METABOLIC SYNDROME IN FIRST EPISODE SCHIZOPHRENIA, BASED ON THE NATIONAL MENTAL HEALTH REGISTRY OF SCHIZOPHRENIA (NMHR) IN HOSPITAL KUALA LUMPUR, 10-YEAR NATURALISTIC FOLLOW UP STUDY

By

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Metabolic syndrome in first episode schizophrenia, based on the National Mental Health Registry of schizophrenia (NMHR) in Hospital Kuala Lumpur, a 10-year naturalistic follow up study.

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MASTER OF PSYCHOLOGICAL MEDICINE

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ABSTRAK (BAHASA MALAYSIA)

Latar belakang:

Metabolic syndrome merupakan satu isu yang membimbangkan. Pesakit yang menghidap penyakit Skizofrenia mempunyai risiko yang lebih tinggi untuk mendapat Metabolic Syndrome. Tajuk kajian ini merupakan kajian pertama untuk jangka-masa panjang (10 tahun) di Malaysia.

Objektif:

Ini merupakan kajian tempatan yang pertama mengkaji *metabolic syndrome* dalam gologan yang menghidap penyakit Skizofrenia di Malaysia 10 tahun selepas diagnosa.

Cara:

Sejumlah 174 pesakit baru yang didaftar dalam *National Mental Heath Registry of Scizophrenia Hospital Kuala Lumpur* (NMHR) pada tahun 2004 dan 2005 ditemu duga semula selepas 10 tahun.

Keputusan:

Selepas 10 tahun, berat badan, BMI, FBS dan tekanan darah semua pesakit telah meningkat dengan mendadak

Seramai 63 subjeks (36.2%) menghidap metabolic syndrome (menggunakan kriteria NCEP ATP III), 36 orang hypertension (23.2%) dan 41 orang (28.1%) diabetes.

3 faktor- Depot (Flupentixol) Fluanxol, aktiviti fizikal dan penyalahgunaan dadah berkaitan dengan *metabolic syndrome* (CI=1.05-5.09, OR: 0.84, p=0.039), (CI=0.13-1.00, OR: -1.04, p=0.050), (CI=1.40, 13.89, OR: 1.48, p=0.012). Selepas *Multiple Logistic Regression* penyalahgunaan dadah masih berkaitan dengan perubahan *metabolic syndrome*.

Untuk parameter individual, Perempuan mempunyai perubahan SBP yang lebih ketara berbanding lelaki (CI=1.08-11.82, OR: 6.45, p=0.019). Mereka yang bersenam fizikal aktiviti (moderate to vigorous) mempunyai perubahan SBP (CI=0.33-15.60, coeff B: 7.96, P=0.041) dan DBP (CI= 1.51-12.91, coeff B: 7.21, P=0.014). yang lebih ketara.

Salah satu keputusan ialah mereka yang mengunakan Atypical antipsychotic mempunyai 1.91 lebih kenaikan BMI berbanding dengan yang mengunakan typical antipsychotic.

Kesimpulan:

Metabolic syndrome merupakan issue kesihatan yang membimbangkan dan semakin menjadi. Pesakit yang mempunyai penyakit skizofrenia untuk 10 tahun didapati mempunyai peningkatan parameter untuk metabolic syndrome.. Factor yang berkaitan dengan peningkatan kadar metabolic syndrome yang ketara islah penyalahgunaan dadah, tahap akitiviti fizikal, dan pengunaan depo IM Flupentixol. Oleh demikian, doctor perlu mengenal-pasti resiko dari peringkat awal dan memberi perhatian terhadap golongan ini.

ABSTRACT (ENGLISH)

Introduction:

Metabolic Syndrome is a worrying issue globally. Patients with Schizophrenia have a higher risk then normal in developing this disease. This is the first 10 year retrospective outcome study of metabolic syndrome and schizophrenia in Malaysia.

Objective:

To investigate the rate of metabolic syndrome in schizophrenia over ten years and its associated factors.

Method:

174 patients who were registered with the National Mental Health Registry of Schizophrenia (NMHR) Hospital Kuala Lumpur in 2004 - 2005, were analyzed and their progress was reviewed over the last ten years.

Results:

After 10 years, all patients weight, body mass index, fasting blood sugar and blood pressure are significantly increased.

A total of 63 subjects (36.2%) developed metabolic syndrome while 36 (23.2%) are hypertensive, and 41 (28.1%) are diabetic.

There are 3 variables which are significantly associated with metabolic syndrome namely Intra-Muscular Fluphenthixol depot (CI=1.05-5.09, OR:0.84, p=0.039), physical activity (CI=0.13-1.00, OR: -1.04, p=0.050), and substance use disorder (CI=1.40, 13.89, OR: 1.48, p=0.012). Comorbid substance abuse is still significantly associated

with metabolic syndrome despite adjusting for physical activity and intra-muscular depot.

Female gender is more likely to have an increase in systolic blood pressure (CI=1.08-11.82, OR: 6.45, p=0.019), while the low physical activity group has lower change in systolic BP (CI=0.33-15.60, OR: 7.96, P=0.041). High physical activity was also associated with an increase in diastolic BP (DBP) (CI= 1.51-12.91, OR: 7.21, P=0.014). Atypical antipsychotic group is 1.91 times more likely to have an increase in BMI compared to those on typical antipsychotics.

Conclusion:

Schizophrenia patients have a higher risk of developing metabolic syndrome. Factors which are significant in causing a greater rise in Metabolic Syndrome are the usage of IM depo fluanxol (flupentixol), comorbid substance abuse, and the lack of physical activity. A more holistic approach in assisting patients to modify the modifiable risk is needed in the management of schizophrenia. More research needs to be done in the long-term outcome of patients with schizophrenia to aid in the long term planning and management of this chronic disease.

1. Introduction

Schizophrenia is a major mental disorder that alters the patients' perception, thought, affect and behavior. The course of illness tends to be chronic and relapsing, leading to profound disability. [1]According to the WHO, it is one of the major mental illnesses that lead to global burden of disease[2]. Not only that, it has been listed as the 14th most moderate and severe disability and 6th in the list for the most causes of years lost due to disability (YLD)[2]. Why is it so? There is a research reporting that patients with Schizophrenia have a shorter life expectancy, as much as 6-7 years shorter[3]. In the beginning of 1940s, the assessment of mortality among patients with Schizophrenia was mainly about Tuberculosis as most of patients are managed in the mental institution. [4] What was alarming about that major cause of death at that time was it reflects how badly the treatment of those that suffered from the mental illness as they were confined in a crowded mental hospitals where risk of the infection and mortality was high. [4] With the de-institutionalization and improvement of pharmacological and rehabilitation program, there was a change in cause of death among patients with Schizophrenia. One of the major causes of mortality during that time, and also still is a crucial cause is suicide. Up till now, suicide is still a major preventable cause of death. According to Allebeck, the suicidal risk among patients with Schizophrenia is 10 times higher than general population.[5] The same author also examined the overall mortality among the cohort, found after excluded suicide, the mortality rate are twice as high as population among patients with Schizophrenia. [5] currently, there is a shift of pattern of cause of death in recent decade. One of the major causes being given significant attention to is cardiovascular risk and complications of Metabolic Syndrome.

Although there is no data regards burden of schizophrenia in Malaysia, according to Malaysia Global Burden Of Diseases, injuries and risk factor study 2010, mental disorders is one of the leading cause of Years Lived With Disability (YLDs), and the 3rd leading cause of Disability-Adjusted Life years (DALYs). The percentage of Years Lived With Disability (YLD) and non fatal burden was as high as 21%.[6]

From Malaysia National Mental Health Registry Report 2008, 60% of Malaysia Schizophrenia patients had a normal Body Mass Index (BMI less than 25), while 14% of them were overweight (BMI more than 25) and 4% obese. (BMI more than 30) [7]

The weight drastically increased after being diagnosed especially in those who is on atypical neuroleptic medications. Not only that, schizophrenia patients have higher risk of develop other physical health illnesses due to change in socioeconomic and lifestyle factors which in turn lead to increase mortality risks[8]. Patients with Schizophrenia is not only disabling illness by itself, it also has been links with multiple comorbidities, which are equally disabling[8–10].Among all, one of the main concerns is metabolic syndrome.

Metabolic Syndrome is always a worrying issue globally. The syndrome consists of obesity, elevated blood pressure, impaired insulin sensitivity and dyslipidemia. International Diabetic Federation consensus report in 2006 estimates as high as 20-25% of the world's adult populations have metabolic syndrome not to mention those patients with Schizophrenia who are at even higher risk to develop such syndrome. Not only is this due to the diet intake, but they are less active in their physical activity and to make thing worse, the treatment, especially atypical antipsychotics, put them at higher risk of developing the syndrome compare to general population. For the past 20 years, there are more and more concerns about metabolic syndrome because the continuation of these will predispose the patients to develop Type 2 DM and coronary heart disease[11–13].which is the major cause of morbidity and mortality.

Up till now, there is no long-term outcome study of metabolic syndrome Schizophrenia patients in Malaysia. It is important to know the metabolic outcome among Schizophrenia because of its serious morbidity and mortality so that clinicians can be more sensitive in detecting and intervene these problems and refer to the respective teams earlier if necessary.

National Mental Health Registry of Schizophrenia (NMHR) 2003-2004, reported approximately 2467 new cases registered countrywide within 2 years and in Hospital Kuala Lumpur and there are a total of 394 patients registered in year 2004-2005.

