Development of Objective Measure of Psychotropic Substances Abuse Using Automatic Retinal Image Analysis (ARIA)
利用全自動化視網膜圖像分析技術(ARIA)建立一套精神藥物濫用的檢測標準

Project Reference No.:	BDF180054
Name of grantee:	Centre for Clinical Research and Biostatistics, Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong
Principal Investigator:	Prof. Marc CHONG Assistant Professor, Jockey Club School of Public Health and Primary Care
Co-Investigator(s):	Prof. Benny ZEE Professor / Director, Centre for Clinical Research and Biostatistics Ms. Maria LAI Deputy Director / Nursing Officer, Centre for Clinical Research and Biostatistics
Collaboration parties:	Cheer Lutheran Centre Rainbow Lutheran Centre
Date:	July 2022

Background

In Hong Kong, the total number of substance abusers has steadily declined for the past decade. It decreased from 11572 in 2011 to 5 569 in 2020, a 4% decline from 5 772 in 2019, and 22 per cent of them were polydrug abusers. Despite the decreasing trend, hidden drug abuse and youth drug abusers remain a significant concern locally. According to a report from the Central Registry of Drug Abuse, substance abusers tended to take drugs at hidden locations, including friends' homes [1]. Young substance abusers were commonly found taking drugs at parties, and around 20% of drug-taking students reported that they usually used drugs alone [2]. These concerns challenged the detection of substance abuse, resulting in a delayed identification with treatment as well as a rehabilitation process

Hong Kong shares the problem of increasing abuse of psychotropic drugs with China and the United States [3,4]. Compared to 58.6% in 2007, 61.7% of total drug abusers in Hong Kong will be using psychotropic substances in 2020 [1]. Methamphetamine's popularity has increased from 8.2% to 22.2% within the same period and is now the leading drug abused by young people [1]. A disordering use of psychotropic drugs could result in death and many other adverse health effects, including stroke [5], brain function impairments [6-9], and cardiovascular diseases [10].

In Hong Kong, rehabilitation program and facilities focus on facilitating abusers to quit drugs, controlling of withdrawal or psychological symptoms and providing mental assistance to both abusers and their families. However, adequate monitoring of abusers' condition or rehabilitation progress is reliant on clinical manifestations and psychological expressions from abusers themselves. Moreover, with the increasing trend of late identification of drug abusers, there is a greater need for a rapid and accurate assessment of abusers' health condition, monitoring, or even rapid identification of risk of drug-abuse-related complications.

Automatic Retinal Image Analysis (ARIA) is an advanced non-invasive technology that can screen for different diseases by analyzing a retinal image of an individual at a relatively low cost. ARIA enables a prediction without intensive training or the presence of professional physicians, making it an ideal tool for vast coverage of the population [11]. So far, ARIA has already been tested in various brain conditions and has shown to be effective. A study conducted in Hong Kong on patients with diabetes suggested that retinal characteristics obtained by ARIA could be used for stroke risk assessment quickly and automatically, with a sensitivity of 94.7% [12,13]. ARIA was also able to detect severe white matter hyperintensities in the brain of asymptomatic older adults with a high sensitivity of 92.9%, and the prediction resulted in a high agreement with the traditional Magnetic resonance imaging (MRI) approach [14].

Supported by literature [15,16], psychotropic substances could result in brain damage. Based on the application potentials of ARIA, we hypothesized the effect of psychotropic substances on brain health could be reflected by retinal vascular structure and measured by ARIA technology, as a procedure traditionally done by MRI screening. In this study, we

aim to develop a set of objective measures for detecting psychotropic substance abuse using the ARIA technology. There are two major objectives: 1. To compare the retinal image characteristics of drug abusers under rehabilitation versus age-gender matched healthy subjects, and 2. To establish a prediction model of ARIA for detecting abusers of psychotropic substances.

Methods

Case and control study design

This was a case-control study conducted in Hong Kong. Case subjects were defined as adults who have been or were now abusing psychoactive substances and have registered with local drug treatment and rehabilitation centres. Control subjects were general adults without drug-taking history.

Subject recruitment

Case subjects were recruited from *Cheer Lutheran Centre* and *Rainbow Lutheran Centre*, two counselling centres for psychotropic substance abusers that help substance abusers detox from drugs and reconstruct a healthy life. Control subjects were chosen from an extensive population of people recruited from the general population.

All individuals who satisfied the inclusion criteria were invited to join the study. The inclusion criteria were: 1) equal or greater than the age of 18; 2) case subjects had a history of psychoactive substance abuse; 3) control subjects had no history of psychoactive substance abuse; 4) being willing to sign the informed consent form and comply with the procedures required in the study. The exclusion criteria were: 1) under the age of 18; 2) having inadequate retinal image quality that could not be used in the analysis, such as wearing coloured contacts; 3) having eye diseases that were not able to take retinal images, such as severe cataract, glaucoma, atretopsia, and corneal mucous plaque; 4) unable to sit in the chair for retinal imaging; 5) distressed by the flashlight or having had a photosensitive seizure; 6) unwilling or unable to comply with the procedures required in the study.

Data collection of retinal characteristics

On the day of recruitment, a Canon non-mydriatic digital camera CR-2 was used to photograph the retinal fundus in both eyes of all eligible subjects, with the fovea in the centre. Before analysis, the retinal image quality of each subject was examined, and the images with inadequate quality, such as vessels that were undetectable or not clear enough to identify, were excluded. Next , retinal images were uploaded to an online server with specific algorithms based on previously established models to generate retinal characteristics. ARIA employed fractal analysis, high order spectral analysis, and statistical texture analysis as part of a three-phase analysis approach. The ARIA method was developed using R (University of Auckland, Auckland) and Matlab (MathWorks, Massachusetts, USA), and the detailed procedure can be found in Zee et al. [11].

