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Ten-year cardiovascular disease risk and related factors in lifetime marijuana use with comorbid methamphetamine-associated psychotic disorder: a QRISK®3 study

Dilek Örüm[1], Mehmet Hamdi Örüm[2], Yaşar Kapıcı[3,4*] and Sabri Abuş[3]

Abstract

Background Methamphetamine use and related direct and indirect problems are increasing all over the world. The coexistence of lifetime marijuana use (LMU) and methamphetamine use disorder (MUD) may also be accompanied by psychotic symptoms (MAP). Methamphetamine and marijuana use are known to pose risks for cardiovascular diseases (CVDs). However, ten-year CVD risk and inflammation markers of LMU-MUD (non-psychosis group) and LMU-MAP (psychosis group) subjects and the relationship of various sociodemographic and clinical variables with these markers have not yet been examined.

Methods Thirty-two male subjects were included in non-psychosis group and 72 male subjects in psychosis group. Sociodemographic and clinical characteristics were recorded. Psychotic symptom severity of psychosis group subjects was measured. The ten-year CVD risk was calculated using QRISK®3 model.

Results Age, cigarettes/pack-years, alcohol use onset age, drug use onset age, methamphetamine use onset age, duration of methamphetamine use, education and marital status of the groups were similar ($p > 0.05$). There was a statistical difference between the non-psychosis and psychosis groups in terms of self-mutilation history ($p < 0.001$), suicidal attempt history ($p = 0.007$), homicidal attempt history ($p = 0.002$), psychiatric hospitalization history ($p = 0.010$). Ten-year QRISK®3 score was 4.90 ± 9.30 in the psychosis group, while it was 1.60 ± 1.43 in the non-psychosis group ($p = 0.004$). The mean heart age of the psychosis group was 14 years higher than their chronological age, while the mean heart age of the non-psychosis group was 8 years higher. Neutrophil to lymphocyte ratio (NLR) ($p = 0.003$) was higher in the psychosis group. A significant correlation was detected between ten-year QRISK®3 and positive psychotic symptoms in the psychosis group ($r = 0.274$, $p = 0.020$). Regression analysis showed that self-mutilation history, NLR and relative risk obtained from QRISK®3 can be used to distinguish non-psychosis group and psychosis group subjects (sensitivity = 91.7; Nagelkerke R^2 0.438; $p = 0.001$).

Conclusions This study is important as it demonstrates for the first time that among the subjects using marijuana and methamphetamine, those with psychotic symptoms have a higher NLR and ten-year CVD risk.

*Correspondence:
Yaşar Kapıcı
dryasarkapici@gmail.com

Full list of author information is available at the end of the article

Keywords Cardiovascular diseases risk, Methamphetamine, Psychosis, Marijuana, Cannabis, NLR, Self-mutilation

Background

Cardiovascular diseases (CVDs) are the leading cause of death globally, taking an estimated 17.9 million lives each year [1]. Although it varies depending on geographical differences, the incidence of CVDs is increasing all over the world due to age, metabolic factors such as obesity and high cholesterol, and smoking [2]. Drug use is another important cause of CVDs today. According to the 2023 World Drug Report, which includes 2021 data from the United Nations Office on Drugs and Crime, 296 million people worldwide use illegal drugs, including 219 million marijuana and 36 million amphetamines [3]. Numerous observational studies have demonstrated that marijuana use is associated with CVDs [4].

Methamphetamine, usually consumed in its crystallized form, carries one of the highest burdens of CVDs associated with drug use. The detrimental effect of methamphetamine on the cardiovascular system, which is associated with CVDs such as acute cardiovascular toxicity, hypertension related complications, Takotsubo cardiomyopathy, sudden cardiac death, heart failure, coronary artery disease, myocardial infarction, and stroke, involves various mechanisms such as tachycardia, a combination of excess catecholamine release leading to hypertension, coronary vasospasm, direct cytotoxic effect of increased reactive oxygen species and mitochondrial injury to cardiac myocytes [5, 6]. According to a study conducted in a large population of hospitalized patients, when compared with nonuse, methamphetamine use was associated with a 32% significant increase in CVD, and the majority of methamphetamine users were young males who smoked and misused alcohol [6]. Polydrug use, alcohol use, smoking, and some other unhealthy lifestyle habits increase the risk of methamphetamine use-associated CVD [5, 6].

Methamphetamine use may cause the emergence of new psychotic symptoms or exacerbation of existing psychotic symptoms in users. Although long-term use of methamphetamine is an independent risk factor for the development of psychosis, even a single use of methamphetamine can lead to psychotic symptoms [7]. Although the relationship between methamphetamine use disorder (MUD) and CVDs has been addressed in many studies with different designs, the risk of CVD in MUD-associated psychotic disorder (MAP) has not been adequately examined.

There is an increasing number of studies examining the ten-year CVD risk in psychiatric disorders [8]. In recent years, it has been suggested that QRISK®3 is more appropriate for use in psychiatric disorders compared to previous risk scores that examined CVD risk without including any psychiatric parameters. QRISK®3 is an updated web-based cardiovascular risk calculator that estimates CVD risk based on several demographic and clinical variables including "severe mental illness" and "on atypical antipsychotic medication" factors [9]. When the literature is examined, it is seen that the CVD risk in MAP has not yet been examined with scoring tools. Our aim in this study is to examine and compare the possible CVD risk in subjects of concomitant MUD or MAP in individuals with lifetime marijuana use (LMU) using QRISK®3. Our hypothesis is that psychosis group is associated with an increased risk of CVD.