Hospital Kuala Lumpur one of the largest tertiary referring general hospital in Malaysia and with the 2300 beds it covers large amount of populations. Therefore the number of referrals and registered patients with Schizophrenia was large as well. Thus the reliability and accuracy of patients details was assured with the National Mental Health Registry of Malaysia.

With this ten year outcome study it is hoped that we can find any evidence to help influence the direction of health services in regards to policy making, early intervention and treatment of schizophrenia in Malaysia.

2. Literature Review:

Keywords: *Metabolic Syndrome in Schizophrenia, Schizophrenia outcome study, Schizophrenia 10-year outcome study, schizophrenia outcome in Malaysia, first episode psychosis.*

The purpose of this literature review is to establish the existing knowledge on Metabolic Syndrome in Schizophrenia patients and also the long-term outcome of Schizophrenia.

2.1 Metabolic Syndrome:

Herman Haller first introduced the concept of metabolic syndrome in 1977 when he was trying to find risk factors and factors associated with atherosclerosis. He studied the relationship between obesity, high blood lipids, high uric acid levels, diabetes mellitus and fatty liver disease with atherosclerosis. However, even in 1947, some other physician had also studied these relationships. Soon after Herman Haller, Gerald Phillips put together that the existence of combination risk factors would increase the risk of myocardial infarction. In 1988, Gerald Reaven named the group of abnormalities together and named it syndrome-X.[14,15]

Metabolic syndrome was first defined by World Health Organization (WHO) in 1998. It is a syndrome, which includes obesity, elevated blood pressure, dyslipidaemia and elevated plasma glucose. Metabolic syndrome is a cluster of clinical features including a) hypertension b) Visceral adiposity c) Dyslipidaemia and d) impaired fasting glucose or DM.[16]

Currently there is a number of expert groups developed clinical criteria for the metabolic syndrome and among all, World Health Organization (WHO), the European

Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III) and International Diabetes Foundation (IDF) are widely used and accepted. Although they have different criteria on their own, all groups agreed on the core components of the metabolic syndrome namely obesity, insulin resistance, dyslipidaemia and hypertension. [17,1819]

WHO defined Metabolic syndrome as fulfill criteria of insulin resistant, with 2 additional risk factors.

WHO Criteria for Metabolic syndrome:[3]

A) Insulin Resistance (Impaired Glucose Tolerance Test (IGT), Impaired Fasting Glucose (IFG), type 2 diabetes or other evidence of Insulin Resistance)

B) Plus 2 of the 5 criteria:

1. Waist/hip ration>0.9 (Male), >0.85 (Female) or BMI>30kg/m2
2. TG≥ 150mg/dl or
3. HDL-C<35mg/dl (Male), <39mg/dl (Female)
4. Hypertension BP≥140/90mmHg
5. Microalbuminuria (urinary albumin excretion of ≥20 μg/min or albumin to creatinine ratio of ≥30mg/g)

According to IDF definition, for a person to be defined as having the metabolic syndrome they must have:

A) Central Obesity (defined as waist circumference with ethnicity specific value)

B) Plus any 2 of the following 4 factors:

a. Raised Triglycerides (≥150mg/dL or 1.7mmol/L)

b. Reduced HDL cholesterol (<40mg/dL or 1.03 mmol/L in males and <50mg/dL or 1.29 mmol/L in females)

c. Raised blood pressure (SBP≥130mm Hg DBP≥85mm Hg)

d. Raised fasting plasma glucose (FPG ≥100mg/dL or 5.6mmol/L)

While for waist circumference for Asian populations,

e. Female ≥ 80cm, Male ≥ 90cm

NCEP ATP III Criteria (National Cholesterol Education Program – Third Adult Treatment Panel) (Grundy et. al. 2004) with adjustment for waist size in Asian Subjects (World Health Organization, 2000) includes at least 3 of the following criteria:

a) Central Obesity (man ≥ 90mm, Female ≥ 80mm)

b) High triglyceride (≥ 1.7 mmol/L)

c) A low HDL Cholesterol Concentration (<1.3mmol/L)

d) Elevated Blood Pressure (SBP≥ 130mmHg; SBP ≥ 85mmHg)

e) Glucose intolerance (fasting blood glucose ≥ 6.1 mmol/L)

As mentioned earlier, Metabolic syndrome is one of the major health issues for the general population globally. Internal Diabetes Federation (IDF) consensus statement in 2006 estimated as high as 20-25% of the world's adult population have metabolic syndrome. For the past 20 years, there are more and more concerns about metabolic syndrome because it will predispose the patients to develop Type 2 DM and coronary heart disease.[11–13]

In Malaysia, the Metabolic Syndrome issue is equally worrisome. Wan Nazaimoon Wan Mohamuda et al. 2010 revealed the prevalence of Metabolic Syndrome in Malaysian adult using WHO, ATP III and IDF definitions were 32.1, 34.3 and 37.1 respectively.[20]

According to Malaysia National Mental Health Registry Report 2008, 60% of patients in Malaysia with Schizophrenia have a normal Body Mass Index (BMI less than 25), while 14% of them were overweight (BMI more than 25) and 4% obese. (BMI more than 30) [3]. The weight drastically increased after being diagnosed especially in those who were on atypical neuroleptic medications. Not only that, schizophrenia patients have higher risk of developing other physical health illnesses due to socioeconomic and lifestyle factors which in turn leads to increased mortality risks.[4] Schizophrenia is not only a disabling illness by itself, it also has links with multiple comorbidities, which are equally disabling.[8–10]

Metabolic syndrome has been an alarming issue globally, more so for group of schizophrenia patients due to its variable risk factors.

2.2 Why Metabolic Syndrome is important:

International Diabetes Federation, 2006.

People with Metabolic Syndrome are twice as likely to die from and three times as likely to have a heart attack or stroke compared with people without the syndrome.[21] while one of the biggest issues with metabolic syndrome is its outcome of type 2 diabetes mellitus whereby they will have increased risk as high as five times compared to those without the syndrome. Therefore it is estimated in near future, this group of patients are the one dealing with diabetes, and its complications (e.g. blindness, amputations, kidney failure, stroke) which also directly contributes to the national burden of disease. Not only that, IDF also concluded that the more components of the metabolic syndrome in patients, the higher are the cardiovascular mortality rate. According John D Brunzell, if they were to combine low HDL, high TF and LDL, the risk of cardiovascular disease will be much higher as the dyslipidaemia mentioned is independently artherogenic [22]. These combination of dylipidaemia are sad to say, commonly found in both metabolic syndrome and also type 2 diabetes patients.

Among all, insulin resistance and central obesity are the highest significant factors. The authors also describe obesity itself contributes to hypertension, high cholesterol, low HDL and hyperglycaemia. Therefore, central obesity itself is an independent risk factor for CHD[21].

Henley AJ et. al. 2005.

According to the paper, patients with Metabolic syndrome have a 4 fold increased risk of developing Type 2 Diabetes[23] while Stern M. et. al. reported even higher risk of fivefold developing the same complications[24]

Why is it important to identify the risk of glucose intolerance or diabetes? It is because type 2 diabetes is an independent risk factors for CVD. As mentioned by Isomaa [13], in those with impaired fasting blood glucose (IFG) or impaired Glucose Tolerance (IGT) had rates of metabolic syndrome which was much higher than those with normal blood glucose (64% vs 15%) and the chances of developing coronary heart disease and stroke was significant in relation to the syndrome, even in those in the IFG/IGT group. The risk can differ as high as 3 times compared to those without the syndrome. [13]

One literature specifically looks into metabolic syndrome and diabetes in terms of coronary heart disease (CHD) outcome. He found that those with metabolic syndrome and diabetes are closely related i.e. with presence of diabetes, highly likely the subjects will have metabolic syndrome. He examine the fact that metabolic syndrome itself was associated with higher prevalence of CHD (13.9%). However if with presence of diabetes, the prevalence was even higher (19.2%) [25]That shows how important to aware of the risk of metabolic syndrome.

Gami AS et. al. 2007.

Patients with Metabolic Syndrome are also at a higher risk in developing cardiovascular events and also death. Gami AS et al. reported the risk is as high as 2 folds compare with general populations.[17] Saha et. al. 2007 also reported the same risk of developing cardiovascular disease.[18] The meta-analysis by Apoor S Gami noticed a significant difference between risk of cardiovascular events and death in people with the metabolic syndrome[26]. Not only that, the analysis also found females was a third higher than in men. With the meta-analysis result, we can have more evidence about the important of holistic approach to those with the syndrome to prevent the even more worrying outcome of cardiovascular death.

2.3 Schizophrenia with Comorbidity:

It is well known that metabolic syndrome is the leading cause of coronary heart disease. [9] and due to a variety of risk factors, including genetics, sedentary life-style, dietary and the treatment especially atypical antipsychotics, patients with Schizophrenia are at higher risk of developing other medical illnesses.