In total, retinal characteristics from the left and right eyes were obtained by ARIA, including central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE), arteriole-venule ratio (AVR) calculated as the ratio of CRAE to CRVE, bifurcation coefficient of arteriole (BCA) and venule (BCV), bifurcation angle of arteriole (BAA) and venule (BAV), angular asymmetry of arteriole (AAA) and venule (AAV), tortuosity, haemorrhage, exudates, Arterio-venous (AV) nicking, and arteriole occlusions. The fractal analysis produced two fractal dimensions (Df) from the left and right eyes. These parameters are associated with different diseases related to the brain [16]. The different case groups generated several feature components via ARIA using the deep learning algorithms.

Data collection of demographics, substance abuse history, and health outcomes

During the recruitment, the case subjects were invited to complete a questionnaire including information on their demographics, substance abuse history, and self-reported health outcomes.

The demographics section collected information on age, sex, marital status, education, living condition, employment, and family history (i.e. substance abuse, alcoholism, and psychotic history of the subjects' first-degree relatives and partners. In addition, body weight and height were measured on the recruitment day.

The historical information on psychoactive substance abuse was collected, including the types of substances used, the number of days used in the past 30 days, the duration of substance abuse (in years), the age of initiation, monthly expenditure, and the history of anti-drug treatment and rehabilitation.

The self-reported health outcomes contained: lifestyle information, self-reported psychological conditions, and medical history. The lifestyle information included the subjects' smoking (never, ex-smoker, current smoker) and drinking (never, ex-drinker, current drinker) habits. Self-reported psychological conditions were reported as the frequency of psychological problems in the past 30 days, including depressed mood, mental strain, hallucination, and suicidal ideation. They were classified into three categories: no symptoms, in the short-term, or long-term. The medical history contained the history of chronic diseases (cardiovascular diseases, diabetes, hypertension, hypercholesterolemia, stroke, seizures, and psychiatric disorders) and the history of prescribed psychiatric medications and psychological/mood/psychiatric disorders treatments. To ensure the data validity, the psychiatric doctors in the recruitment centre have confirmed the information on the subjects' psychiatric diagnoses.

Sample size determination

To detect the differences of retinal characteristics between psychoactive substance abusers and general adults, we assumed that retinal characteristics by ARIA could distinguish 85% of subjects in all matched pairs and 65% of discordant pairs within the matched pairs (i.e. the case subjects had the retinal characteristics, but the control subjects did not). Based on

the assumptions, 100 cases were required to have an 80% power of detecting a significant difference using a two-sided test with a 5% type I error. Given a 1:2 matching ratio, 200 control subjects were required. A total sample size of 300 subjects was included in this investigation.

Data analysis

Categorical variables were reported as the number and percentage (n, %), and continuous variables were descriptively summarized as mean ± standard deviation (SD) or median (interquartile range, IQR). To compare continuous and categorical variables between the psychoactive substance abusers and the control subjects, the independent sample t-test and chi-square test were used, respectively, as univariate analysis. For analyzing categorical variables at more than 2 levels (e.g. classes of psychoactive substances), one-way ANOVA was used. If the corresponding assumptions were violated, Kruskal-Wallis one-way ANOVA or Welch's ANOVA was used. To identify significant retinal characteristics for abusers of psychotropic substances generated by the ARIA, we compared the retinal characteristics between the control subjects and the abusers using independent sample t-tests.

For the development of the prediction models, we used machine learning and deep learning techniques. We first applied a transfer net "ResNet50" convolutional neural network with retinal images as input and generated features based on pixels associated with the outcome, such as psychoactive substance abuse. We also extracted the texture/fractal/spectrum-related features associated with the outcome using the automatic retinal image analysis (ARIA) algorithm written in Matlab. We then used the Glmnet approach to select the most important subset of features based on the penalized maximum likelihood using R and Matlab. Finally, we translated the features extracted from machine-learning approaches to commonly used retinal characteristics. After the machine-learning steps are done, a logistic regression was employed including the identified significant retinal characteristics. A backward elimination procedure was carried out to develop a best fitted model after removing the redundant variables with p-values < 0.2. An internal validation and a leave-one-out cross-validation using the same set of data were conducted to evaluate the prediction performance. Classification sensitivity, specificity, accuracy, and area under the curve (AUC) of the receiver operating characteristic (ROC) curve were estimated as measures of prediction performance. A multiple linear regression analysis adjusting with the covariates was conducted to examine the association between retinal characteristics and the duration of substance abuse. The R-square was used to assess the prediction performance of the multiple linear regression model.

Apart from the primary analyses, we regrouped the psychoactive substance abusers into polydrug and non-polydrug abusers for subgroup analysis. A similar analysis procedure was carried out to evaluate the model prediction performance.

A p-value of less than 0.05 was defined as a statistical significance. EpiData 3.1 was used for data management, and for all analyses, SPSS 25.0 (Armonk, NY: IBM Corp) was employed.

Ethics

The ethics approval for this study was obtained from the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (reference number: 2019.440). During the informed consent procedure, the study objectives and overall requirements were informed to each potential subject. The investigator thoroughly explained the study to the subject, including reviewing the informed consent form and giving them a copy. If the subject agreed to participate in the study, they were asked to sign the written informed consent form. The subject and the investigator in charge of the consent process also signed the informed consent form. No personal information was collected during the study. Only subject numbers and initials were labelled on the images and questionnaires.

Results

The recruitment procedure is summarized in Figure 1. Of the 112 psychoactive substance abusers screened, 62 were from the Cheer Lutheran Centre, and 50 were from the Rainbow Lutheran Centre. After a data screening, 100 psychoactive substance abusers were recruited, and their retinal fundus images from both eyes were collected.