Methods

Study design

This cross-sectional study was conducted at Elazığ Mental Health and Diseases Hospital (EMHDH) between February 1, 2024 and May 31, 2024. EMHDH is a mental health complex with a capacity of 450 inpatients, located in Elazığ province in eastern Turkey. It includes outpatient psychiatry clinics, closed inpatient psychiatry units, outpatient alcohol and substance treatment center (AMATEM) clinic, and inpatient AMATEM unit. In psychiatric inpatient units of EMHDH, detailed psychiatric interviews are conducted with inpatients. Verification of patient information is conducted by means of the patient's family members. In addition, the information received from patients and their relatives is subject to final verification via e-nabiz. The national patient registration system, e-nabiz, is a database that contains patient medical histories.

Definitons

AMATEM are centers where outpatient and inpatient treatment of addiction-related disorders is provided.

A cigarette pack-year is defined as the equivalent of smoking one pack of cigarettes a day for one year. There are 20 cigarettes in a pack, so if an individual smokes 20 cigarettes a day for one year, that's literally one pack-year [10].

Three or more marijuana uses in the past 30 days and/or 20 to 40+marijuana uses in past year was considered frequent marijuana use. Having smoked marijuana three times or more in the number of months since starting to use marijuana was considered LMU [11].

Log_{10} (triglyceride (TG)/high-density lipoprotein cholesterol (HDL-C)) is the formula used to compute the atherogenic index of plasma (AIP). AIP is valuable in predicting the risk of coronary artery disease in a low-risk population [12].

The Castelli Risk Index 1 (CRI-1), also known as cardiac risk ratio, reflects the formation of coronary plaques with a diagnostic value as good as the determination of total cholesterol. On the other hand, the CRI-2 has been shown to be an excellent predictor of CVD risk [13].

Inclusion and exclusion criteria

While establishing the inclusion and exclusion criteria, the aim was to increase the homogeneity of the study groups, and in accordance with this purpose, all cases other than LMU-MAP and LMU-MUD diagnoses were excluded. All patients hospitalized in any unit of EMHDH between the specified dates were evaluated for inclusion in the study. A total of 1353 subjects were hospitalized, 1227 subjects in closed psychiatry inpatient units and 126 subjects in inpatient AMATEM unit. Subjects without a diagnosis of drug, alcohol, and gambling use disorder were excluded from the study ($n=1006$). Subjects hospitalized with alcohol ($n=46$) and gambling disorders ($n=4$) were excluded from the study. Subjects who were hospitalized with a diagnosis of drug use disorder but no drug was detected in laboratory analysis were excluded ($n=73$). Subjects diagnosed with comorbid drug use disorder and alcohol use disorder were excluded ($n=3$). Subjects diagnosed with drug use disorder and other primary psychiatric disorders were excluded ($n=11$). Subjects with multiple polydrug use disorders other than marijuana and methamphetamine were excluded ($n=6$). Subjects diagnosed with methamphetamine ($n=40$), marijuana ($n=39$), opioid ($n=17$), cocaine ($n=1$), ecstasy ($n=1$), and inhalant use disorder ($n=1$) were excluded. As a result, 32 male subjects with LMU, meeting the MUD diagnostic criteria, and being positive for methamphetamine and marijuana in laboratory analysis were included in the study (non-psychosis group). Also, 72 male subjects with LMU, meeting the MAP diagnostic criteria, and being positive for methamphetamine and marijuana in laboratory analysis were included in the study (psychosis group). There were no females among the subjects included in the study. All subjects ($n=104$) were regular cigarette smokers and had a history of alcohol use. None of the included subjects ($n=104$) had hypertension, diabetes mellitus, chronic kidney disease, rheumatoid arthritis, systemic lupus erythematosus, atrial fibrillation, severe neurological diseases other than migraine, immunological or systemic diseases, and received any medication. A semi-structured psychiatric interview lasting approximately 15–20 min was conducted with all the subjects ($n=104$) in order to exclude additional psychiatric disorders, and no additional psychiatric disorders were detected at the disorder level in any of the subjects [14]. Figure 1 shows the flow chart of inclusion. The diagnostic and statistical manual of mental disorders, 5th edition, text revised (DSM-5-TR) [15] was used in psychiatric diagnosis. A trained clinical psychiatrist confirmed the psychiatric diagnoses.

The information obtained from the subjects was verified through the *e-nabiz* application, the national medical registration system, is a database where all medical histories of individuals (surgery, hospitalization, laboratory, imaging, allergies, diagnoses, medications, vaccination schedule, cancer screening data, intensive care information, reports, emergency notes) can be accessed.

Procedure

Detailed laboratory analyzes are performed on all patients hospitalized at EMHDH. This laboratory analysis includes complete blood count (CBC), albumin, cholesterols, and C-reactive protein (CRP). Lymphocyte-related ratios, CRI-1, CRI-2, AIP, CRP to albumin ratio (CRP/Albumin) and monocyte to HDL-C ratio (M/HDL-C) were calculated.

Blood ethyl alcohol and urine drug analyzes are performed for all subjects hospitalized with a diagnosis of alcohol or drug use disorder.

Sociodemographic data and the psychometric scale scores of all subjects included were recorded. The ten-year CVD risk of the inpatients was calculated with the QRISK®3 model. All of these procedures were carried out following the patient's admission and before any medication administration or other interventions in order to prevent the results from being affected.

Measurements

At EMHDH, hospitalization decisions are made by psychiatrists. For the subjects hospitalized on the specified dates and eligible to be included in the study, the author who collected the data was informed by any psychiatrist who performed the hospitalization, and all data including sociodemography, psychometric scale, and laboratory analysis were obtained by a single author who is a five-year psychiatry specialist and trained in the administering psychometric scales used in this study.