In general, patients with Schizophrenia have shorter life expectancy compared with the general population. Hennekens CH et al. 2005 reported they have 20% less life expectancy, mainly due to coronary heart disease (CHD).[20] which is strongly related to Metabolic Syndrome. Patients with Schizophrenia have 2-3 folds increase risk of dying especially from cardiovascular events. [27]A review by Marc De Hert [27]mentioned patients with Schizophrenia has a 2 to 3 times higher rate of developing metabolic syndrome. Other findings, e.g. from CATIE study, approximately 30% of schizophrenia have metabolic syndrome at baseline while Meyer Stahl et al. 2009 conclude that Schizophrenia patient has higher risk of developing metabolic dysfunction independent on environmental.[19]

There is always a great debate on whether the cause of metabolic syndrome is due to the disease of Schizophrenia itself or due to other environmental factors among Schizophrenia patients. Environmental factors refers to physical inactivity, smoking and poor dietary habits. However, evidence of direct biological contributions related to the disease is less clear.

How the diet can lead to metabolic syndrome? There is research conducted that shows patients with Schizophrenia tends to have a life-style which put them on higher risk, including sedentary life-style, lack of physical activity and poor food intake. [27] Not only that, imbalance in the diet can lead to nutritional deficiency which may also lead to

metabolic syndrome. [28–32] for instant, James P McClung et al found the prevalence of iron deficiency was high among those obese clients.[29] Another author Karen G.Nead shows children who were overweight, or at least those with risk of overweight are 2 times higher risk to have iron deficiency[30]. Antje Damms-Machado et al. did a study on those pre and post laparoscopic Sleeve Gastrectomy for morbid obesity found out of the 51 subjects, they will at least one micronutrient deficiency- vitamin D, iron vitamin B6, B12, folate and also potassium[31,33]That shows nutrition deficiency might play an important role in obesity.

While some authors found that Vitamin D plays a role in obesity [32,33] Why is it so? There is a hypothesis that obese people are less active especially in regards to outdoor activity, hence less exposure to sunlight and in result of low level of vitamin D level.[31–33]

2.4 Situation in Asia:

Malaysia has one of the highest prevalence of metabolic syndrome, 34.3% (2011)[21] compare with other countries in Asian. For example, China recorded prevalence of only 9.8%; Indian recorded 24.9%; while Korea, Hong Kong, Taiwan and Thailand were all reported low prevalence of metabolic syndrome of 13.1%, 13.4%, 16.4% and 15% respectively.[26-32] Research done by Paul Nestel MD. et. al. 2007, using Asian-adapted definitions of obesity (BMI ≥ 25 kg/m2) and increased waist circumference (for male ≥ 90 cm; for female ≥ 80 cm) reported prevalence of metabolic syndrome among east and Southeast Asia appears to be between 10 to 30% only.[29] That means Malaysia has one of the highest prevalence of metabolic syndrome in this region. This is a worrisome finding. As mentioned above, we are expecting Schizophrenia patients will have an even higher prevalence compare to the general populations. As per literature reviewed, the prevalence of metabolic syndrome among Schizophrenia patients is higher than the general populations in most of the Asian countries. For example, Japan recorded prevalence of 27.5% among schizophrenia patients have metabolic syndrome.[22] while India registered 33.3% compare to 11.9% among general populations[24]; Thailand reported prevalence of 22.8% compare to 15% of general populations[25]. The rates of Metabolic Syndrome in patients with schizophrenia in those countries however are still lower the rates of Metabolic Syndrome in the general population in Malaysia. A Systemic review and meta-analysis by Mitchell AJ et. Al, metabolic syndrome among schizophrenia patients are as high as 32.5% [23]

Despite expecting a higher prevalence of metabolic syndrome among Schizophrenia patients, the data is not known among patients with schizophrenia 10 years after initial diagnosis.

3.1 RATIONALE OF STUDY

Metabolic syndrome is increasing among the population in Malaysia, and schizophrenia patients are at a higher risk to develop such a syndrome.[26-32] as they are exposed to many risk factors of metabolic syndrome including genetic predisposition, environmental factors, sedentary life-style, smoking, imbalance in dietary intake. However, up to this date, there is no long-term study on this topic in Malaysia.

The research findings may assist in direction of service, development of guidelines especially dealing with these disabling and major morbidity and mortality among patients with Schizophrenia in our country.

3.2 RESEARCH QUESTIONS

The research questions in this study are as follows:

1. What is the Metabolic Syndrome rate in schizophrenia patients after 10 years?
2. What are the associated factors among these patients in relation to metabolic syndrome?.
3. Is there any relationship between physical activity and metabolic syndrome in this group of patients?

3.3 OBJECTIVES

GENERAL OBJECTIVE

The aim of the study is to determine the rate of metabolic Syndrome and its associated factors among Schizophrenia patients with Schizophrenia in General Hospital Kuala Lumpur in 10 years prospectively.

SPECIFIC OBJECTIVES

1. To determine the metabolic syndrome rate among Schizophrenia patients 10 years after first contact with GHKL.
2. To determine other factors influencing the metabolic syndrome outcome among these patients.
3. To determine the relationship between physical activities with metabolic syndrome among these patients

OPERATIONAL DEFINITIONS

1. With regards to "Metabolic Syndrome criteria":

   In this study, the author uses National Cholesterol Education Program-- Third Adult Treatment Panel (NCEP ATP III) (Grundy et. al. 2004) with adjustment for waist size in Asian Subjects as recommended by the WHO Asia-Pacific Region, Sterring Committee, 2000. (World Health Organization, 2000) includes at least 3 of the following criteria:

   a) Central Obesity (man ≥ 90mm, Female ≥ 80mm)

   b) High triglyceride (≥ 1.7 mmol/L)

   c) A low HDL Cholesterol Concentration (<1.3mmol/L)

d) Elevated Blood Pressure (SBP≥ 130mmHg; SBP ≥ 85mmHg)

e) Glucose intolerance (fasting blood glucose ≥ 6.1 mmol/L)

The reason why the author choose this criteria over IDF or WHO criteria is because IDF criterion put emphasis on central obesity as major criterion, i.e. subject must have central obesity to diagnose metabolic syndrome. This will miss those subjects who fulfil other risk factors without central obesity. Not only that, there are more local literature published using NCEP-ATP III criteria than WHO or IDF. By choosing this criterion, author hope can have better comparison with the literature. [34]

2. With regards to "first episode schizophrenia in Hospital Kuala Lumpur":
    a. Patients meeting the criteria for schizophrenia based on DSM IV having their first contact in Hospital Kuala Lumpur and enrolled in the Mental Health Registry of Schizophrenia.

4. METHODOLOGY

4.1 STUDY DESIGN

This is a retrospective 10-year cohort study to determine the metabolic outcome and its associated factors among patients with first episode schizophrenia in Hospital Kuala Lumpur Wilayah Persekutuan.

4.2 SUBJECT AND SETTING

The source populations for this study are those who were newly diagnosed patients with Schizophrenia from 1st January 2004 till 31st December 2005 in Hospital Kuala Lumpur and registered with the National Mental Health Registry. (Complete sampling method). Investigator will go through the NMHR- HKL registered patients and check via the clinic computer system to label and identify the subjects. After that, he will met with the subjects either during their clinic appointment or would call them for an appointment if they had defaulted. Those who had lost contact or follow up will be identified as well. Each subject will be interviewed by the investigator.

4.3 INCLUSION CRITERIA

1. Diagnosed with Schizophrenia based on DSM IV-TR.
2. First episode contact and Registered with the national registry (NMHR) GHKL in year 2004-2005.
3. Adult age between 18-60 years of age.
4. Consent either from patients or family members/care takers.

   Able to give consent means "patient is able to understand the nature of the research, ability to communicate of a choice, to understand a relevant

information, and to appreciate the meaning of a decision within the context of one's life and able to understand his right to withdraw from the research at any point of time." [34-38]

4.4 EXCLUSION CRITERIA

1. Patient who had passed away (confirm with Jabatan Pendaftaran Negara)
2. Change of Diagnosis since 2004/2005.
3. Lost to follow up (to be analysed and compared to study group later).
4. Foreigner or no longer in the system.
5. Pre-existing Metabolic Syndrome.

4.5 STUDY PERIOD

Assessment and data collection will be carried out for 6 months from December 2014 to May 2015.

See Appendix 1

4.6 DATA COLLECTION

All patients diagnosed as first episode schizophrenia in 2004 and 2005 in Hospital Kuala Lumpur and registered with the National Mental Health Registry of Schizophrenia (NMHR) will be recruited as study subjects. The diagnosis of schizophrenia is ascertained from the patients' case notes and the National Mental Health Registry Schizophrenia Notification Form. Investigator will then run an initial analysis to assess the inclusion and exclusion of the subjects.

The next appointment date for these patients will be confirmed by the investigator and will be reviewed by him if it is within the data collection phase of 3 months. If not, the subjects will be contacted via phone and an early appointment would be arranged. Consent must be obtained at this point of time using the Consent Form (Appendix 2B, 3B). The diagnosis will be re-ascertained using the DSM 5. Investigators will measure the weight in kilogram (kg), height in centimeters (cm), waist circumference, in centimeters (cm), (measured at midpoint between inferior costal margin and the superior border of the iliac crest, during end of a normal expiration in standing position), and calculate the BMI. Blood pressure was measured using a calibrated scale in mmHg and investigator will trace the latest blood investigations taken including serum lipid profile, serum blood sugar.

According to the Malaysian CPG of Schizophrenia, each patient should have blood monitoring at least yearly and every 2 years if lipid levels are normal, while if the LDL level is > 3.3 mmol/L, he or she should have his or her blood monitor every 6 months.[33]

Results will be traced and obtained during the assessment which was done based on the Malaysia CPG of Schizophrenia.