The mean age of the psychotropic substance abusers and the controls was 34.6 and 34.5 years, respectively, with 60% of males in both groups (Table 1). The mean BMI was 24.4 kg/m^2 and 23.8 kg/m^2 for the substance abusers and the control groups, respectively. Of all the psychoactive substance abusers, 83% were born in Hong Kong, 61% never married or currently cohabited, and 6% only completed primary school as their highest level of education. Public housing was the majority of housing reported by the substance abusers (62%), and a majority (89%) lived with their families or partners. Most of the cases got their full-time jobs (35%). Significantly higher proportions of the psychoactive substance abusers (87%) were smokers (87%, $p<0.001$) and drinkers (24%, $p<0.001$). In addition, a higher proportion of the substance abusers reported their medical histories (67%) compared to the controls ($p<0.001$).

As shown in Table 2, 15%, 11%, and 18% per cent of the substance abusers reported their first-degree relatives had a history of substance abuse, alcoholism, or psychotic problems, respectively. Methamphetamine (49%) and ketamine (48%) were the most often reported psychoactive substances, with average durations of abuse of 8.9 years and 9.3 years, respectively (Table 3). Approximately half of the psychoactive substance abusers (52%) were polydrug abusers. Of all self-reported psychological outcomes (Table 4), depressed mood was the most commonly reported condition, including both short-term (35%) and long-term (20%), followed by mental strain (35% and 11%, respectively).

In the comparison of the retinal characteristics between the control subjects and the psychoactive substance abusers (Table 5), exudates, BCV, BAA, and BAV were significantly different ($p<0.05$). For the fractal analysis, the Df in the substance abusers was significantly larger than in the control subjects in both the left ($p=0.012$) and right eye ($p=0.015$). The complex retinal characteristic components obtained by deep learning algorithms were all significantly different between the cases and controls ($p<0.001$).

To establish a prediction model of ARIA for detecting abusers of psychotropic substances, the significant variables were included in multivariate analysis as a prediction model building. Using logistic regression with backward elimination, BAV (adjusted odds ratio [OR]=0.733, 95% CI: 0.514-1.047, p=0.088) and exudates (adjusted OR=1.139, 95% CI: 1.033-1.257, p=0.009), as well as two complex retinal characteristic components, DL_PSAfeature001 (adjusted OR=0.026, 95% CI: 0.004-0.165, $p<0.001$) and DL_PSAfeature003 (adjusted OR=0.008, 95% CI: 0.001-0.039, $p<0.001$) were included in the model (Table 6). An internal validation and a leave-one-out cross-validation using the same set of data were conducted to evaluate the prediction performance. Using a cut-off value of 0.5 probability, the model with simple retinal characteristics and complex components exhibited a sensitivity of 94.0%, a specificity of 95.5%, and an accuracy of 95.0% (Table 7). The leave-one-out cross-validation was employed to avoid model overfitting, and the sensitivity and specificity were 94.0% and 95.0%, respectively. The AUC of ROC curve achieved 0.987 (95% CI: 0.974-0.999, $p<0.001$) (Figure 2).

To establish a prediction model of ARIA for detecting the length of substance abuse, a linear regression analysis with backward elimination was conducted (Table 8). Two fractal dimensions were significantly associated with the length of substance abuse, and tortuosity was additionally included in the model. The R-square of the model was 0.181.

In the subgroup analysis (Table 9), the polydrug abusers and the control subjects had significantly different BCA, BCV, exudates, BAA, and BAV ($p<0.05$). To establish a prediction model of ARIA for detecting polydrug abusers, a multiple logistic regression with backward elimination was built (Table 10). AVR, CRAE, CRVE, BCA, BAA, exudates, and DL_PAfeature002 were included in the model. In the internal validation using the same set of data, the model for predicting polydrug abusers exhibited a sensitivity of 90.4%, a specificity of 98.4%, and an accuracy of 96.7% (Table 11). The AUC of ROC curve achieved 0.997 (95% CI: 0.992-1.000, $p<0.001$) (Figure 3). A similar performance was observed when using the leave-one-out cross-validation.

Discussion

In drug abusers, brain damage can be typically observed through MRI, which is an expensive and relatively time-consuming procedure. However, ARIA is a well-developed technology in which many brain-related diseases are correlated with retinal vessel architecture. In this case-control study, we compared the retinal characteristics of drug abusers with that of healthy subjects and established a prediction model for identifying abusers of psychotropic substances. According to the results, several retinal characteristics,

fractal dimensions, and complex characteristic components were associated with the abuse of psychotropic substances. Compared with the findings by Leung et al. [14] showing cocaine abusers were associated with a larger bifurcation angle, our findings were reasonably consistent with them. We additionally demonstrated that the complexity and density of retinal vasculature as determined by the retinal image fractal analysis differed considerably between the psychoactive substance abusers and the control subjects, with the substance abusers having greater values of fractal dimensions. To the best of our knowledge, there is no study on psychoactive substance abusers investigating the retinal vascular complexity or providing a comprehensive picture of the retinal fundus image complexity. Thus, our findings suggested that psychoactive substance abuse induced alterations in the retinal vasculature, and retinal characteristics generated by ARIA with deep learning algorithms could distinguish psychoactive substance abusers from the general population.

Apart from identifying retinal characteristics for drug abusers, we developed multivariate models for a prediction of drug abusers utilizing the features of retinal images, and the prediction models were highly accurate (>90%) with outstanding discrimination power between drug abusers and non-abusers (AUC>0.90). While the performance was better than Qu et al. [18], showing the ARIA algorithm was able to achieve an accuracy of 85% for risk estimation of coronary heart disease, our findings are generally consistent with Lai et al. [19], demonstrating the AUC of ROC curve was 0.97 for classifying patients with autism spectrum disorder, provided that thinning of retinal nerve fibre layer was a risk factor. This is also echoed by Lau et al. [14], indicating a machine learning model accounting for ARIA features could generate >90% sensitivity and specificity for a prediction of the volume of white matter hyperintensities in the brain measured by MRI. Based on these observations, we speculate that retinal characteristics and ARIA features were more likely to relate to the diseases involving adverse brain conditions, corroborated by literatures showing brain damage could be led by abuse of psychotropic substances [15,16]. However, further research is warranted to confirm this clinical implications.