Sociodemographic Form

Age, gender, education level, marital status, working status, mandatory military service status, self-mutilation history, suicide history, homicide history, prison history, probation history, drug use onset age, first drug used, first drug addicted, methamphetamine use onset age, methamphetamine use duration, psychiatric hospitalization history, outpatient psychiatric admission history, AMATEM hospitalization history, outpatient AMATEM admission history, hospitalization history with a diagnosis of MAP, smoking status, cigarette pack-year, alcohol use onset age, and exhibiting some of the characteristics of antisocial personality disorder (ASPD) as defined in

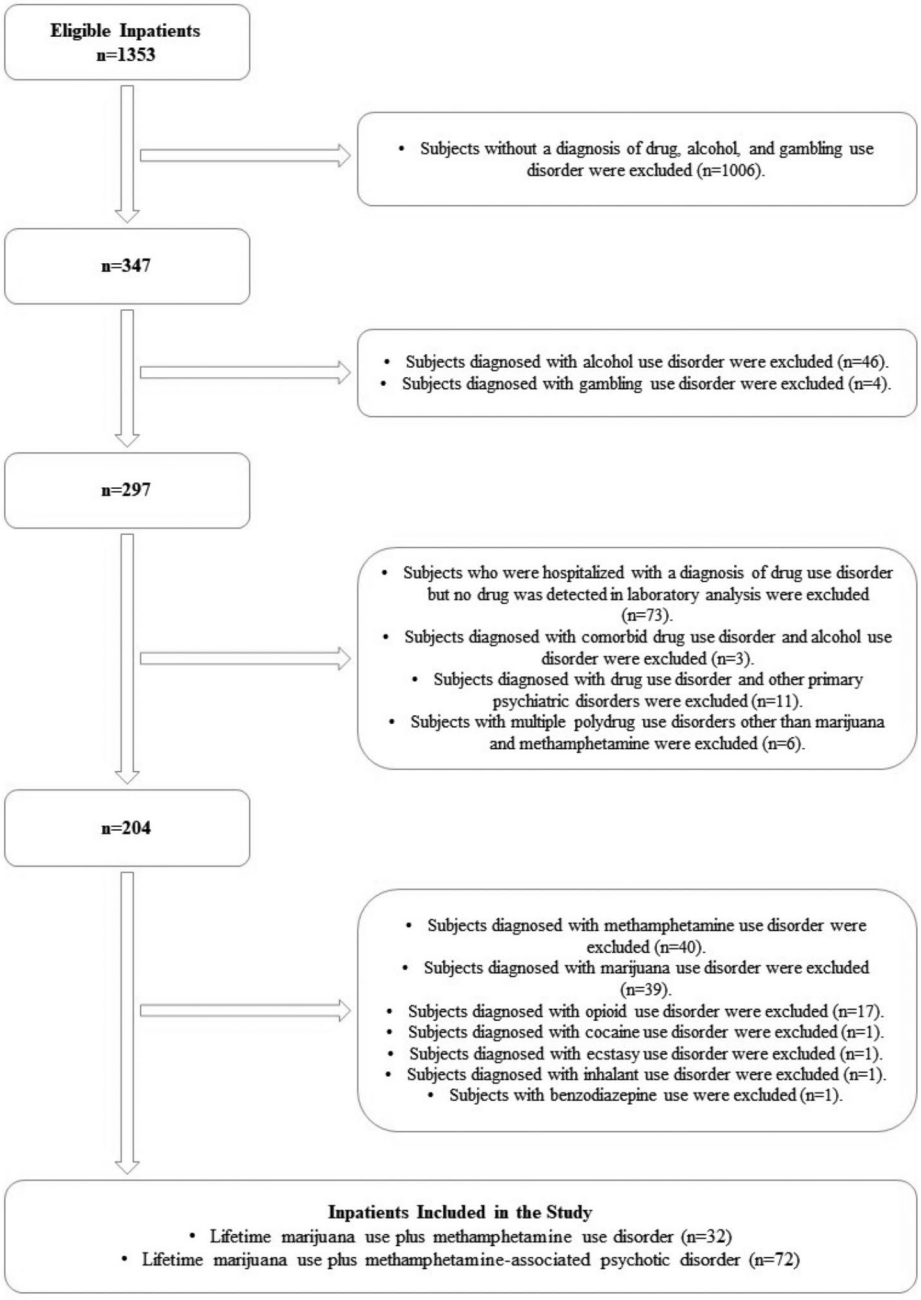

Fig. 1 Flowchart of Inclusion

the DSM-5-TR were among the sociodemographic factors considered.

The Scale for the Assessment of positive symptoms (SAPS) and the Scale for the Assessment of negative symptoms (SANS)

The SAPS and SANS were developed to fill a conspicuous gap in tools that could effectively measure the severity of negative and positive symptoms in psychotic processes [16]. SANS and SAPS are both utilized frequently in clinical and research settings. Instructions for the scales are available at the beginning of the forms. Scales are scored based on the interview with the patient, observations during the interview, and information obtained from people around the patient. The scales provide a six-point Likert type measurement, and the scoring of each item varies between 0 and 5. Subscale total scores are obtained by summing the subscale items, and the scale total score is obtained by summing the subscale total

scores. These scales were administered only to the psychosis group.

SAPS includes four subscales including hallucination, delusion, bizzare behaviour, positive formal thought disorder and 34 items. Items 1–7 belong to hallucination, items 8–20 belong to delusion, items 21–25 belong to bizzare behavior, and items 26–34 belong to positive formal thought disorder subscales. Total score varies between 0 and 170.