Besides this, the investigator will assess the patients' physical activity by using International Physical Activity Questionnaire (IPAQ) (Appendix 5).

During the assessment, investigator will record down any comorbidity among the subjects. The presence of comorbidity is either based on the medical records available or whether patients is still currently on medications, example those still on antidepressant. However, investigator did not assess the severity of the comorbidity during the interview. Investigator also did not apply any scale or instrument at the point of interview as no scales or instruments were used in the initial diagnosis of comorbidity thus limiting its usefulness.

All research information will be recorded in the Schizophrenia Outcome Study Form i.e. Demographic data, work history, as well as other clinical data.

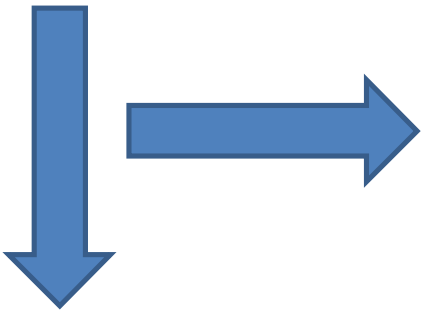
4.7 SAMPLE SIZE

National Mental Health Registry of Schizophrenia in General Hospital Kuala Lumpur had registered a total number of 394 schizophrenia patients, which 239 in year 2004 and total of 155 in year 2005. In this research, investigator is using the total sample (total number of patients in both 2004 and 2005).

This approach provides a true measure of the population, eliminating the possibility of sampling error and allows benchmark data to be obtained for future studies. Hospital Kuala Lumpur was the pioneer in starting the National Mental Health Registry and has registered the most patients since its inception in 2003. The most number of patients collected were also in 2004 and 2005.

4.8 STUDY FLOW CHART

Total of 394 patients diagnosed with first episode Schizophrenia (DSM IV-TR) and register under NMHR GHKL.



Exclusion Criteria:

1. Passed away (Verified with Jabatan Pendaftaran Negara). **[37]**
2. Diagnosis changed since 2004/2005**.[8]**
3. Foreigner/not in system. **[58]**
4. Lost to follow up**.[117]**
5. Pre-existing Metabolic Syndrome.

Total:
Consented: N=174

- face to face interview.
- To measure the Blood Pressure, weight and height for calculation of BMI.
- To review case notes – latest blood investigation results.

4.9 INSTRUMENTS

4.9.1 SCHIZOPHRENIA OUTCOME STUDY QUESTIONNAIRE

This is a self-generated questionnaire which will be used to record patient's demographic data, other related information e.g. clinical data, current status, employment status, process of care, and also includes the Personal and Social Performance scale, physical data e.g.: weight, height, BMI. Investigator also includes smoking habits, substance comorbidity and also previous investigations done. Family history of diabetes mellitus, hypertension, previous and current medications will be recorded and assessed as well.

See Appendix 4

4.9.2 INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ):

Background on IPAQ

IPAQ was developed during a conference in Geneva in 1998 to measure physical activity in general populations. It is suitable for use in regional, national and international monitoring and survey systems and for research projects and public health program planning and evaluation. It is extensively tested on reliability and its validity in 12 countries (14 sites) across 6 continents during 2000.

Why is it important to exercise? Physical activity has well known independent and significant protective effects against multiple medical conditions. It reduces risk of ischemic heart disease and stroke. It is also important for weight control and also maintaining bone density which can then reduce risk of falls and fractures especially in the elderly.

Not only that, physical activity also increases insulin sensitivity, increase levels of HDL cholesterol and hence reducing incidence of type 2 DM.

IPAQ has a total of 4 versions- Short and Long questionnaires (Short and Long questionnaires by phone and self administration). It is used to measure the health-related physical activity, which includes time spent in vigorous intensity activity, moderate intensity activity and walking, which at least lasted 10 minutes or more per session. Not only that, the questionnaire also measured time spent for sedentary activity (eg: sitting/ watching TV etc).

The short versions needed about 3-4 minutes while long version needed 15-20 minutes.

For its validity and reliability, IPAQ has extensively tested around the world including Malaysia. It has been translate into many languages including Malay version.

It was designed and tested for population age of 15-69 years.

Interpretation of the results:

Data collected with IPAQ can be reported as a continuous measure. Specific activities within each major heading with its intensity, defined as the ratio of work metabolic rate to a standard resting metabolic rate (MET). Energy expenditure in MET-minutes, MET-hours, kcal. or kcal per kilogram body weight can be estimated for specific activities by type or MET intensity.

Another way to define MET is, one metabolic equivalent is the amount of oxygen used while sitting at rest and is equal to 3.5ml O2 per kg body weight times (X) minute. MET is a easy way to count the energy cost of different types of physical activities as a multiple of the resting metabolic rate.

Formulation:

MET- multiply of the resting metabolic rate

MET-min: multiplying the MET score of an activity by the minutes performed.

MET-minute score are equivalent to kilocalories for a 60 kg person.

Therefore kilocalories= MET-min X (Weight of body in kilograms / 60 kilograms)

For Cut point values:

The score from METs can then divided into 3 groups:

1. Low
2. Moderate
3. High

High:

IPAQ research committee proposes a measure which equates to about at least one hour per day or more. Or

At least moderate-intensity activity above the basal level of activity (basal-approximately 5000 steps per day) ie: propose walk more than 12,500 steps per day at least. Or

An hour more moderate-intensity activity; or

Half hour of vigorous intensity exercise.

a) Vigorous-intensity activity on at least 3 days achieving a minimal total physical activity of at least 1500 MET-minutes/week OR
b) 7 or more days of any combination of walking, moderate-intensity or vigorous-intensity activities achieving a minimum total physical activity of at least 3000 MET-minutes/week.

Moderate:

Defined as doing some activity more than low active category.

0.5 hour of at least moderate-intensity physical activity on most days.

a) 3 or more days of vigorous-intensity of at least 30 minutes per day OR

b) 5 or more days of moderate-intensity activity and /or walking of at least 30 minutes per day OR

c) 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum total physical activity of at least 700 MET-minutes/ week

Low:

Defined as not meeting any of the criteria for either of the previous categories.

The formulation (MET-minutes/week), is based on the work during IPAQ Reliability Study undertaken in 2000-2001, the formulation of MET-minutes/week was concluded. By using Ainsworth et al. Compendium (Med Sci Sports Med 2000) as reference, an average MET score was derived for each type of activity. Different type of activities will attribute to different METs, as bellow:

Walking= 3.3 METs

Moderate PA= 4.0 METs

Vigorous PA- 8.0 METs

Formulation:

Walking MET-minutes/week= 3.3*walking minutes*walking days

Moderate MET-minutes/week= 4.0* Moderate-intensity activity minutes* moderate days

Vigorous MET-minutes/week= 8*vigorous-intensity activity minutes* vigorous-intensity days

Total physical activity MET-minutes/week= sum of walking+ moderate+ vigorous MET-minutes/week scores.

MET-min X (Weight of body in kilograms / 60 kilograms)=Kilocalories used.

In the study, the investigator is using Malay validated version from IPAQ official website. It is free to download and can be used without permission. The validity and reliability was done by Yee Chu AH et. al, published in 2012. The IPAQ-M demonstrated good reliability and validity for the evaluation of physical activity among Malaysian populations. The examples of different activities (i.e. vigorous, moderate and walking) are well given in the IPAQ-M version.[35]

5 STATISTICAL ANALYSIS

Data collected will be analyzed using the version 23 of Statistical Package for Social Science (SPSS). Descriptive analysis was done for the baseline characteristic and clinical features. Frequencies and percentages were calculated for categorical variables and mean and standard deviation were calculated for continuous variables. Simple logistic regression is used to analyze the association between social-demographic and clinical variables with metabolic syndrome; the association of each variables with individual metabolic parameters. Significant variables were included into multiple logistic regressions to examine the influence of independent variables with metabolic syndrome and its parameters.

(Appendix 6)

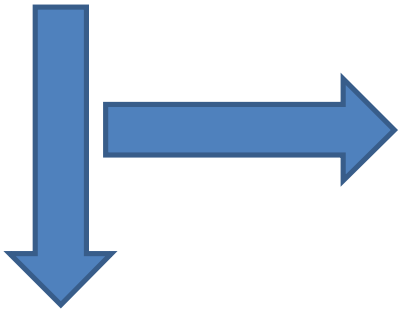
6 ETHICAL CONSIDERATION

This research requires approval by the both CRC GHKL and Malaysian Research Ethics Committee (MREC). Permission to recruit and assess patients in this study was obtained from the Medical Director of the Psychiatry and Mental Health Department Hospital Kuala Lumpur. The confidentiality of the study subjects is assured and informed consent taken from each of them.

NMRR ID: NMRR-14-1830-23530 (IIR) reference no: KKM/NIHSEC/P15-938. Appendices 7

7. RESULTS:

Total of 394 patients diagnosed with first episode Schizophrenia (DSM IV-TR) and register under NMHR GHKL.



Exclusion Criteria:

6. Passed away (Verified with Jabatan Pendaftaran Negara). **[37]**
7. Diagnosis changed since 2004/2005**.[8]**
8. Foreigner/not in system. **[58]**
9. Lost to follow up**.[117]**
10. Pre-existing Metabolic Syndrome.

Total
Consented: N=174

- face to face interview.
- To measure the Blood Pressure, weight and height for calculation of BMI.
- To review case notes – latest blood investigation results.