In this study, we showed the complexity and density of the blood vessels in the retina were associated with the length of substance abuse. The retinal asymmetry has been documented in the literature. Mahmudi et al. [20] measured retinal morphology using optical coherence tomography and summarised the asymmetric properties in the general population. Another paediatric study also suggested that the difference above a normal limit of retinal asymmetry was related to several pathological disorders [21].

Our study has several limitations. First, clinical information on the cases that may confound the study findings was lacking as our study was not conducted in a clinical setting. Second, our study did not restrict a specific type of psychoactive substance, making it difficult to generalize the link of the retinal characteristics to the risk of complications of a particular substance. Third, given the limited sample size, external validation of the prediction models was lacking. Hence, further investigations are recommended to ensure the validity of our study findings.

Implications

Using the retinal image via ARIA technology, we established a prediction model for identifying abusers of psychotropic substances. With the involvement of AI technology, the ARIA prediction greatly reduces the manpower for sample collection and laboratory assessment for traditional drug abuse screening, which is labor intensive and time-consuming. In addition, with the advanced development of portal and remote collection of fundus images [22], our prediction model is able to be adopted as a convenient, fast, and inexpensive screening tool for psychotropic substance abuse, especially for a telemedicine application. Apart from that, our study shows a high reliability of abuser discrimination. Hence, the tool is helpful to support clinicians and social workers for monitoring the effectiveness of treatment for the diseases of rehabilitee, allowing progress-based planning of rehabilitation programs. In our data, we also observed half of the substance abusers suffering from the mental health diseases such as depression and anxiety, and they lacked sufficient supports in treating their diseases. With the promising prediction performance of ARIA model, we expect the tool can be considered as an integrated intervention for guided treatment application, not only for reliving the substance addiction, but also for treating their diseases.

Conclusion

Our study identified the objective retinal measures for detecting psychotropic substance abuse using the ARIA technology. Furthermore, we demonstrated that retinal characteristics of ARIA, together with the complex retinal characteristic components generated by the deep learning algorithms, were associated with psychoactive substance abuse. Based on the identified features, the prediction models achieved outstanding performance in discriminating the abusers of psychoactive substances. With these promising findings, ARIA is expected to be a fast and inexpensive innovative tool for screening applications, for examples, effective monitoring of different anti-addiction treatments or rehabilitation programs for rehabilitee, thus helping clinicians and social workers plan suitable programs. Also, psychoactive substance abuse screening can be integrated into a physical examination in schools, to prevent youth drug abuse.

Reference

1. Narcotics Division Security Bureau. *Central Registry of Drug Abuse Seventieth Report 2011-2020*. (2020). doi:10.4325/seikeikakou.21.527

2. Narcotics Division Security Bureau. *2017/18 Survey of Drug Use among Students*. (2018).

3. 2007-2016 中国国家禁毒委员会办公室. 2016 年中国毒品形势报告. 中国禁毒网. 2017. Available from: http://www.nncc626.com/2017-03/27/c_129519255.htm

4. National Survey on Drug Use and Health (United States). Key Substance Use and Mental Health Indicators in the United States: Results from the 2016 National Survey on Drug Use and Health. 2017. Available from: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf

5. Westover, A. N., McBride, S. & Haley, R. W. Stroke in Young Adults Who Abuse Amphetamines or Cocaine. Arch. Gen. Psychiatry 64, 495 (2007).

6. Wollman, S. C. *et al.* White matter abnormalities in long-term heroin users : a preliminary neuroimaging meta-analysis. *Am. J. Drug Alcohol Abuse* **2990**, 133–138 (2015).

7. Krasnova, I. N. & Cadet, J. L. Methamphetamine toxicity and messengers of death. *Brain Res. Rev.* **60**, 379–407 (2009).

8. Potvin, S. *et al.* Cognitive deficits in individuals with methamphetamine use disorder: A meta-analysis. *Addict. Behav.* **80**, 154–160 (2018).

9. Sekine, Y. *et al.* Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. *Am. J. Psychiatry* **158**, 1206–1214 (2001).

10. Tait, R. J., Caldicott, D., Mountain, D., Hill, S. L. & Lenton, S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clin. Toxicol.* **54**, 1–13 (2016).

11. Zee B, Lee J, Li Q, “Method and Device for Retinal Image Analysis”, patent no, 20120257164, http://www.faqs.org/patents/app/20120257164

12. Zee, B. *et al.* Stroke Risk Assessment for the Community by Automatic Retinal Image Analysis Using Fundus Photograph. *Qual. Prim. Care* **24**, 114–124 (2016).

13. Zhuo, Y. *et al.* Prediction Factors of Recurrent Stroke among Chinese Adults Using Retinal Vasculature Characteristics. *J. Stroke Cerebrovasc. Dis.* **26**, 679–685 (2017).

14. Lau, A. Y. *et al.* Retinal image analytics detects white matter hyperintensities in healthy adults. *Ann. Clin. Transl. Neurol.* 1–8 (2018). doi:10.1002/acn3.688

15. Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, Gatley SJ, Miller E, Hitzemann R, Ding YS, Logan J. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. Journal of Neuroscience. 2001 Dec 1;21(23):9414-8.

16. Wang C, Zheng D, Xu J, Lam W, Yew DT. Brain damages in ketamine addicts as revealed by magnetic resonance imaging. Frontiers in neuroanatomy. 2013 Jul 17;7:23

17. Leung, I. Y.-F. *et al.* Early retinal vascular abnormalities in African-American cocaine users. *Am. J. Ophthalmol.* **146**, 612–619 (2008).