SANS includes five subscales including affective blunting, alogia, avolition/apathy, anhedonia/asociality, attention and 25 items. Items 1–8 belong to affective blunting, items 9–13 belong to alogia, items 14–17 belong to avolition/apathy, items 18–22 belong to anhedonia/asociality, items 23–25 belong to attention.

The schedule for assessing the Three Components of Insight (SAI)

With the idea that insight cannot be evaluated as whether it is present or absent, David [17] developed the SAI, which is administered by the clinician and evaluates insight quantitatively, based on three components such as awareness of having a mental illness, compliance with treatment, and the ability to relabel unusual mental events as pathological. It is a semi-structured scale consisting of eight questions and administered by the clinician. The highest total score is 18. A patient's high score indicates a high level of insight. In this study, all of the subjects included in the group defined as LMU-MAP had psychotic symptoms. In the subjects included in the group defined as LMU-MUD, there were no psychotic symptoms, that is, there was no impairment in their insight. Since SAI investigates the components of insight, it was administered only to the psychosis group (LMU-MAP group).

QRISK®3 model

Hippisley-Cox et al. [9] described the QRISK model and updated the model as QRISK®3 in 2017 [9]. The QRISK®3 model calculated ten-year cardiovascular disease and heart age according to demographic and clinical variables. These variables are listed as follows: age, gender, ethnicity, smoking status, diabetes status, angina or heart attack in a first-degree relative under 60 years old, chronic kidney disease (stage 3, 4 or 5), atrial fibrillation, blood pressure treatment, migraine, rheumatoid arthritis, systematic lupus erythematosus, severe mental illness, atypical antipsychotic medication, steroid use, erectile dysfunction, total cholesterol to HDL-C ratio, systolic blood pressure, height, and weight. After the parameters are entered into the web-based QRISK®3 calculator, four data appear as output: 'Your ten-year QRISK®3 score', 'the score of a healthy person with the same age, gender, and ethnicity', 'relative risk', 'your QRISK®3 healthy heart age'. 'The score of a healthy person with the same age, gender, and ethnicity' means with no adverse clinical indicators and a cholesterol ratio of 4.0, a stable systolic blood pressure of 125, and body mass index of 25. 'Your relative risk' is your risk divided by the healthy person's risk. 'Your QRISK®3 healthy heart age' is the age at which a healthy person of your gender and ethnicity has your ten-year QRISK®3 score.

Laboratory analysis

Venous blood and urine samples were examined at hospital admission. CBC parameters were measured using an automated hematology analyzer CELL-DYN Ruby (Abbott Diagnostics, USA) and expressed as ×1000 cells/mm^3. Using commercial kits from Abbott Diagnostics the levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), TG, and HDL-C were examined. Beckman Coulter AU480 Biochemical Auto-Analyser (Beckman Coulter, Inc.; CA, USA) device was used in urine toxicology. The reference ranges of the substances were as follows: marijuana (0–50 ng/mL), methamphetamine (0-500 ng/mL), opioid (0-2000 ng/mL), cocaine (0-150 ng/mL), ecstasy (0-500 ng/mL).

Ethical approval

was obtained from the Fırat University Non-invasive Research Ethics Committee and the 1964 Declaration of Helsinki was complied with (Date: 01/02/2024; Number: 2024/02–40). All respondents provided their consent for the information provided to be used for research purposes.

Statistical analysis

Windows SPSS 26.0 (Statistical Package for the Social Sciences Inc.) was used for the statistical analysis. Continuous variables and descriptive statistics are presented as mean ± standard deviation, while categorical variables are presented as frequency and percentage. The categorical data were analysed using the chi-square test. The Kolmogorov-Smirnov test was used to determine whether a normal distribution was appropriate. Independent-samples t-test was used to make comparisons between two groups to determine significant differences between groups. ROC curve analysis was used to measure the diagnostic value of various parameters. Pearson correlation analysis was performed. Binary logistic regression analysis was used in psychotic disorder prediction. Hedges' *g*, which provides a measure of effect size weighted according to the relative size of each sample, is an alternative where there are different sample sizes. In the present study, Hedges' *g* was calculated to determine the effect size. A value of less than 0.05 (p value) was considered statistically significant.

Results

There were 72 males in the psychosis group and 32 males in the non-psychosis group. The groups were similar in terms of mean age ($p=0.494$), mean education level ($p=0.058$), marital status ($p=0.273$), mandatory military service status ($p=0.586$), prison history ($p=0.108$), probation history ($p=0.522$), exhibiting ASPD traits as defined in the DSM-5-TR ($p=0.895$), outpatient psychiatric admission history ($p=0.295$), AMATEM hospitalization history ($p=0.973$) and outpatient AMATEM admission history ($p=0.356$), drug use onset age ($p=0.451$), methamphetamine use onset age ($p=0.504$), duration of methamphetamine use ($p=0.971$), age of starting cigarette smoking ($p=0.480$), cigarettes/pack-years ($p=0.455$), and alcohol use onset age ($p=0.593$) (Table 1).

There was a statistical difference between the psychosis and non-psychosis groups in terms of various variables. In the psychosis group, the rate of self-mutilation history ($p<0.001$), suicidal attempt history ($p=0.007$), homicidal attempt history ($p=0.002$), and psychiatric hospitalization history ($p=0.010$) was higher (Table 1).

The findings of the comparison of QRISK®3 parameters of the groups are shown in Table 1. While the groups were similar in terms of score of healthy person ($p=0.187$), they were different in terms of ten-year QRISK®3 score ($p=0.004$), relative risk ($p<0.001$), and QRISK®3 healthy heart age ($p=0.005$) (Table 1).

