# 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

**Beat Drugs Fund 2018 Funding Exercise**
**Regular Funding Scheme**

Centre for Clinical Research and Biostatistics,
Jockey Club School of Public Health and Primary Care,
The Chinese University of Hong Kong

# Significance of the proposed study

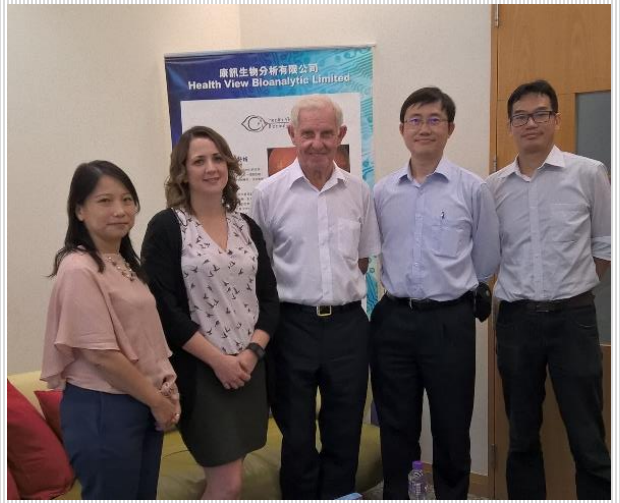
- Many literatures have shown that psychotropic substances may result in certain degree of damages in the brain, heart, and kidney. For example:
  - Long term use of marijuana has been found to associate with differences in grey matter in the brain and affect connectivity (Wang et al. 2013)
  - Lesions may be found in many regions of the brain of abusers 2-4 years after ketamine addiction (Filbey et al. 2014)
- Early detection and intervention may increase the chance of recovery and reduce the chance of recurrence
  - ARIA can be used for general health check including eye diseases such as macular edema due to extensive duration of computer gaming, and systemic diseases such as stroke, heart disease, kidney disease and diabetes.
  - Identification of substance abusers may be one of many objectives related to general health assessments, so that subjects such as students would be less resistant to the test.



**References**

- 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.
- Filbey FM, Aslan S, Calhoun VD, Spence JS, Damaraju E, Caprihan A, Segall J. Long-term effects of marijuana use on the brain. Proceedings of the National Academy of Sciences. 2014 Nov 25;111(47):16913-8.

# Automatic Retinal Image Analysis (ARIA) - Background




## Patents

- US Non-provisional (*US8787638 B2*) "Method and device for retinal image analysis", ***obtained July 2014***
- Taiwan Patent No. I578977 "Method and device for retinal image analysis", ***obtained April 2017***
- China Patent No. CN103458772B "视网膜图像分析方法和装置", ***obtained October 2017***

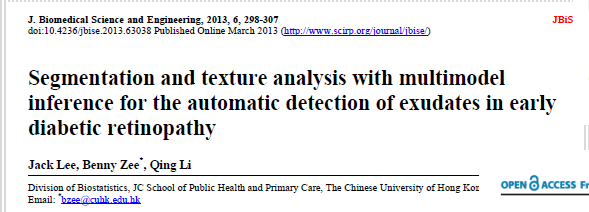
## Recent Awards

- Hong Kong Award for Industries 2018 - Equipment and Machinery Design Merit Award
- Bayer-HKSTP Grants4Apps Accelerator 2018
- Hong Kong Award for Industries 2016 – Technological Achievement Award
- Talent Unleashed Award 2016 "Best Startup - Social Impact", Asia-Pacific Region Finalist 2016
- 5th Bank of China "Technology Start-up " 『香港創新科技及製造業聯合總會』(FITMI) 第五屆中銀香港 Merit Award, 2015

## International Research Collaborations

- Diabetic Eye Screening Wales (DESW), United Kingdom with more than 180,000 diabetes patients with annual follow-up since 2003
  - Zee B, Lee J, Mok V, Thomas R, Owens D, "Early detection of dementia in subjects with type 2 diabetes based on white matter hyperintensities estimated by automatic retinal image analysis (ARIA) method", *Innovation Technology Funds (ITF) Midstream Research Program* (MRP/037/17X), 2018-2020
  - Zee B, Lee J, Wong M, and Owens D. "Retinal risk factors for stroke and coronary heart disease in patients with type 2 diabetes - Are they different?", *General Research Fund of RGC*, 2017 to 2019
  - Diabetic retinopathy and diabetic macular edema grading
- Strategy for Patient-Oriented Research (SPOR) Network in Diabetes and its Related Complications", Canadian Institute of Health Research