18. Qu Y, Lee JJ, Zhuo Y, Liu S, Thomas RL, Owens DR, Zee BC. Risk Assessment of CHD Using Retinal Images with Machine Learning Approaches for People with Cardiometabolic Disorders. Journal of Clinical Medicine. 2022 May 10;11(10):2687.

19. Lai M, Lee J, Chiu S, Charm J, So WY, Yuen FP, Kwok C, Tsoi J, Lin Y, Zee B. A machine learning approach for retinal images analysis as an objective screening method for children with autism spectrum disorder. EClinicalMedicine. 2020 Nov 1;28:100588.

20. Mahmudi, T., Kafieh, R., Rabbani, H., Mehri, A. & Akhlaghi, M. R. Evaluation of asymmetry in right and left eyes of normal individuals using extracted features from optical coherence tomography and fundus images. *J. Med. Signals Sens.* **11**, 12–23 (2021).

21. Altemir, I., Oros, D. & Eli, N. Retinal Asymmetry in Children Measured With Optical Coherence Tomography. *Am. J. Ophthalmol.* **156**, 1238–1243 (2013).

22. Panwar, N.; Huang, P.; Lee, J.; Keane, P.A.; Chuan, T.S.; Richhariya, A.; Teoh, S.; Lim, T.H.; Agrawal, R. Fundus Photography in the 21st Century—A Review of Recent Technological Advances and Their Implications for Worldwide Healthcare. Telemed. J. E Health 2016, 22, 198–208.

Table 1. Characteristics of the psychoactive substance abusers and the control subjects

Basic characteristics	**Psychoactive substance abusers (N=100)**	**Control subjects (N=200)**	**p-value**
Age *(mean ± SD, years)*	34.58 ± 8.77	34.45	0.899
Gender *(n, %)*			1.000
Male	60 (60.0%)	120 (60.0%)	
Female	40 (40.0%)	80 (40.0%)	
BMI *(mean ± SD, kg/m^2)*	24.39 ± 5.17	23.82 ± 3.90	0.337
Smoking *(n, %)*			**<0.001**
No	13 (13.1%)	169 (84.5%)	
Yes	86 (86.9%)	31 (15.5%)	
Alcohol drinking *(n, %)*			**<0.001**
No	75 (75.8%)	192 (96.0%)	
Yes	24 (24.2%)	8 (4.0%)	
Marital status *(n, %)*			
Never married/Cohabited	61 (61.0%)		
Married	19 (19.0%)		
Divorced/Separated	18 (18.0%)		
Education *(n, %)*			**<0.001**
Primary	6 (6.0%)		
Secondary	80 (80.0%)	81 (40.7%)	
Post-secondary	13 (13.0%)	31 (15.6%)	
Undergraduate		77 (38.7%)	
Postgraduate		10 (5.0%)	
Medical history *(n, %)*			**<0.001**
No	32 (33.0%)	189 (95.5%)	
Yes	65 (67.0%)	9 (4.5%)	
Cardiac diseases	1		
Eye injury	1		
Paroxysmal nocturnal dyspnoea	1		
Asthma	2		
Diabetes	2		
Seizures	2		
Urological diseases	2		

Anaemia	5	
Hypercholesterolemia	6	5
Hypertension	7	6
Psychiatric disorders	**54**	
Depression	22 (40.7%)	
Psychosis	17 (31.5%)	
Anxiety	9 (16.7%)	
Insomnia	6 (11.1%)	
Mood disorder	4 (7.4%)	
Attention deficit hyperactivity disorder	1 (1.9%)	
Adjustment disorder	1 (1.9%)	
Obsessive-compulsive disorder	1 (1.9%)	
Personality disorder	1 (1.9%)	
Schizophrenia	1 (1.9%)	
Housing *(n, %)*		
Public house	62 (62.0%)	
Private house	21 (21.0%)	
Homeownership scheme court	9 (9.0%)	
Hostel/Workplace	4 (4.0%)	
Residential care home	1 (1.0%)	
Street sleeper	1 (1.0%)	
Employment *(n, %)*		
Full-time (>40 hrs/week)	35 (35.0%)	
Housewife	19 (19.0 %)	
Unemployment	18 (18.0%)	
Casual work	14 (14.0 %)	
Part-time (steady)	9 (9.0%)	
Student	4 (4.0%)	

Table 2. Family history of the psychoactive substance abusers

	Substance abuse	Alcoholism	Psychotic disorders	Relationship
First-degree relatives	15 (15.0%)	11 (11.0%)	18 (18.0%)	Father (13, 41.9%) Mother (12, 38.7%) Brother (4, 12.9%) Sister (3, 9.7%) Younger sister (3, 9.7%) Younger brother (2, 6.5%)
Partners	7 (7.0%)	6 (6.0%)	5 (5.0%)	Husband (3, 30.0%) Boyfriend (3, 30.0%) Wife/Ex-wife (2, 20.0%) Girlfriend (2, 20.0%)

Statistics were reported as n, %.