The SAI score of the psychosis group was determined as 4.75±4.24.

In the correlation analysis performed in the psychosis group, significant relationships were detected between

Table 1 Sociodemographic and clinical variables of participants

Parameters	Psychosis group (*n* = 72) mean ± SD & *n*	Non-psychosis group (*n* = 32) mean ± SD & *n*	*p* value
Age (years)	30.72 ± 6.30	31.65 ± 6.63	0.494
Education level (years)	8.19 ± 2.54	9.28 ± 2.67	0.058
Marital status (single/married/divorced)	42/22/8	14/15/3	0.273
Working status (no working/irregular/regular)	40/25/7	11/12/9	0.031*
Mandatory military service status (did not/did/certificate of disability for discharge)	11/37/24	7/17/8	0.586
Self-mutilation history (yes/no)	60/12	16/16	< 0.001**
Suicidal attempt history (yes/no)	31/41	5/27	0.007*
Homicidal attempt history (yes/no)	72/0	28/4	0.002*
Prison history (yes/no)	37/35	21/11	0.108
Probation history (yes/no)	58/14	24/8	0.522
ASPD traits as defined in the DSM-5-TR	60/12	27/5	0.895
First drug used (marijuana/methamphetamine/inhalant/ecstasy)	59/2/9/2	28/1/2/1	0.821
First drug addicted (marijuana/methamphetamine/inhalant/ecstasy)	66/2/2/2	30/2/0/0	0.478
Psychiatric hospitalization history (yes/no)	40/32	9/23	0.010*
Outpatient psychiatric admission history (yes/no)	49/23	25/7	0.295
AMATEM hospitalization history (yes/no)	29/43	13/19	0.973
Outpatient AMATEM admission history (yes/no)	43/29	16/16	0.356
Drug use onset age (years)	15.50 ± 3.08	15.09 ± 2.23	0.451
Methamphetamine use onset age (years)	26.98 ± 6.71	27.93 ± 6.39	0.504
Duration of methamphetamine use (years)	3.73 ± 2.51	3.71 ± 1.54	0.971
Marijuana use onset age (years)	15.76 ± 2.90	15.31 ± 2.27	0.438
Duration of marijuana use (years)	14.95 ± 6.34	16.34 ± 7.02	0.323
Age of starting cigarette (years)	13.59 ± 2.02	13.31 ± 1.82	0.480
Cigarettes/pack-years	22.26 ± 11.08	20.59 ± 8.95	0.455
Alcohol use onset age	16.16 ± 2.34	15.90 ± 2.13	0.593
Having angina or heart attack in a first degree relative < 60 years (yes/no)	21/51	6/26	0.263
Ten-year QRISK®3 score	4.90 ± 9.30	1.60 ± 1.43	0.004*
Score of a healthy person with the same age, gender and ethnicity (QRISK®3)	0.72 ± 1.45	0.47 ± 0.44	0.187
Relative risk (QRISK®3)	8.25 ± 8.40	3.86 ± 2.31	< 0.001**
QRISK®3 healthy heart age (years)	44.98 ± 10.84	39.87 ± 6.98	0.005*

*$p<0.05$, **$p<0.001$; Independent-samples t-test and Chi-square test were used. *Abbreviations* Psychosis group=Lifetime marijuana use plus methamphetamine-associated psychotic disorder (LMU-MAP); Non-psychosis group=Lifetime marijuana use plus methamphetamine use disorder (LMU-MUD); SD=Standard deviation; ASPD=Antisocial personality disorder; DSM-5-TR=Diagnostic and statistical manual of mental disorders, fifth edition, text revision; AMATEM=Alcohol and substance treatment centre

CBC parameters, lymphocyte-related ratios, CRI-1, CRI-2, AIP, and CRP/Albumin ratio of the psychosis and non-psychosis groups were calculated (Table 2)

Table 2 Laboratory analysis of participants

Parameters	Psychosis group ($n=72$) mean ± SD	Non-psychosis group ($n=32$) mean ± SD	p value	Hedges' g
TG (mg/dL)	125.28 ± 78.54	155.93 ± 90.85	0.108	0.36
Total cholesterol (mg/dL)	167.76 ± 44.12	167.21 ± 28.78	0.949	0.01
HDL-C (mg/dL)	49.08 ± 10.95	51.84 ± 12.77	0.264	0.18
LDL-C (mg/dL)	92.43 ± 27.92	86.12 ± 27.92	0.325	0.22
CRP turbidimetric (mg/L)	5.95 ± 13.97	2.64 ± 2.51	0.190	0.28
WBC (10^9/L)	9.13 ± 2.58	7.78 ± 1.90	0.011*	0.56
PLT (10^9/L)	278.98 ± 65.72	304.96 ± 74.61	0.095	0.38
MPV (fL)	8.83 ± 0.95	8.46 ± 0.66	0.049*	0.42
LYM (10^9/L)	5.42 ± 30.31	9.40 ± 42.99	0.590	0.11
MONO ((10^9/L)	0.85 ± 0.89	0.71 ± 0.24	0.399	0.18
NEU (10^9/L)	7.29 ± 6.51	5.04 ± 1.72	0.008*	0.40
EOS(10^9/L)	0.21 ± 0.32	0.21 ± 0.11	0.992	0.01
BASO(10^9/L)	0.010 ± 0.008	0.007 ± 0.004	0.016*	0.42
NLR	4.17 ± 3.11	2.86 ± 1.29	0.003*	0.48
PLR	167.03 ± 79.34	173.57 ± 60.68	0.647	0.09
MLR	0.46 ± 0.27	0.39 ± 0.13	0.115	0.29
ELR	0.09 ± 0.06	0.12 ± 0.08	0.158	0.27
BLR	0.006 ± 0.005	0.004 ± 0.003	0.022*	0.44
CRI-1	3.53 ± 1.08	3.40 ± 0.94	0.530	0.12
CRI-2	2.01 ± 0.75	1.76 ± 0.69	0.168	0.26
AIP	2.77 ± 1.86	3.34 ± 2.41	0.201	0.24
CRP/Albumin	0.13 ± 0.33	0.05 ± 0.04	0.106	0.29
M/HDL-C	0.018 ± 0.020	0.014 ± 0.006	0.180	0.28