Out of the 394 patients registered in 2004-2005, there are 37 patients who have passed away and 117 of them were lost to follow up and not able to trace the record. 58 of the total subjects are not able to assessed, either they are foreigners, or was not in the system (likely due to wrongly entered data). The investigator was unable to obtain the information of the 117 defaulters, either because they had defaulted for a long period of time, no contact number was available or they had changed their contact number.

7.1 Demographic Data:

Table 1: Socio-demographic Characteristics of Study Participants.

Variables	Subtypes	Mean, n (%)	Mean, (SD)
Age			42.3 (10.67)
Gender	Male	113(64.9)	
	Female	61 (35.1)	
Ethnicity	Malay	90 (51.7)	
	Chinese	59 (33.9)	
	Indian	19 (10.9)	
	Others	6 (2.9)	
Religion	Islam	94 (54.0)	
	Buddhist	42 (24.1)	
	Hinduism	12 (6.9)	
	Others	26 (14.9)	
Marital Status	Single	122 (70.1)	
	Married	32 (18.4)	
	Others	20 (11.5)	

Education Level	No School	5 (2.9)
	Primary School	17 (9.7)
	Secondary School	120 (69.0)
	Tertiary School	32 (18.4)
Employment	Unemployed	111 (63.8)
	Employed	63 (36.2)
Family History of DM	Yes	53 (30.5)
	No	101 (58.0)
	Unknown	20 (11.5)
Family History of HPT	Yes	75 (43.1)
	No	79 (45.4)
	Unknown	20 (11.5)

Table 1A: Age of onset for Education level

Group	Mean (SD)	95% CI	
		Upper	Lower
None, 1 and 2 education	28.74 (8.86)	27.26	30.23
Tertiary Education	26.42 (7.27)	23.75	29.08

Among subjects identified, the mean age group of the subjects is 42.3 (SD:10.67). There were more males in gender (64.9%) and most of the subjects were still single (70.1%). 20 of them (11.5%) are divorced, separated or widowed. Surprisingly among the subjects, 32 of them (18.4%) completed tertiary school and most of them 69.0% at least completed secondary school. For those who successfully completed their tertiary school, they have a mean (SD) age of onset at 28.7 year-old (8.9, CI=23.8-29.1). (Table

1A). It means the onset of the illness for those completed tertiary educations are after the tertiary educations.

However sad to say, only 36.2% are employed and 63.8% of them are unemployed. It portray the outcome of the cohort is not favorable, i.e. relatively poor.

From the cohort, 30.5% of the subjects have family history of diabetes mellitus while 43.1% of them have family history of hypertension. There is an association between family history of diabetes and prevalence of diabetes all over the world [36–38]. In Malaysia, family history play a important role with 14.% of those with Diabetes having significant family history [38]

7.2 Clinical Data of study participants:

In the current study, the DUP is 12 months (IQR:18). 59.2% of them present to psychiatric service within 1 year of DUP, but 4.6% of them come to psychiatry only after 1 year of psychosis onset. (Table 2A)

Table 2: Clinical Data of study participants

Table 2A: DUP

Variables	Median (min, max, IQR)
DUP	12 (1, 480, 18)

Categorize: DUP

Durations (months)	n (%)
<12 months	103 (59.2)
>12 months	63 (36.2)
Unknown	8 (4.6)

*DUP= duration of untreated psychosis

Table 2B: Comorbidity

Variables	Subtypes	n (%)
Comorbidity: 2.1 None		130 (74.7)
2.2 Substance		27 (15.5)
	Cannabis	12 (44.4)
	Opiates	5 (18.5)
	Methamphetamine	17 (63.0)
	Inhalants	1 (3.7)
	Alcohol	4 (14.8)
	Others	2 (7.4)
2.3 Depression		9 (5.2)
2.4 Medical Illness		
	DM	
	Yes	22 (12.6)
	No	137 (78.7)
	Unknown	15 (8.6)
	HPT	
	Yes	23 (13.2)
	No	136 (78.2)
	Unknown	15 (8.6)
	IHD	
	Yes	4 (2.3)
	No	155 (89.1)

	Unknown	15 (8.6)
	Dyslipidaemia	
	Yes	19 (10.9)
	No	140 (80.5)
	Unknown	15 (8.6)

2.5 Smoking	Yes	97 (55.7%)
	No	77 (44.3%)
2.6 Follow Up	Regular	101 (58.0)
	Irregular	73 (42.0)
2.7 Traditional Healer	Yes	66 (37.9)
	No	104 (59.8)
	Unknown	4 (2.3)

Table 2C: Treatment

2.8 Antipsychotic Oral:		n (%)
2.8.1 Typical	Total	62 (35.6)
	Chlorpromazine	11 (17.4)
	Haloperidol	14 (22.6)
	Trifluoperazine	2 (3.2)
	Perphenazine	1 (1.6)
	Sulpiride	28 (45.2)
	Others	6 (9.8)

2.8.2 Atypical	Total	102 (58.6)
	Risperidone	57 (55.9)
	Olanzepine	21 (20.6)
	Quetiapine	8 (7.8)
	Clozapine	11 (10.8)
	Aripiprazole	3 (2.9)
	Others	2 (2.0)
2.8.3 Depot	Total	67 (38.5)
	Modecate	11 (16.4)
	Fluanxol	49 (73.1)
	Zuclopenthixol	2 (3.0)
	Paliperidone	4 (6.0)
	Others	1 (1.5)
2.8.4 Combination Treatment:		
	Yes	62 (35.6)
	No	112 (64.4)

2.8.4.1 Type of Combination	n,(%)
Risperidone and I.M. Fluanxol	24 (39.3)
Risperidone and I.M. Modecate	3 (4.9)
Chlorpromazine and I.M. Fluanxol	5 (8.2)
Sulpiride and I.M. Fluanxol	4 (6.6)
Other combinations	25 (41.0)

Table 2D: Other concomitant treatment

2.9 Antidepressant	Yes No	6 (4.0) 168 (96)
2.10 Anticholinergic	Yes No	63 (36.2) 111 (63.8)
2.11 Benzodiazepine	Yes No	32 (18.4) 142 (81.6)

In table 2B, 27 of the subjects (15.5%) had comorbidity of substance abuse and 9 (5.2%) of them suffered from depression. Among those with comorbid substance abuse, cannabis (12, 44.4%) and methamphetamine (17, 63.0%) are the highest prevalence. About half of them (55.7%) are smokers. In terms of follow up, half of them come for regular follow up (58% Vs. 42%). After 10 years of treatment and follow up, 22 of them (12.6%) are diagnosed to have Diabetes Mellitus, 23 of them (13.2%) have hypertension, while 19 (10.9%) of them has dyslipidaemia and 4 (2.3%) has Ischemic Heart Disease (IHD). However, many of them are undiagnosed and did not go for follow up.

Presently, a total of 102 (58.6%) subjects are on atypical antipsychotic and 62 of them (35.6%) on typical antipsychotic. Sulpiride is the commonest typical antipsychotic used (28, 45.2%) while Risperidone is the highest atypical antipsychotic used (57, 55.9%). Out of the cohort, there are total of 67 (38.5%) subjects on depot injection, with I.M. Fluanxol the most common among all, 49 (73.0%). (Table 2C). Among 174 subjects, 62 (35.6%) are taking more than one antipsychotic (combination treatment), while 112 (64.4%) of them are only on one type of treatment, either on typical or atypical antipsychotics. For those who has combination treatment, most common combinations treatment are Risperidone combine with I.M. Fluanxol (24, 39.3%), Chlopromazine

with I.M. Fluanxol (5, 8.2%), Sulpiride with I.M. Fluanxol (4, 6.6%), Risperidone with I.M. Modecate (3, 4.9%) and other combinations (25, 41.0%). (Table 2C)

Table 2D shows high usage of anticholinergic agents, 63 subjects (36.2%), and 18.4% of all the subjects are on concomitant benzodiazepine used.

Table 3: Metabolic parameter measurement at baseline

Variables	*N*	*Median (IQR)*
4.1 FBS	159	4.4 (1.0)
Missing	15	Min: 2
		Max:11.2
Normal	128 (80.5%)	
Impaired	9 (5.7%)	
DM	7 (4.4%)	

Variables	*N*	*Mean (SD)*
4.2 Weight	174	58.6 (12.28)
4.3 Height	174	161.7 (8.59)
4.4 Systolic BP	174	117.4 (14.09)
4.5 Diastolic BP	174	73.8 (9.82)

Variables	*N*	*Mean (SD)*	
4.4 BMI	163	22.38 (4.15)	
	Normal	102 (58.6%)	
	Overweight	22 (12.6%)	
	Obese	37 (21.3%)	
HPT Subject	6 (3.8%)		*
DM Subject	7 (4.4%)		*

* Set at BP=140/90mmHg, FBS=6.1mmol/l

Table 3 shows the baseline metabolic parameters. 10 years ago, the mean (SD) weight of the cohort was 58.6 kg (12.28) with the mean (SD) BMI of 22.38 kg/m2 (4.15). At the initial stage, 102 (58.6%) have normal BMI, while 22 (12.6%) of them overweight and 37 (21.3%) are obese. Mean systolic blood pressure (SBP) is 117.4 (SD:14.09) while mean (SD) diastolic blood pressure (DBP) is 73.8 mmHg (9.82). The median (IQR) of Fasting Blood Sugar (FBS) is 4.4mmol/l (1.0). Among all, at baseline, 6 (3.8%) persons are hypertensive and 7 of them have diabetes (4.4%).