## *Publications (links)*


J. Biomedical Science and Engineering, 2013, 6, 298-307
doi:10.4236/jbise.2013.63038 Published Online March 2013 (http://www.scirp.org/journal/jbise)

JBiS

**Segmentation and texture analysis with multimodel inference for the automatic detection of exudates in early diabetic retinopathy**

Jack Lee, Benny Zee*, Qing Li

Division of Biostatistics, JC School of Public Health and Primary Care, The Chinese University of Hong Kong
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*Quality in Primary Care (2016) 24 (3): 114-124* ©2016 Insight Medical Publishing Group

Research Article

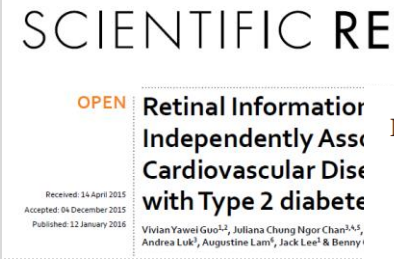
Stroke Risk Assessment for the Community by Automatic Retinal Image Analysis Using Fundus Photograph


OPEN ACCESS Freely available online PLOS ONE

**Detection of Neovascularization Based on Fractal and Texture Analysis with Interaction Effects in Diabetic Retinopathy**

Jack Lee, Benny Chung Ying Zee*, Qing Li

Division of Biostatistics, Jockey Club School of Public Health and Primary Care, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong


SCIENTIFIC REPORTS

OPEN

**Retinal Information Independently Associated with Cardiovascular Disease with Type 2 diabetes**

Received: 14 April 2015
Accepted: 04 December 2015
Published: 12 January 2016

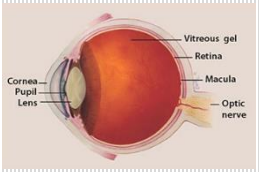
Vivian Yawei Guo[1,2], Juliana Chung Ngor Chan[3,4,5], Andrea Luk[3], Augustine Lam[6], Jack Lee[3] & Benny


**Prospective Association between Diabetic Retinopathy and Cardiovascular Disease—A Systematic Review and Meta-analysis of Cohort Studies**

Vivian Yawei Guo, PhD,*† Bing Cao, PhD,‡ Xinyin Wu, PhD,§ Jack Jock Wai Lee, PhD,* and Benny Chung-ying Zee, PhD*‖

# Health Promotion Tool for Risk Assessment in the Community

Stroke, Dementia
中風，認知障礙



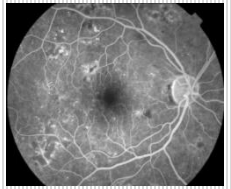

Vision Health
視力健康

Diabetes 糖尿病

Coronary Heart Disease
冠狀動脈心臟疾病

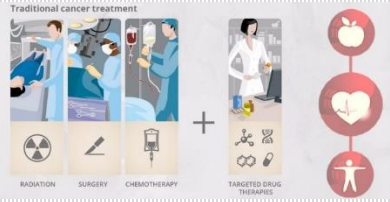
Chronic Kidney Disease
腎病

# Medical Device for Screening, Diagnosis and Prognosis in the Hospital

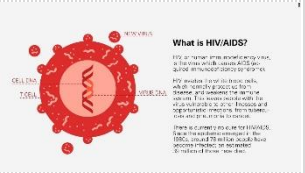


Diabetic Retinopathy, and AMD
糖尿病性視網膜病變及年齡相關性黃斑變性

Diabetic neuropathy
糖尿病神經病變




Cerebral & Cardio-toxicity for Cancer Treatment (e.g. NPC)
癌症治療後的心腦血管副作用




HIV Infection comorbidities
HIV病毒傳染病合併症

# Study rationale

- Automatic Retinal Image Analysis (ARIA) as a Screening Tool in the Community
  - **Fast, non-invasive, and completely digital without blood taking**
  - Ability in screening health and brain conditions e.g. Stroke and dementia

- We postulate that the effect of psychotropic substances to brain health could be reflected by retinal characteristics measured by ARIA technology, as a procedure traditionally done by MRI screening
- **Potential application in identification of drug abusers and monitoring the treatment/rehabilitation progress!**

# Study objectives

Objectives:

1. To compare the retinal images characteristics of drug abusers under rehabilitation versus age-gender matched healthy subjects
2. To establish a prediction model for detecting abusers of psychotropic substances