*$p<0.05$, **$p<0.001$; Independent-samples t-test was used. *Abbreviations*: Psychosis group=Lifetime marijuana use plus methamphetamine-associated psychotic disorder (LMU-MAP); Non-psychosis group=Lifetime marijuana use plus methamphetamine use disorder (LMU-MUD); SD=Standard deviation; TG=Triglyceride; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; CRP=C-reactive protein; WBC=White blood cell; PLT=Platelet count; MPV=Mean platelet volume; LYM=Lymphocyte count; MONO=Monocyte count; NEU=Neutrophil count; EOS=Eosinophil count; BASO=Basophil count; NLR=Neutrophil to lymphocyte ratio; PLR=Platelet to lymphocyte ratio; MLR=Monocyte to lymphocyte ratio; ELR=Eosinophil to lymphocyte ratio; BLR=Basophil to lymphocyte ratio; CRI-1=Castelli risk index 1; CRI-2=Castelli risk index 2; AIP=Aterogenic index of plasma, CRP/Albumin=CRP to albumin ratio; M/HDL-C=Monocyte count to HDL-C ratio

ten-year QRISK®3 score and SAPS-delusion ($r=0.326$, $p=0.005$), SAPS-positive formal thought disorder ($r=0.263$, $p=0.026$), SAPS-total ($r=0.274$, $p=0.020$).

In the correlation analysis performed by controlling the effect of age in the psychosis group, a significant relationship was detected between ten-year QRISK®3 score and CRI-1 ($r=0.312$, $p=0.008$). There was no significant correlation between ten-year QRISK®3 score and cigarette pack-years ($r=0.176$, $p=0.145$).

In the correlation analysis performed by controlling the effect of age in the psychosis group, no significant relationships were detected between cigarette pack-years and CRI-1 ($r=0.298$, $p=0.116$), CRI-2 ($r=0.241$, $p=0.209$), AIP ($r=0.099$, $p=0.610$).

Table 3 Binary logistic regression analysis of psychosis and non-psychosis groups

Independent Variables	B	Sig.	Exp (B)	95% C.I. for EXP (B)	
				Lower	Upper
Self-mutilation history	1.965	0.001*	7.136	2.131	23.897
Relative risk of QRISK®3	0.328	0.003*	1.388	1.119	1.722
NLR	0.479	0.009*	1.615	1.126	2.316
Constant	-2.847	0.001*	0.058		

*$p<0.05$; *Abbreviations*: Psychosis group=Lifetime marijuana use plus methamphetamine-associated psychotic disorder (LMU-MAP); Non-psychosis group=Lifetime marijuana use plus methamphetamine use disorder (LMU-MUD); NLR=Neutrophil to lymphocyte ratio; Binary logistic regression analysis was used; Model Summary: In beginning block, -2 log-likelihood=128,386[a]; In block one, -2 log-likelihood=89.675[a], Cox & Snell $R^2=0.311$; Nagelkerke R^2 0.438; Hosmer and Lemeshov test $p=0.190$

In the correlation analysis performed in the psychosis group, significant relationships were detected between SAPS-delusion and CRI-1 ($r=0.352$, $p=0.003$), CRI-2 ($r=0.316$, $p=0.050$), AIP ($r=0.325$, $p=0.008$).

In the correlation analysis performed in the non-psychosis group by controlling th effect of age, no significant relationship was detected between ten-year QRISK®3 score and cigarette pack-years ($r=0.109$, $p=560$).

Binary logistic regression analysis was performed to determine the dependent variables that predicted the study group with psychotic symptoms. Binary logistic regression analysis was applied separately for each independent variable. According to the binary logistic regression analysis, the p value of relative risk of QRISK®3, self-mutilation history, and neutrophil to lymphocyte ratio (NLR) was determined to be less than 0.05. Data from the binary logistic regression model were presented in Table 3. According to the binary logistic regression analysis, the sensitivity of our model was 91.7, and the specificity was 50.0%.

ROC curve analysis performed on the basis of 72 psychosis group subjects and 32 non-psychosis group subjects. The area under the ROC curve of relative risk of QRISK®3 was 0.794 ($p<0.001$; 95% CI (0.695–0.893)). The area under the ROC curve of the QRISK®3 healthy heart age was 0.639 ($p=0.024$; 95% CI (0.527–0.750)).

Discussion

The present study aimed to investigate ten-year CVD risk and its correlation with symptom severity in patients diagnosed with LMU-MAP. The main findings of the present study are (i) Ten-year QRISK®3 risk score of the patients with psychosis is 4.90%, relative risk is 8.25, and their mean heart age is almost 14 years higher than their chronological heart age, (ii) Ten-year QRISK®3 risk of the patients with non-psychosis group is 1.60%, relative risk is 3.86, and their mean heart age is almost 8 years higher than their chronological heart age, (iii) Severity of positive symptoms and total cholesterol to HDL-C ratio are

positively correlated with ten-year CVD risk in patients with psychosis. The fact that the age, cigarette smoking onset age, cigarettes/pack-years, alcohol use onset age, drug use onset age, methamphetamine use onset age, duration of methamphetamine use, education and marital status of the subjects included in this study were similar and that all the subjects were males and smokers of cigarettes and marijuana reduced the limitation and facilitated the interpretation of the findings.