During the current assessment, all the metabolic parameters are significantly increased (Table 4). The mean (SD) weight is 70.1 kg (17.12) while BMI has increased to a mean of 26.4 kg/m2 (5.76). Out of all subjects studied, only 27.6% of subjects are within normal BMI while 24 (16.6%) are overweight and the most worrying aspect is 81 (55.9%) has fall into the obese categories. These excludes those 117 subjects who do not have information, but investigator felt the prevalence would be much higher if were to include those missing.

For the waist circumference, the mean (SD) is 88.41 cm (12.93), 43 of male cohort (45.7%) has obese waist and 51 (54.3%) of them has normal waist compared to females with 18 (31.0%) normal waist and 40 (69.0%) obese waist. There is a significant difference where female has higher waist circumference compare with male (p-value 0.007).

Of the cohort, after 10 years of diagnosis and treatment, 63 (36.2%) developed metabolic syndrome, with 23.2% of them are hypertensive, and 41 (28.1%) of them are diabetes. (Table 4A)

For the blood parameters, the mean (SD) for total Cholesterol is 5.04 mmol/l (1.18), LDL is 3.01 mmol/l (1.06), while median (IQR) for HDL is 1.2 mmol/l (0.60) and TG is 1.2mmol/l (1.1). 49 of them (23.9%) has high LDL, 88 (42.9%) of them has low HDL and another 49 of them (35.8%) has high TG levels. (Table 4)

Table 4: Latest metabolic parameter measurement:

Variables	n (%)	Mean (SD)
4.1 Weight		70.05 (17.12)
4.2 Height		162.79 (8.69)
4.3 BMI		26.35 (5.76)
Normal	40 (27.6%)	
Overweight	24 (16.6%)	
Obese	81 (55.9%)	
4.4 Waist (cm)		88.41 (12.93)
Waist by Gender:		
Male:		
Total	94	
Obese waist	43 (45.7)	
No Obese waist	51 (54.3)	
Female:		
Total	58	
Obese waist	40 (69.0)	
No Obese waist	18 (31.0)	
Chi-Square: 7.82	*P-value: 0.007*	

Variables	*n (%)*	*Mean (SD)*
4.5 Cholesterol:	137	
missing	37	
4.5.1 Total Chol		5.04 (1.18)
4.5.2 LDL		3.01 (1.06)
Normal Level	88 (42.9%)	
High Level	49 (23.9%)	

Variables	*n (%)*	*Median (IQR)*
4.5.3 HDL		1.2 (0.6)
Min		0.5
Max		4
Normal HDL	49 (35.8%)	
Low HDL	88 (64.2%)	
4.5.4 TG		1.2 (1.1)
Min		0.5
Max		5.5
Normal Level	88 (64.2%)	
High Level	49 (35.8%)	
4.6 FBS		5 (1.1)
Min		3.8
Max		29
Normal	105 (71.9%)	
Impaired	16 (11.0%)	
DM	25 (17.1%)	

Variables	*Mean (SD)*
Systolic BP	128.39 (12.87)
Diastolic BP	80.94 (9.21)
Hypertensive	**36 (23.2%)**
DM	**41 (28.1%)**

Table 4A: Metabolic Syndrome:

Metabolic Syndrome	n (%)
Yes	63 (36.2)
NO	73 (42.0)
Unknown	38 (21.8)

Table 5: Association factors with Metabolic Syndrome

Variable		B	Unadjusted Odd ratio	95% CI Low	Up	Wald (df)	P-value
5.1 Smoker:							
	No	0	1				
	Yes	0.379	1.46	0.73	2.91	1.15 (1)	0.283
5.2 Age:							
	No						
	Yes	-0.147	0.86			0.74 (1)	0.392
5.3 Education:							
	No	0	1				
	Yes	-1.266	0.28	0.08	1.06	3.50 (1)	0.061

5.4 Gender:							
Male	No	0	1				
	Yes	0.18	1.20	0.60	2.39	0.26(1)	0.610
5.5 Ethics:							
Malay	No	0	1				
	Yes	-0.545	0.58	0.29	1.15	2.46 (1)	0.117
Chinese	No	0	1				
	Yes	0.365	1.44	0.70	2.95	1.00 (1)	0.317
Indian	No	0	1				
	Yes	0.610	1.84	0.59	5.71	1.12 (1)	0.290
5.6Medication							
Typical	No						
	Yes	0.464	1.59	0.76	3.35	1.50(1)	0.221
Atypical	No						
	Yes	-0.696	0.50	0.24	1.04	3.44 (1)	0.064
5.7 Depot	No						
	Yes	0.812	2.25	1.10	4.60	4.95 (1)	**0.026**

5.7.1							
Modecate							
	No						
	Yes	0.735	2.09	0.52	8.44	1.06 (1)	0.302
Fluanxol							
	No						
	Yes	0.835	2.31	1.05	5.09	4.28 (1)	**0.039**
5.8 Substance	No						
	Yes	1.482	4.40	1.40	13.89	6.39 (1)	**0.012**
5.9 Depression	No						
	Yes	-0.174	0.841	0.20	3.51	0.06 (1)	0.812
6.0 PA	No						
	Yes	-1.036	0.355	0.126	1.00	3.85 (1)	**0.050**
6.1 DUP							
	No						
	Yes	0.381	1.46	0.72	2.96	1.12 (1)	0.289

Table 5A: Association Between Combination Treatment and Metabolic Syndrome:

Group	n	MetS, n(%)	No MetS, n(%)	X^2-statistic (df)	P-value
Combination Treatment:					
Yes	50	18 (36)	32 (64)	3.389 (1)	0.066
No	86	45 (52.3)	41 (47.7)		

*Chi-square test

Those subjects on Depot are associated with metabolic syndrome (CI=4.60-4.95,OR: 0.81, p=0.026) and in particular Fluanxol, (CI=1.05-5.09, regression coeff: 0.84, p=0.039).

Moderate to high physical activity group is significantly associated with lower metabolic syndrome or in other words, physically active group is negativly associated with metabolic syndrome. (CI=0.13-1.00, OR: -1.04, p=0.050). Therefore moderate or vigorous activities are recommended as protective factors for metabolic syndrome.

However, another significant finding is comorbidity substance abuse/ substance use disorder. From the result, comorbid substance disorder positively associated with metabolic syndrome, whereby the group has increase by 1.48 (CI=1.40-13.89, OR: 1.48, p=0.012) compare those without substance abuse to develop metabolic syndrome.

Significant factors were included into multiple regression analysis.

Table 6: Multiple Logistic Regression analysis of comorbidity of substance abuse, physical activity and I.M. Fluanxol depot with metabolic syndrome.

Variable	*B*	*Adjusted Odd ratio*	*95% CI*		*Wald (df)*	*P-value*
			Low	*Up*		
6.1 Substance	1.20	3.32	1.02	10.81	4.0 (1)	0.047 **
6.2 PA	-0.88	0.41	0.14	1.21	2.6 (1)	0.107
6.3 I.M. Fluanxol	0.76	2.12	0.91	4.94	3.0 (1)	0.082

Multiple Logistic Regression:

Three variables are significant associated with metabolic syndrome based on simple logistic regression, i.e. physical activity, I.M. Fluanxol and also comorbid substance abuse. By using multiple logistic regression and check for 2 way interaction between variables, the substance abuse is still significantly associated with metabolic syndrome despite adjusted both physical activity and depot of I.M. Fluanxol. (Table 6).

7.3 Comparison Between Parameters:

In the research conducted, investigator also looks into differences between the metabolic parameters, namely the Systolic BP, Diastolic BP, BMI and Fasting Blood Glucose (FBS) after 10 years.

Table 7: Comparison of mean metabolic parameters after 10 years:

Group	*Mean (SD)*	*Mean Difference (95% CI)*	*t-statistic (df)*	*P-value*
7.1 Systolic BP				
Before	117.1 (14.49)	(8.24,13.39)	8.29 (146)	<0.001
After	127.9 (12.85)			
7.2 Diastolic BP				
Before	73.6 (9.91)	(5.19,9.01)	7.35 (146)	<0.001
After	80.7 (9.21)			
7.3 BMI				
Before	22.35 (4.15)	(3.23,4.81)	10.07 (142)	<0.001
After	26.37 (5.72)			

* Paired t-test.

Table 8: Changes in Blood Glucose Level after 10 years.

Group	*Median (IQR)*	*Z-Statistic*	*P-value*
FBS			
Before	4.4 (1.0)	-7.402	<0.001
After	5.0 (1.1)		

*Wilcoxon Signed Rank Test

From the table 7 and 8, there are significant differences between all the metabolic parameters, Systolic BP, Diastolic BP, BMI and Fasting Blood Sugar level ($p<0.001$). By using paired t-test, the means and Confident Interval (CI) are calculated. The mean (SD) of SBP changes from 117.1 mmHg (14.49) to 127.9 mmHg (12.85) (CI: 8.24, 13.39), DBP changes from 73.6 mmHg (9.91) to 26.37 mmHg (5.72) (CI: 5.19, 9.01), BMI change from 22.35 kg/m2 (4.15) to 26.37 kg/m2 (5.72) (CI: 3.23, 4.81).

