes. These should be explored in future research.

Ethical Considerations: This study was conducted with the approval of the Ethics Committee of Recep Tayyip Erdogan University (Date: 07.11.2022; No: 2022/189), and necessary institutional permissions were obtained.

Conflict of Interest: The authors declare no conflict of interest.

This study was presented at the 13th International Family Medicine Congress (AHEKON), held in Antalya, Turkey, on November 1–5, 2023.

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