Table 3. Psychoactive substance abuse experience according to the types

Psychoactive substance abusers (N=100)	**Using days in the past 30 days**	**Duration of abuse (in years)**	**Initial age (in years)**
Stimulants			
Methamphetamine (N=49)	6.63 ± 10.74	8.87 ± 7.11	19.00 ± 6.18
Cocaine (N=39)	3.93 ± 6.99	6.03 ± 5.40	22.15 ± 7.56
MDMA (N=22)	0.75 ± 1.5	3.86 ± 4.55	18.64 ± 4.90
Hallucinogens			
Ketamine (N=48)	9.67 ± 13.65	9.29 ± 5.81	17.88 ± 4.58
LSD (N=1)	-	-	18 ± 0.00
Cannabis			
Cannabis (N=28)	1.75 ± 2.06	5.90 ± 6.07	17.14 ± 3.94
Opiates			
Cough medicine (N=17)	22.17 ± 12.34	14.56 ± 10.51	19.12 ± 7.73
Heroin (N=4)	30 ± 0.00	15.00 ± 7.07	25.25 ± 12.15
Depressants			
Midazolam/Triazolam/Zopiclone (N=12)	12.00 ± 16.43	9.40 ± 7.41	32.08 ± 13.19
Methaqualone (N=2)	-	1.25 ± 1.06	14.00 ± 1.41
Nimetazepam (N=2)	-	1.00 ± 0.00	21.50 ± 4.95
Flunitrazepam (N=2)	-	0.5 ± 0.00	22.00 ± 8.49
Diazepam (N=1)			25.00 ± 0.00
Inhalants			
Organic solvent (N=1)	-	1 ± 0.00	14 ± 0.00

Statistics were reported as mean ± standard deviation. MDMA: Methylenedioxymethamphetamine

Table 4. Self-reported psychological outcomes of the psychoactive substance abusers

Self-reported psychological outcomes *(n, %)*	**Psychoactive substance abusers (N=100)**
Depressed mood	
Never	44 (44.9%)
Short-term	34 (34.7%)
Long-term	20 (20.4%)
Mental strain	
Never	53 (54.1%)
Short-term	34 (34.7%)
Long-term	11 (11.2%)
Hallucination	
Never	81 (85.3%)
Short-term	12 (12.6%)
Long-term	2 (2.1%)
Suicidal ideation	
Never	79 (83.2%)
Short-term	13 (13.7%)
Long-term	3 (3.2%)

Table 5. Comparison of the retinal characteristics between the control subjects and the psychoactive substance abusers

Retinal characteristics *(mean ± SD)*	**Control subjects (N=200)**	**Psychoactive substance abusers (N=100)**	**p-value**
lCRAE	13.72 ± 0.73	13.78 ± 0.67	0.481
lCRVE	20.52 ± 0.77	20.66 ± 0.74	0.115
lAVR	0.67 ± 0.02	0.67 ± 0.02	0.400
lBCA	1.65 ± 0.09	1.64 ± 0.10	0.226
lBCV	1.34 ± 0.03	1.34 ± 0.04	**0.063**
lBAA	72.87 ± 1.75	72.73 ± 1.83	0.544
lBAV	69.88 ± 1.84	69.49 ± 1.78	**0.081**
lAAA	0.82 ± 0.01	0.82 ± 0.02	0.130
lAAV	0.78 ± 0.01	0.78 ± 0.01	0.282
lTortuosity	0.26 ± 0.07	0.27 ± 0.07	0.895
lHaemorrhages	0.17 ± 0.06	0.18 ± 0.06	0.103
lExudates	0.12 ± 0.06	0.14 ± 0.07	**0.004**
lAV nicking	0.19 ± 0.07	0.18 ± 0.06	0.322
lArteriole occlusions	0.06 ± 0.05	0.06 ± 0.05	0.303
rCRAE	13.54 ± 0.66	13.46 ± 0.68	0.295
rCRVE	20.34 ± 0.74	20.25 ± 0.71	0.296
rAVR	0.67 ± 0.02	0.66 ± 0.02	0.520
rBCA	1.65 ± 0.10	1.63 ± 0.09	0.104
rBCV	1.31 ± 0.03	1.30 ± 0.03	**0.021**
rBAA	71.97 ± 1.80	72.87 ± 2.00	**<0.001**
rBAV	69.99 ± 2.09	70.69 ± 2.50	**0.016**
rAAA	0.83 ± 0.02	0.83 ± 0.01	0.943
rAAV	0.78 ± 0.01	0.78 ± 0.01	0.933
rTortuosity	0.30 ± 0.07	0.30 ± 0.07	0.473
rHaemorrhages	0.20 ± 0.07	0.20 ± 0.06	0.806
rExudates	0.13 ± 0.06	0.11 ± 0.06	**0.077**
rAV nicking	0.22 ± 0.07	0.22 ± 0.06	0.683
rArteriole occlusions	0.05 ± 0.03	0.05 ± 0.04	0.968
lDf	1.935 ± 0.01	1.937 ± 0.01	**0.012**
rDf	1.935 ± 0.01	1.938 ± 0.01	**0.015**
Deep learning feature 1	0.96 ± 0.15	0.14 ± 0.32	**<0.001**
Deep learning feature 2	0.04 ± 0.15	0.86 ± 0.32	**<0.001**
Deep learning feature 3	0.94 ± 0.20	0.06 ± 0.20	**<0.001**
Deep learning feature 4	0.06 ± 0.20	0.94 ± 0.20	**<0.001**

The prefix of each variables indicates left (l) or right (r) eye. Statistics were reported as mean ± standard deviation. Independent sample t-tests were used to obtain the p-values. Deep learning feature 1 – 4 are complex retinal characteristic components obtained by deep learning algorithms. CRAE: Central retinal arteriolar equivalent; CRVE: Central retinal venular equivalent; AVR: Arteriole-venule ratio; BCA: Bifurcation coefficient of arteriole; BCV: Bifurcation coefficient of venule; BAA: Bifurcation angle of arteriole; BAV: Bifurcation angle of venule; AAA: Angular asymmetry of arteriole; AAV: Angular asymmetry of venule, AV: Arterio-venous: Df: fractal dimensions produced by fractal analysis

Table 6. Prediction model for the psychoactive substance abusers with retinal characteristics

Retinal characteristics	Adjusted odds ratio	95% confidence intervals	p-value
lBAV	0.733	0.514, 1.047	0.088
lExudates	1.139	1.033, 1.257	**0.009**
Deep learning feature 1	0.026	0.004, 0.165	**<0.001**
Deep learning feature 3	0.008	0.001, 0.039	**<0.001**