For Blood Glucose level, the changes is not normally distributed, therefore author is using Milcoxon Signed Rank Test for the statistic analysis. (table 8).

The difference of blood glucose level are significantly difference ($p<0.001$) with Median (IQR) of 4.4mmol/l (1.0) to 5.0 mmol/l (1.0).

Univariate analysis association of change in metabolic variables:

Table 9: Change in Systolic Blood Pressure

Group		*n*	*Change in SBP Mean (SD)*	*95% CI*	*B*	*T*	*p-value*
9.1 Age	<43	88	8.88 (14.91)	-10.02, 0.41		-1.82	0.071
	>43	59	13.69 (16.79)				
9.2 Gender	Male	91	8.56 (15.58)				
	Female	56	14.48 (15.64)	0.68, 11.16	5.92	2.24	0.027 **
9.3 DUP	<12 months	90	10.46 (16.10)	-6.24,4.67		-0.29	0.776
	>12 months	54	11.24 (15.89)				
9.4 Treatment	Yes	134	11.33 (15.75)	-17.25, 2.41		-1.49	0.138
	No	11	3.91 (17.20)				
9.5 antipsychotic	Typical	44	11.91 (17.34)	-7.34,4.06		-0.57	0.570
	Atypical	94	10.88 (14.74)				
9.6 antipsychotic	Depot	60	10.23 (14.28)	-4.41,6.23		0.34	0.059
9.7 Substance		20	10.20 (13.19)	-7.07,8.12		0.14	0.891
9.8 Depression		7	4.14 (16.21)	-5.32,19.00		1.11	0.268
9.9 PA	Low PA	121	9.74 (16.94)				

	High PA	19	17.58 (15.03)	0.07, 15.60		2.00	**0.048 ****
9.10 Education	0, 1	15	7.27 (13.04)	-12.25, 4.81		-0.86	0.390
	2,3	130	10.98 (16.09)				

* Independent t-Test

		n	*Mean (SD)*	*F statistic (df)*	*p-value*
9.11 Race	Malay	76	9.79 (14.17)	1.35(3,143)	0.262
	Chinese	50	14.14 (16.76)		
	Indian	17	6.53 (19.97)		
	Others	4	7.00 (10.39)		

*one way ANOVA

+PA=Physical Activity

Table 10: Linear Regression of systolic Blood Pressure:

Variable	*B*	*t*	*95% Ci*		*P-value*
			Low	*Up*	
Gender	5.92	2.24	0.68	11.16	0.027
PA	7.83	2.00	0.07	15.60	0.048

Multiple Logistic Regression:

Table 11: association between changes of systolic BP with variables.

Variable	*B*	*t*	*95% CI*		*P-value*
			Low	*Up*	
Low Physical Activity	7.96	2.06	0.33	15.60	0.041
Gender (Female)	6.45	2.37	1.08	11.82	0.019

Table 9 is the result of association between variables with changes in systolic blood pressure (SBP). By using independent t-test, 2 variables are significant association with change in systolic BP, i.e. gender and physical activity. Linear regression shows Female gender and physical activity is significantly associated with change in systolic blood pressure. (Table 9 and 10).

After multiple logistic regression (table 11), both variables (gender and physical activity) are still significantly associated with changes in systolic BP. Female is more likely to have increase in systolic blood pressure compare with male (CI=1.08-11.82, OR: 6.45, p=0.019). However from the research conducted, low physical activity group has lower change in systolic BP, i.e. high physical activity group are having higher change in SBP (CI=0.33-15.60, OR: 7.96, P=0.041)

Table 11: Change in Diastolic Blood Pressure:

Group		*n*	*Change in DBP Mean (SD)*		*(95% CI)*	*t*	*p-value*
11.1 Age	<43	88	7.75 (11.31)		-2.29, 5.51	0.82	0.415
	>43	59	6.14 (12.33)				
11.2 Gender	Male	91	6.13	(11.13)	-1.38,6.47	1.28	0.202
	Female	56	8.68	(12.55)			

11.3 DUP	<12 months	90	6.58	(11.65)	-6.21,1.62	-1.16	0.249
	>12 months	54	8.87	(11.26)			
11.4 Treatment	Yes	134	7.16	(11.76)	-8.01, 6.59	-0.19	0.848
	No	11	6,45	(11.82)			
11.5 antipsychotic	Typical	44	7.48	(12.16)	-4.73,3.67	-0.25	0.805
	Atypical	94	7.55	(11.72)			
11.6 antipsychotic	Depo	60	5.40	(12.45)	-0.98,6.81	1.48	0.141
11.7 Substance		20	7.20	(9.33)	-5.56,5.69	0.02	0.981
11.8 Depression		7	2.14	(14.80)	-3.63,14.38	1.18	0.240
11.9 PA	High PA	19	13.53	(11.17)	1.51, 12.91	2.50	**0.014 ****
	Low PA	121	6.31	(11.75)			
11.10 Education	0, 1	15	4.40	(9.78)	-9.38,3.29	-0.95	0.344
	2,3	130	7.45	(11.95)			

*Independent t-test

Race	*n*	*Mean (SD)*	*F statistic (df)*	*p-value*
Malay	76	7.16 (12.27)	0.77 (3,143)	0.514
Chinese	50	8.34 (11.52)		
Indian	17	3.35 (10.14)		
Others	4	6.50 (9.68)		

*one way ANOVA

Table 11 is the result of association between variables with change in diastolic BP. Among the variables, only physical activity is significantly associated with changes, after 10 years. However, the high physical activity is associated with more change in DBP, after linear regression analysis. (Table 12)

Table 12: Linear Regression of systolic Blood Pressure:

Variable	*B*	*t*	*95% CI*		*P-value*
			Low	*Up*	
PA	7.21	2.50	1.51	12.91	0.014

Table 13: Change in BMI:

Group		*n*	*Change in BMI Mean (SD)*		*95% CI*	*t*	*p-value*
13.1 Age	<43	83	4.25	(4.77)	-1.06,2.14	0.66	0.508
	>43	60	3.71	(4.80)			
13.2 Gender	Male	88	3.42	(4.65)	-0.06,3.16	1.91	0.058
	Female	55	4.97	(4.85)			
13.3 DUP	<12 months	87	4.57	(5.23)	-0.50,2.78	1.50	0.170
	>12 months	52	3.43	(3.73)			
13.4 Treatment:	Yes	128	4.08	(4.72)	-3.77, 2.18	-0.53	0.598
	No	11	3.28	(5.60)			
13.5 antipsychotic	Atypical	89	4.72	(4.77)	-3.54,-0.28	-2.32	0.022**
	Typical	51	2.80	(4.54)			
13.6 antipsychotic	Depot	53	3.36	(4.52)	-0.59,2.71	1.27	0.205
13.7 Substance		20	3.33	(3.50)	-1.41,3.16	0.97	0.339
13.8		8	4.00	(4.45)	-3.37,3.54	0.048	0.961

Depression							
13.9 PA	Low PA	117	3.81	(4.43)	-5.52,-0.89	-1.50	0.148
	High PA	19	6.12	(6.47)			
13.10 Education	0, 1	15	2.06	(5.11)	-4.82,0.36	-1.70	0.091
	2,3	124	4.29	(4.76)			

*Independent t-test

Race	*n*	*Mean (SD)*	*F statistic (df)*	*p-value*
Malay	72	4.85 (5.34)	2.00 (3,139)	0.116
Chinese	52	3.25 (3.95)		
Indian	15	2.29 (3.80)		
Others	4	5.57 (4.90)		

*one way ANOVA

Table 14: Linear Regression analysis

Variable	*B*	*t*	*95% CI*		*P-value*
			Low	*Up*	
Atypical antipsychotic	1.91	2.32	0.28	3.54	0.022

For the changes in BMI, table 13 shown type of antipsychotic play an association with change in BMI. Author found that there is a positive relationship between atypical antipsychotic with change in BMI. With every change of 1 unit of BMI, atypical antipsychotic group has increase by 1.91 compare with those on typical antipsychotic. (CI=0.28-3.54, OR: 1.91, P=0.022). (Table 14)

Table 15: Change in Fasting Blood Sugar:

Group		n	Change in FBS Median (IQR)		z-statistic	p-value
15.1 Age	<43	85	0.60	(0.90)	-0.02	0.977
	>43	59	0.60	(1.51)		
15.2 Gender	Male	88	0.60	(0.98)	-0.43	0.670
	Female	56	0.60	(1.28)		
15.3 DUP	<12 months	88	0.75	(1.17)	-2.29	0.022**
	>12 months	54	0.40	(1.04)		
15.4 antipsychotic	Typical	50	0.60	(1.23)	-0.38	0.705
	Atypical	93	0.60	(0.95)		
15.5 antipsychotic	Depot	58	0.45	(0.90)	-1.07	0.285
	No Depot	85	0.70	(1.25)		
15.6 Substance	Yes No	21 121	0.30 0.69	(0.90) (1.20)	-1.44	0.151
15.7 Depression	Yes No	8 134	0.60 0.50	(1.10) (1.28)	-0.31	0.757

15.8 PA	Low PA	122	0.60	(1.10)	-0.01	0.990
	High PA	18	0.55	(1.25)		
15.9 Education	0, 1	14	0.25	(1.55)	-2.06	**0.040****
	2,3	128	0.65	(1.15)		

* Mann-Whitney U Test

Race	*n*	*Median (IQR)*	*X^2 statistic (df)*	*p-value*
Malay	72	0.60 (1.00)	3.86(3)	0.277
Chinese	52	0.40 (1.20)		
Indian	15	0.95 (1.73)		
Others	4	0.65 (3.80)		

*Kruskal-Wallis test

Table 15 shows the relationship between changes in FBS with variables. There is a relationship between education level and duration of untreated psychosis (DUP) with change in fasting blood sugar level (FBS). Having a shorter DUP has a greater median increase in FBS 0.75 (IQR=1.17, z=-2.29) when compared with the median difference in FBS for patients with DUP more than 12 months (040, IQP=1.04) (p=0.022). Education level of secondary or tertiary has higher median difference of FBS 0.65 (IQR=1.15, z -2.06) when compared to those with lower levels of education 0.25 (IQR=1.55) p=0.040.