One of the variables that constitutes QRISK®3 is cigarette smoking. It has been reported in many studies that cigarette smoking status is higher in drug users than in the general population. It has also been shown that polydrug users are more likely to be cigarette smokers than monodrug users [18]. Although the mechanisms underlying why cigarette smoking increases the risk of CVD have not yet been clearly revealed, it is suggested that smoking may cause this by increasing inflammation, thrombosis, and oxidation of low-density lipoprotein cholesterol [19]. All of the subjects included in this study were heavy cigarette smokers and this formed one of the most important reasons for the high ten-year CVD risk in this presented study. However, the fact that all cases were heavy smokers and the cigarette pack-years of the groups were similar may be the possible reason why no significant correlation was detected between the ten-year QRISK®3 score and cigarette pack-years in both groups. Also, whether there is a distinct direct dose-dependent correlation between cigarette smoke exposure and risk is debatable, as some recent experimental clinical studies have shown a non-linear relation to cigarette smoke exposure [19, 20].

Severe mental illness, one of the variables queried in QRISK®3, is covered for all subjects in the psychosis group. This contributes to the finding that the ten-year CVD risk of the psychosis group was significantly higher than that of the non-psychosis group. Conditions associated with marijuana and methamphetamine may require different treatment approaches. In subjects where these drugs cause psychotic disorders, treatment may become more challenging. Antidepressants and benzodiazepines are psychotropics frequently used in both conditions [21, 22]. While antipsychotics are used to reduce impulsivity, for treatment augmentation, and to treat insomnia in drug use disorders that are not accompanied by psychotic disorder, they are used to improve psychotic symptoms in psychotic disorders due to drug use [22]. Atypical antipsychotics, which are frequently used in drug use-associated psychotic disorder, are strongly associated with metabolic syndrome through mechanisms involving weight gain, dyslipidemia, insulin resistance, and hypertension [23]. It has long been known that metabolic syndrome is an independent risk factor for increased CVDs [24]. Indeed, atypical antipsychotic use is a variable of QRISK®3 [9]. The fact that the psychosis group subjects included in this study had a history of hospitalization with a diagnosis of MAP is one of the findings that may explain the increased ten-year CVD risk in this group. Atypical antipsychotics used in the treatment of psychosis group cause dyslipidemia and hyperinsulinemia, and therefore, it is likely to cause metabolic syndrome [25]. On the other hand, drug use causes QRISK®3 scores to be lower than the normal population because it reduces appetite, lowers body mass index, reduces blood glucose, cholesterol, and triglyceride levels [26]. It is possible that the history of hospitalization was higher in the psychosis group than in the non-psychosis group and that atypical antipsychotics were administered to these subjects during these hospitalizations. This feature may explain the potential impact of possible differences in the rates of history of atypical antipsychotic use on the findings.

Unlike Framingham Risk Score and other CVD risk calculation algorithms, QRISK®3 includes the presence of severe mental illness and the use of atypical antipsychotic medications to calculate CVD risk. This feature makes QRISK®3 superior to other CVD risk calculators [8]. However, it is known that methamphetamine use directly and indirectly causes CVDs through different mechanisms than the variables questioned in QRISK®3. Alcohol use, which has a close relationship with CVDs [27], is also more common in drug users and is not included in QRISK®3 [28]. In this sense, newer CVD risk calculators that query variables related to methamphetamine and other drugs are needed.

The incidence of self-mutilation, suicide, and homicide behaviors is increasing in various drug use, especially hallucinogen and methamphetamine, and in personality disorders [29]. The majority of the subjects included in this study had antisocial personality disorder traits and polydrug use, which may have led to a higher rate of self-mutilation, suicidal attempt and homicidal attempt history. In this study, it was determined that self-mutilation history is a significant parameter that can be used to distinguish subjects with and without psychotic symptoms. However, based on the available data, it is not possible to claim that self-mutilation is directly related to a history of psychotic disorder. Further studies are needed to clarify the source of this finding. Another variable that affects the frequency of these risky behaviors is the presence of psychotic symptoms. Risky behaviors were found to be significantly higher in the subjects with psychotic symptoms included in this study than in those without psychotic symptoms. In addition, the history of psychiatric hospitalization is more common in drug use accompanied by psychotic symptoms. It appears that the findings of this presented study are compatible with the literature. In the study conducted by Al-Imam et al. [30], it was reported that methamphetamine use for more than

one year and the incidence of visual hallucinations made users more susceptible to ideas of suicide. It is stated that those who admit to the emergency department with methamphetamine intoxication may be violent, agitated and suicidal [31]. Kuo et al. [32] reported that a history of suicidal attempts and additional psychiatric symptoms predict future suicide attempts. Unadkat et al. [33] showed that methamphetamine use was associated with a 21.7% rate of admission to an acute psychiatric inpatient unit, half of these admisions showed aggression against the staff, and most of the subjects had psychotic symptoms. It was reported in the same study that 65.7% of methamphetamine users in the emergency department exhibited aggressive behavior towards the staff and 50% towards other patients. McKetin et al. [34] reported that hostility is detected more frequently in MAP. It has been stated that hostility increases as the severity and duration of psychotic symptoms increases [34].