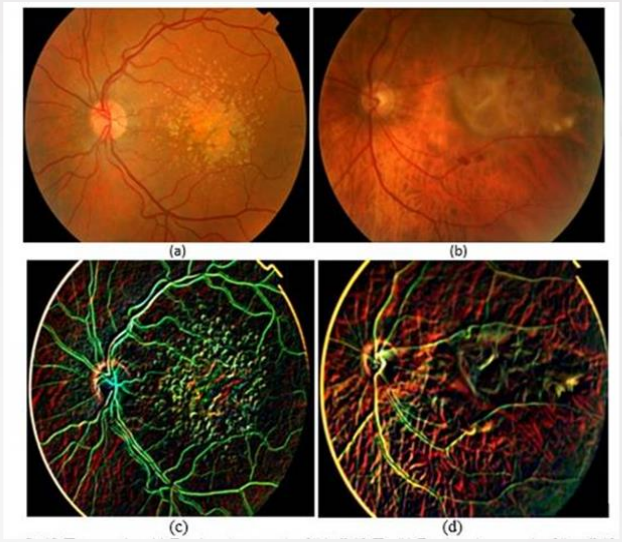
# Study design

- A case-control study matching the subjects by age and gender
- Sample size: 1:2 matching, 100 cases versus 200 controls
- Case subjects:
  1. They are adults aged ≥ 18 years;
  2. They had drug abuse experience before the screening date;
  3. Subjects do not have any eye diseases that are not suitable for retinal imaging
  4. Subjects will not be distress with flashlight or have experience with photosensitive seizure;
  5. They agree to join the study by signing the informed consent

- Control subjects: General population had no history of psychoactive substance abuse

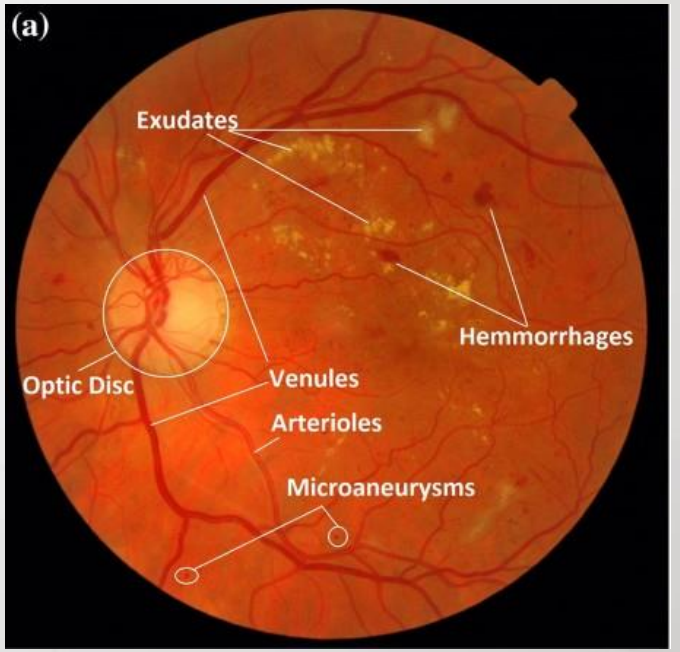
- Retinal images on both eyes were taken from all subjects
- No personal information was collected and disclosed.
- Assisted by **Cheer Lutheran Centre** (香港路德會青欣中心) and **Rainbow Lutheran Centre** (香港路德會青彩中心)

# Measurements





- **Retinal information**: 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, arteriole occlusions, fractal dimensions (Df).