BAV: Bifurcation angle of venule

Table 7. Prediction performance of the model using retinal characteristics in identifying psychoactive substance abusers

		Predicted				
		Control subjects	Psychoactive substance abusers	Sensitivity	Specificity	Accuracy
Original (n)	Control subjects (N=200)	191	9	94.0%	95.5%	95.0%
	Psychoactive substance abusers (N=100)	6	94			
Cross-validated (n)	Control subjects (N=200)	190	10	94.0%	95.0%	94.7%
	Psychoactive substance abusers (N=100)	6	94			

Table 8. Association between retinal characteristics and the length of substance abuse

Retinal characteristics	Estimate	Standard error	95% confidence intervals	p-value
lTortuosity	-19.856	10.133	-39.970, 0.258	0.053
lDf	320.034	139.281	43.562, 596.505	**0.024**
rDf	-481.151	124.655	-728.589, -233.712	**<0.001**

Df: fractal dimensions produced by fractal analysis

Table 9. Comparison of retinal characteristics between the psychoactive substance abusers who were polydrug abusers and who were not polydrug abusers and the control subjects

Retinal characteristics	Control subjects (N=190)	Polydrug abusers (N=52)	Non-polydrug abusers (N=48)	p-value[1]	p-value[2]
lCRAE	13.73 ± 0.71	13.76 ± 0.68	13.79 ± 0.78	0.778	0.821
lCRVE	20.53 ± 0.76	20.68 ± 0.73	20.64 ± 0.75	0.201	0.789
lAVR	0.67 ± 0.02	0.67 ± 0.02	0.67 ± 0.02	0.185	0.376
lBCA	1.66 ± 0.09	1.62 ± 0.09	1.66 ± 0.11	**0.024**	0.079
lBCV	1.34 ± 0.03	1.35 ± 0.04	1.34 ± 0.03	**0.020**	**0.040**
lBAA	72.89 ± 1.77	72.57 ± 1.83	72.92 ± 1.84	0.251	0.340
lBAV	69.84 ± 1.84	69.61 ± 1.77	69.35 ± 1.79	0.430	0.471
lAAA	0.82 ± 0.01	0.82 ± 0.02	0.82 ± 0.02	0.676	0.167
lAAV	0.78 ± 0.01	0.78 ± 0.01	0.78 ± 0.01	0.696	0.576
lTortuosity	0.27 ± 0.07	0.26 ± 0.07	0.27 ± 0.07	0.857	0.843
lHaemorrhages	0.17 ± 0.06	0.18 ± 0.06	0.19 ± 0.06	0.578	0.312
lExudates	0.12 ± 0.06	0.14 ± 0.07	0.14 ± 0.07	**0.020**	0.791
lAV nicking	0.19 ± 0.07	0.18 ± 0.05	0.18 ± 0.07	0.535	0.692
lArteriole occlusions	0.06 ± 0.05	0.06 ± 0.06	0.06 ± 0.04	0.316	0.676
rCRAE	13.56 ± 0.65	13.41 ± 0.69	13.51 ± 0.67	0.125	0.453
rCRVE	20.36 ± 0.73	20.15 ± 0.71	20.36 ± 0.70	**0.065**	0.135
rAVR	0.67 ± 0.01	0.67 ± 0.02	0.66 ± 0.02	0.676	0.569
rBCA	1.65 ± 0.10	1.63 ± 0.09	1.63 ± 0.09	0.125	0.842
rBCV	1.31 ± 0.03	1.30 ± 0.03	1.30 ± 0.03	**0.081**	0.585
rBAA	71.91 ± 1.77	72.52 ± 1.91	73.26 ± 2.05	**0.032**	0.064

rBAV	69.91 ± 2.09	70.64 ± 2.26	70.75 ± 2.76	**0.030**	0.830
rAAA	0.83 ± 0.02	0.83 ± 0.01	0.83 ± 0.01	0.621	0.451
rAAV	0.78 ± 0.01	0.78 ± 0.01	0.78 ± 0.02	0.586	0.412
rTortuosity	0.30 ± 0.07	0.29 ± 0.07	0.30 ± 0.07	0.325	0.332
rHaemorrhages	0.20 ± 0.07	0.20 ± 0.05	0.21 ± 0.06	0.828	0.194
rExudates	0.13 ± 0.06	0.11 ± 0.06	0.12 ± 0.06	**0.086**	0.464
rAV nicking	0.22 ± 0.07	0.21 ± 0.06	0.23 ± 0.07	0.183	0.091
rArteriole occlusions	0.05 ± 0.03	0.04 ± 0.03	0.05 ± 0.04	0.458	0.326
lDf	1.935 ± 0.01	1.937 ± 0.01	1.938 ± 0.01	0.261	0.591
rDf	1.935 ± 0.01	1.937 ± 0.01	1.939 ± 0.01	0.447	0.120
DL_PAfeature001	0.96 ± 0.17	0.11 ± 0.28		**<0.001**	
DL_PAfeature002	0.97 ± 0.12	0.11 ± 0.27		**<0.001**	
DL_PAfeature003	0.03 ± 0.12	0.89 ± 0.27		**<0.001**	

The prefix of each variables indicates left (l) or right (r) eye. Statistics were reported as mean ± standard deviation. Independent sample t-tests were used to obtain the p-values. Deep learning feature 1 – 4 are complex retinal characteristic components obtained by deep learning algorithms. p-value[1]: the comparison between the control subjects and the polydrug abusers. p-value[2]: the comparison between the substance abusers who were polydrug abusers and who were not. CRAE: Central retinal arteriolar equivalent; CRVE: Central retinal venular equivalent; AVR: Arteriole-venule ratio; BCA: Bifurcation coefficient of arteriole; BCV: Bifurcation coefficient of venule; BAA: Bifurcation angle of arteriole; BAV: Bifurcation angle of venule; AAA: Angular asymmetry of arteriole; AAV: Angular asymmetry of venule, AV: Arterio-venous: Df: fractal dimensions produced by fractal analysis