Another important finding of this study is that it compared the inflammatory parameters of non-psychosis group and psychosis group subjects and reached significant findings in terms of white blood cell (WBC), mean platelet volume (MPV), neutrophil count, basophil count, basophil to lymphocyte ratio (BLR) and NLR. There are various studies in the literature examining CBC parameters in methamphetamine-related situations. In their study comparing MUD subjects with healthy controls, Gürbüzer et al. [35] showed that the leukocyte, platelet, neutrophil, monocyte, NLR, platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR) levels of the MUD group were significantly increased compared to the healthy control group. Additionally, in the same study [35], it was reported that M/HDL-C ratio and CRP levels were higher than the healthy control group. In their study comparing MUD and healthy control groups, Turan et al. [36] reported that WBC, neutrophil, monocyte, platelet, NLR, and MLR levels were higher in the MUD group than in the healthy control group. In the study of Ng et al. [37], it was determined that the NLR and MLR values of MAP subjects were higher than the healthy control group. In this study, CBC parameters of non-psychosis group and psychosis group subjects were compared and it was demonstrated that WBC, MPV, neutrophil, basophil, NLR, and BLR were significantly higher in psychosis group. These findings support the literature that psychotic symptoms are associated with increased inflammation. Cholesterol, triglyceride, albumin, and CRP levels were found to be similar between the groups. CBC parameters in marijuana use disorder have been examined in various studies. In the study conducted by Örüm and Kara [38], it was reported that monocyte count and MLR increased significantly in subjects with marijuana use disorder compared to the healthy control group. Alshaarawy [39] reported that WBC count was higher among heavy marijuana users when compared to never users. Amaechi et al. [40] reported that the platelet levels of marijuana users were lower and the lymphocyte levels were higher than healthy controls. The findings of this study show laboratory data of subjects using marijuana and methamphetamine together.

Methamphetamine use is associated with an increased incidence of psychosis. McKetin et al. [41] stated that the persistent MAP was associated with delusions of reference, thought interference and complex auditory, visual, olfactory, and tactile hallucinations, while primary psychosis was also associated with delusions of thought projection, erotomania and passivity. The positive and negative symptoms of the psychosis group subjects included in this study were measured using a scale, and the relationship between these symptoms and various clinical parameters was examined. Accordingly, a positive significant relationship was detected between the ten-year QRISK®3 score of psychosis group subjects and the positive symptom scores of delusion and positive formal thought disorder and the total positive symptom score. In the correlation analysis, where the effect of age was controlled, a significant positive relationship was detected between the ten-year QRISK®3 score and CR1. Additionally, significant positive relationships were found between the delusion subscale score and cholesterol and triglyceride values. These findings support that psychotic symptoms may be associated with an increased risk of metabolic syndrome and CVD. A model consisting of variables that can be used to predict possible psychotic symptoms in subjects with LMU and MUD/MAP was created. It was suggested that self-mutilation history, relative risk obtained from QRISK®3, and NLR could be used for this purpose.

The most important strength of this study is that it examines the relationship between psychotic symptoms and CVD risk and inflammatory markers for the first time in male subjects where lifetime marijuana use is accompanied by methamphetamine use, together with sociodemographic and clinical variables. The cross-sectional nature of this study is the most important limitation. Although subjects with drug use other than marijuana and methamphetamine were excluded, the possible effect of the drugs used by the subjects in the past on the results was not excluded. The effect of possible drugs that were not detected in laboratory analyzes and could affect the results could not be excluded. The possible impact of subthreshold psychiatric symptoms on outcomes is unknown. It is possible that unregistered medications that were not reported and not included in the e-pulse application were used by the subjects. This study examines data on male subjects, and it is not appropriate to comment on female subjects with similar characteristics based on these findings. Considering the

well-established effect of sex, which refers to the biological characteristics of an individual as determined by chromosomal complement and sex hormones [42], on CVD risk, it is indisputable that studies addressing both genders are needed.

Conclusion

This study examined the ten-year CVD risk, CBC parameters including lymphocyte-related ratios, cholesterol, and triglyceride values of non-psychosis group and psychosis group subjects and reported that the ten-year CVD risk of patients with psychotic symptoms was higher. A significant association was found between positive psychotic symptoms and ten-year CVD risk. It has been shown that inflammation markers including neutrophil and basophil in psychosis group subjects are higher than in non-psychosis group subjects. It has been emphasized that the self-mutilation history, suicidal and homicidal attempts is higher in psychosis group subjects than in non-psychosis group subjects. It demonstrates that self-mutilation history, relative risk obtained from QRISK®3 and NLR can be used to distinguish non-psychosis and psychosis group subjects. The findings of this study need to be examined with further longitudinal studies.

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Author contributions
Concept – DÖ, MHÖ, SA; design – DÖ, MHÖ, YK; supervision –YK, SA; resource –MHÖ; materials – MHÖ; data collection and/or processing –MHÖ, SA; analysis and/or interpretation – MHÖ, YK, SA; literature search – DÖ, MHÖ, SA; writing – DÖ, MHÖ; critical reviews – DÖ, YK, SA. All authors contributed to and have approved the final manuscript.

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Data availability
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Fırat University Non-invasive Research Ethics Committee and the 1964 Declaration of Helsinki was complied with (Date: 01/02/2024; Number: 2024/02–40). All respondents provided their consent for the information provided to be used for research purposes.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Elazığ Fethi Sekin City Hospital, Elazığ, Turkey
[2]Elazığ Mental Health and Diseases Hospital, Elazığ, Turkey
[3]Adıyaman University Faculty of Medicine, Adıyaman, Turkey
[4]Department of Psychiatry, Adıyaman University, Adıyaman, Turkey

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