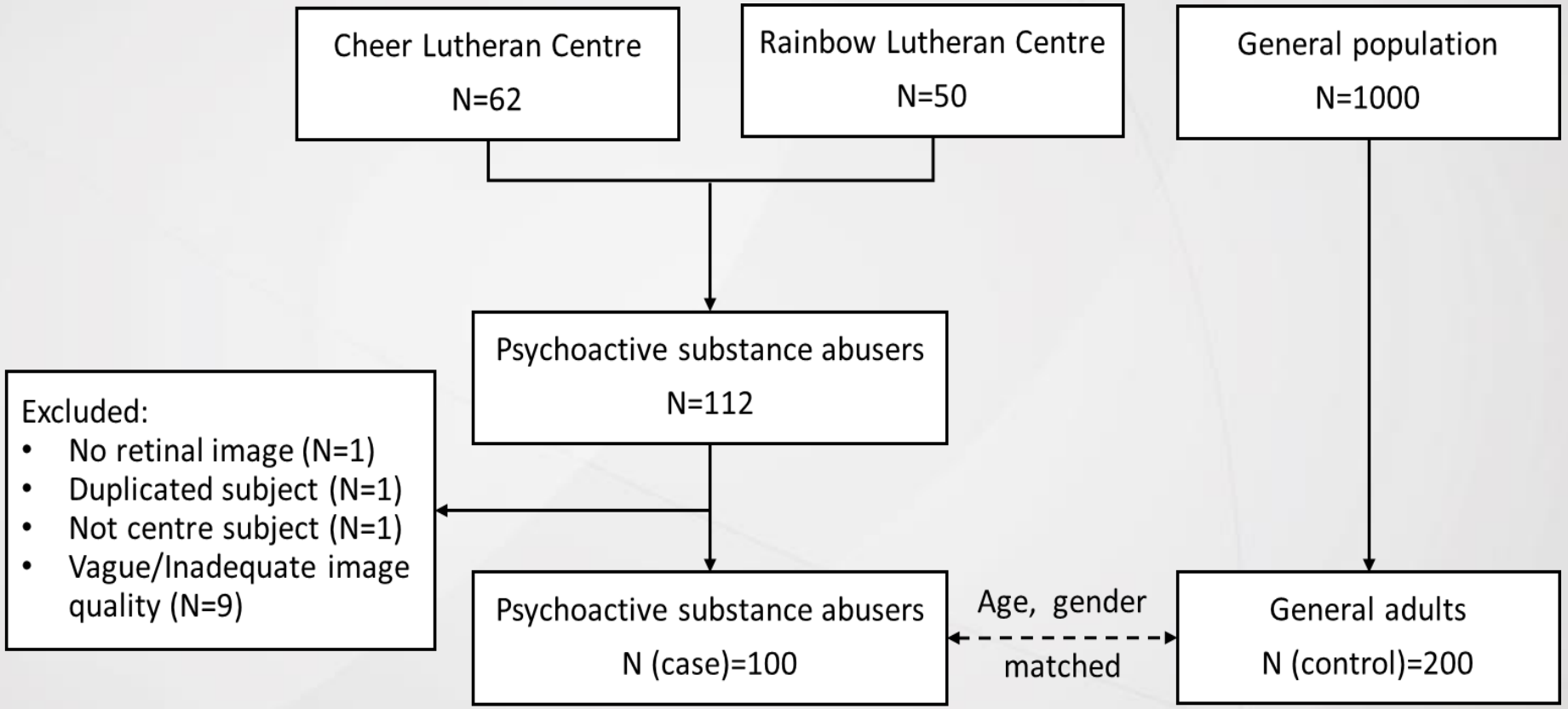
# Measurements

- **Socio-demographics**: Age, sex, body weight, height, marital status, education, living condition, employment, and family history of substance abuse, alcoholism, and psychotic history of the subjects' first-degree relatives and partners
- **Drug abuse history**: 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
- **Self-reported health outcomes**: Lifestyle information (e.g. smoking and drinking habit), self-reported psychological conditions, and medical history

# Statistical analysis

- Descriptive statistics
- Hypothesis testing
- Model building: Logistic regression + machine learning and deep learning techniques

# Results – Recruitment



# Results - Demographics

- 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).

**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/m²)* | 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%) | |

# Results – Characteristics of drug abuse

**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

- 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.

- Approximately half of the psychoactive substance abusers (52%) were polydrug abusers.

# Results – Health condition

**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%) |

- Of all self-reported psychological outcomes, 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)

# Results - comparison of retinal characteristics

- In the comparison of the retinal characteristics between the control subjects and the psychoactive substance abusers, **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.
- The complex retinal characteristic components obtained by deep learning algorithms were all significantly different between the cases and controls ($p<0.001$)

**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** |

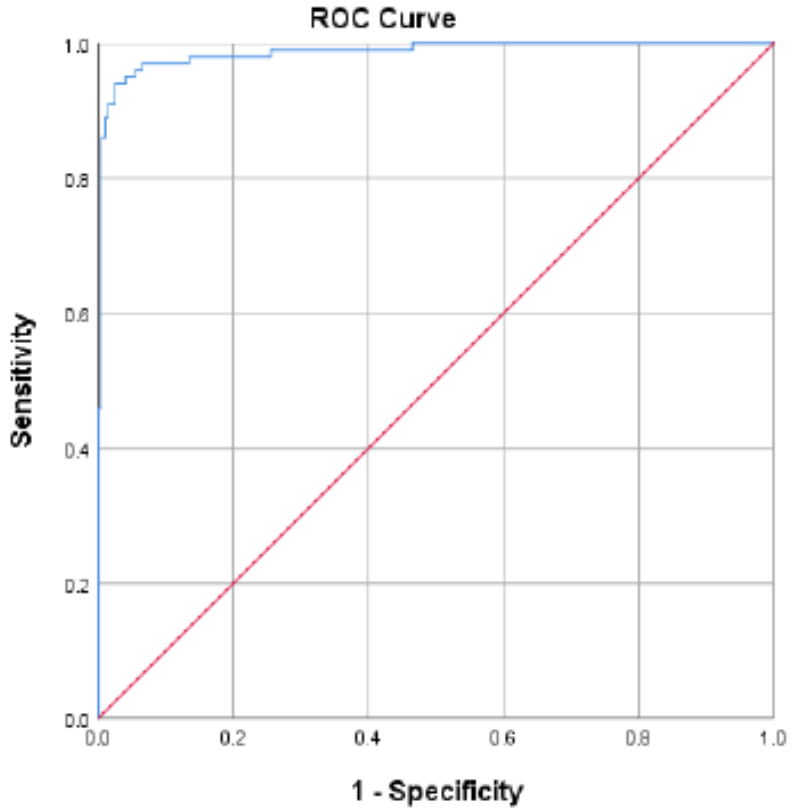
Abbreviations: Bifurcation coefficient of arteriole venule (BCV), bifurcation angle of arteriole (BAA) and venule (BAV) and, fractal dimensions (Df).