Table 10. Model with retinal characteristics for polydrug abuser characterization

Retinal characteristics	Adjusted odds ratio	95% confidence intervals	p-value
lAVR	0.122	0.020, 0.745	**0.023**
lBCA	0.904	0.809, 1.011	0.076
lExudates	1.243	0.948, 1.628	0.115
rCRAE	1.059	1.000, 1.121	**0.048**
rCRVE	0.962	0.923, 1.003	0.067
rBAA	2.866	1.061, 7.741	**0.038**
Deep learning feature 2	0.845	0.754, 0.948	**0.004**

CRAE: Central retinal arteriolar equivalent; CRVE: Central retinal venular equivalent; AVR: Arteriole-venule ratio; BCA: Bifurcation coefficient of arteriole; BAA: Bifurcation angle of arteriole

Table 11. Prediction performance of the model using retinal characteristics in identifying polydrug abusers

			Predicted				
			Control subjects	Psychoactive substance abusers	Sensitivity	Specificity	Accuracy
Original (n)	Control (N=190)	subjects	187	3	90.4%	98.4%	96.7%
	Polydrug (N=52)	abusers	5	47			
Cross-validated (n)	Control (N=190)	subjects	186	4	90.4%	97.9%	96.3%
	Polydrug (N=52)	abusers	5	47			

Figure 1. Flow of subject recruitment.

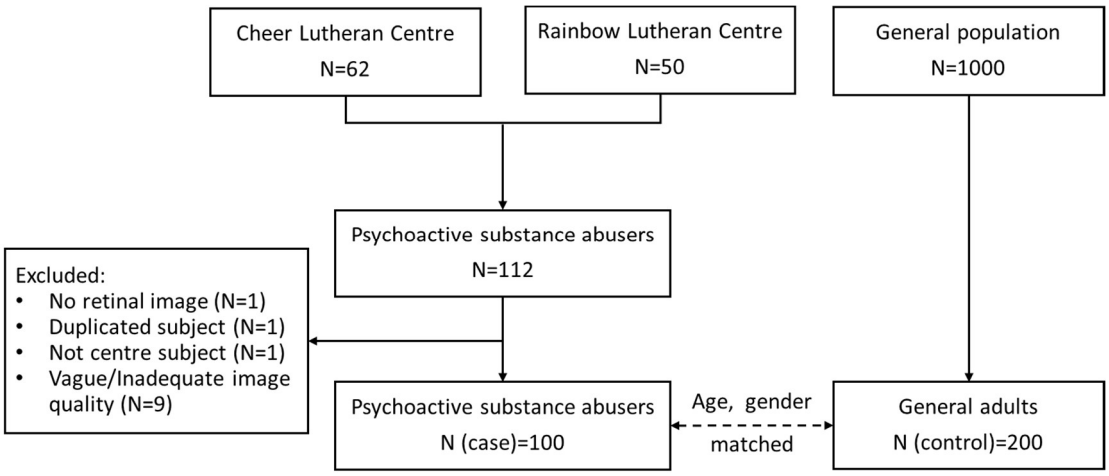

Figure 2. Receiver operating characteristic curve of the prediction model using retinal characteristics of ARIA.

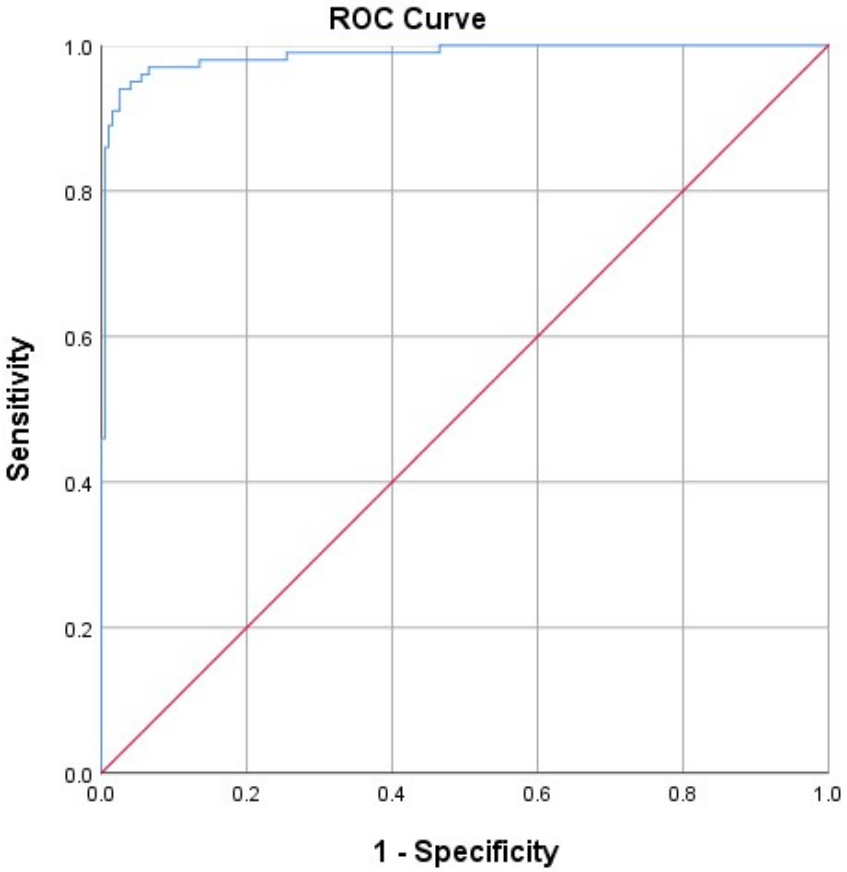

Figure 3. Receiver operating characteristic curve of the model for predicting polydrug abuser.