# Results – Prediction model of drug abuers

- 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.

- 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**. Receiver operating characteristic curve of the prediction model using retinal characteristics of ARIA.





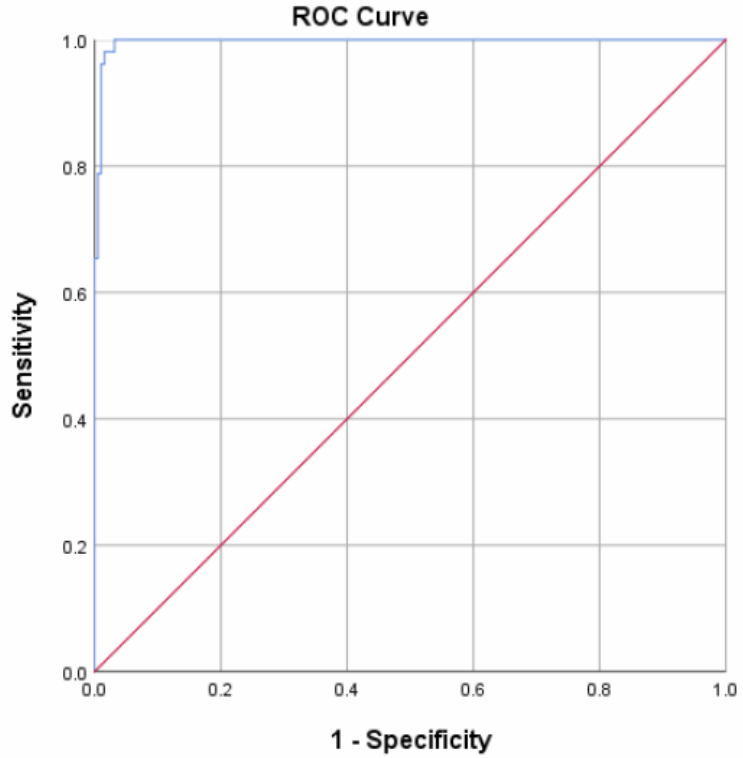

Abbreviations: Bifurcation angle of venule (BAV)

# Results – Subgroup analysis for prediction of polydrug abusers

- AVR, CRAE, CRVE, BCA, BAA, exudates, and DL_PAfeature002 were included in the model.

- 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).

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






Abbreviations: Central retinal arteriolar equivalent (CRAE), central retinal venular equivalent (CRVE ), arteriole-venule ratio (AVR, bifurcation coefficient of arteriole (BCA), bifurcation angle of arteriole (BAA)

# Discussion

- 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. 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.

- 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.



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

# Discussion

- 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).
  - The performance was better than Qu et al., showing the ARIA algorithm was able to achieve an accuracy of 85% for risk estimation of **coronary heart disease**
  - Consistent with Lai et al., demonstrating the AUC of ROC curve was 0.97 for classifying patients with **autism spectrum disorder**
  - Echoed by Lau et al., 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



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.
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.
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

# Conclusion

1. Our study identified the objective retinal measures for detecting psychotropic substance abuse using the ARIA technology.
2. 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.
3. Also, psychoactive substance abuse screening can be integrated into a physical examination in schools, to prevent youth drug abuse.

## Future Direction:

- External validation
- ARIA + **portable** fundus cameras
- Cost-effectiveness/benefit analysis

# Acknowledgement

- Colleagues in Beat Drugs Fund Association


Centre staff of HKLSS Rainbow Lutheran Centre

CCRB staff at HKLSS Cheers Lutheran Centre

Centre staff of HKLSS Cheers Lutheran Centre

# Thank you!