8.1 Discussions:

Schizophrenia patients are well known to have higher morbidity and mortality compared with the general populations, namely - obesity, type 2 diabetes mellitus, dyslipidaemia, hypertension. Current literature reveals they might have a shorter life-expectancy of 20% less than others[39].

Among all, metabolic syndrome is one of the major leading cause of morbidity and mortality especially among patients with schizophrenia, as it will lead to higher risk of coronary heart disease, myocardial infarction as found by Isomaa. B et al (2001) and Trevisan M et al. (1998)[40,41].

Some investigators also have the opinion that those with mental health issues are lacking in physical activity and that they also have poor nutritional intake, a sedentary life-style, increased rates of smoking and also abnormalities of hypothalamic-pituitary-adrenal axis[13 42–45]. This put our patients with schizophrenia at a much higher risk.

For the patients registered with the National Mental Health Registry of Schizophrenia HKL in the year 2004-2005, there was a cohort of 394 subjects. In the cohort there are more Males (113, 64.9%) than Females (61, 35.1%). The ethnicity of groups are the same as Malaysia population which consists mainly of Malays (90, 51.7%), Chinese (59, 33.9%) and Indians (19, 10.9%). Surprisingly among the cohorts studied, most of them are single (122, 70.1% Vs 32, 18.4%) while the other 20 (11.5%) are divorced, separated or widowed. Most of them had studied till secondary school (120, 69.0%) and some (32,18.4%) even achieved tertiary education. Out of the 174 subjects, 63 (36.2%) are unemployed. that is worrying as it portrays the outcome of the cohort is relatively poor.

For the Duration of untreated psychosis (DUP), the median is 12 months (18). 103 (59.2%) of then had DUP of less than 1 year (12 months) while 63 of them (36.2%) hads DUP of more than 1 year.

Schizophrenia patients have high risk of comorbidities. Peter F.Buckley (2008) [49] found that anxiety disorder (15-23%), substance abuse (47%) and depression (50%) are among highest comorbidities associated with schizophrenia. One of the latest literature reviews by Raphael J. Braga (2013) also found prevalence of anxiety disorders are as high as 38.3%, consist mainly social phobia, PTSD and Obsessive Compulsive Disorder[46].

In the current research, author noticed that among the cohort, 15.5% are actively involved in substance, mainly methamphetamine (63%) and cannabis (44.4%). Other substances involved are Opiates and alcohol. There are 9 subjects (5.2%) diagnosed that have depression. Depression has been known to be common in schizophrenia. However, it always being underestimated and under-reported. There are many reasons behind that. One of the reason is the overlapping of depressive symptoms and the common symptoms of schizophrenia symptoms e.g. Negative symptoms of Schizophrenia; Extrapyramidal Side Effects which can mimic depression[47,48]. Literature reported up to 30-40% of patients with Schizophrenia have depressive symptoms during follow up post-discharge[49]. Among the group, they also associated with poorer outcome, work impairment, low activity and suicidal tendencies. Another author examined female patients suffering from Schizophrenia and reported 20% has depression[50]. Some even reported rates as high as 20-80%[45]

The prevalence found from the research above is shows a figure much less than the others. The author believes under-reporting and recognition is the main problem. In a study conducted in USA, despite high awareness of the presence of depression among patients with Schizophrenia, more than quarter of the psychiatrist hardly ever or even

never prescribed adjunctive antidepressants.[48] Peter Bosanac identify social isolation, unemployment, low income and poor physical health plus misuse of alcohol or substances are contributing to higher rate of depression among patients with Schizophrenia.[51]therefore it is important to be able to pick up and manage depression in Schizophrenia.

According to the NMHR outcome study published in 2008 [52], 70% were never or unemployed at the time of registration. After 10 years, 63.8% remains unemployed while 36.2% are holding a job at time of assessment.

The mean weight at the initiation of the study was 58.6 kg (SD:12.3), mean BMI was 22.38 (SD: 4.2). 102 (58.6%) of them were normal weight, 22 (12.6%) were overweight while 37 (21.3%) were obese.

After 10 years, most of them are either overweight or obese (72.5%). The mean weight is 70.1 kg (SD:17.12) with mean BMI of 26.35 (SD:5.76).

27.6% (40 subjects) remains within normal BMI, but 24 (16.6%) are overweight and 81 (55.9%) are obese now. Among male gender, 43 (45.7%) had obese waist circumference(more than 90cm) while for female, 40 (69.0%) of them are having obese waist (more than 80cm). There is a significant difference between Male Vs. Female obese waist with P-value=0.007.

For fasting blood glucose (FBS), during registration year, the median of blood glucose was 4.4 mmol/l (IQR:1.0), while after 10 years down the road, the median of blood fasting glucose is 5.0mmol/l (IQR: 1.1).

Among the cohort at beginning, 7 (4.4%) are diabetic. However, after 10 years, the amount of abnormal glucose test has increase dramatically. A total of 16 (11%) of them are having impaired glucose test, whereby 25 (17.1%) are diabetic and 36 (23.2%) of them have hypertensive.

8.1 PHYSICAL ACTIVITY:

Physical activity is important in maintaining a good physical health. Physical activity uses energy and for different type of activity, i.e. sedentary, mild, moderate or vigorous activities uses up different total energy.

As it has been extensively studied, one of the risk factors of developing metabolic syndrome is life-style factor. Among all, one of the more significant factors is physical activity. From the research conducted by the author, subjects with moderate to high level of physical activity are less likely to develop metabolic syndrome ($P<0.05$) with regression coefficient 0.36 (CI=0.126,1.00. regression coeff: 0.36, $p<0.05$). This means with increased physical activity of moderate to vigorous amount, the metabolic syndrome is reduced by 0.36 compare with those low in physical activity. This is the similar findings from most of the research done all over the world. David E. Laaksonen et al. (2002)[53] found low levels physical activity (sedentary) can predict the chance of develop metabolic syndrome. With an increase in physical activity, the risk can be reduced as much as 75%.[53] One literature also described vigorous and moderate physical activity have odd ratios of 0.52 (95% CI: 0.40,0.67) and 0.78 (95% CI: 0.63, 0.96) adjusted the confounders.[54] Aerobic exercise also is proven to reduce each metabolic parameter.[55]

How much physical activity will significantly reduce risk of metabolic syndrome? Till date, there is no clear-cut on how much minimal physical activity to prevent metabolic syndrome. However, it is important to have regular, moderate to vigorous activity and persistent. Current recommendation[56,57] is 30 minutes or more moderate-intensity physical activity or at least 20 minutes, 3 times a week of vigorous activity.[58] Persistent

is a key word in dealing with metabolic syndrome. Soren Brage also found physical activity are inversely related to metabolic risk with p-value 0.008[59]. .

Bear in mind that not only increased physical activity is important, reduction in sedentary life-style is equally important. Several studies also conclude sedentary life-style (watching television/ videos) can lead to obesity and type 2 diabetes mellitus in future[60–62].

Randomized controlled trials also proves that regular physical activity are able to prevent type 2 diabetes in those high-risk group, especially those who are having impaired glucose tolerance test or overweight[63].

Although physical activity is important, sad to say only a few people practice adequate exercise. From the cohort, only 20 people has moderate to high intensity physical activity compared to 126 people who did not fulfill the minimal requirement of physical activity. Not only that, another corner stone from many studies also shows the drop out from regular exercise group is as high as around 50% of the supervised program[64]. One of the good ways to promote compliance to physical exercise is to make it enjoyable, affordable and easy accessible[64].

In view of our patients with schizophrenia are at higher risk of both developing metabolic syndrome and non-compliance to the physical activity, a therapist should emphasize more on life-style behavior and also diet control. Not only that, harmful life-style like over-eating, smoking, drinking alcohol, substance abuse should be advised and stopped.

8.2 SUBSTANCE ABUSE/DEPENDENCE:

From the research conducted, after multiple logistic regression, substance abuse is associated with metabolic syndrome after adjusted I.M. Fluanxol and physical activity. The substance group has significantly 1.20 more compare non-substance abuser (CI=1.02-10.81, Regression coeff: 1.20, p=0.047) to develop metabolic syndrome.

Substance abuse has been a major issue among schizophrenia patients. They have poorer outcome and also compliance[65,66] . Not only that, those with the substance problems, tends to have more psychotic symptoms, more agitation and aggression, less support and home to stay, blood born infection (e.g. needle sharing) and also uses medical facilities more frequently.[66]. They also have more frequent relapses and admissions to hospital compared to those schizophrenia patients without substance issues.[67] Older age group, higher education, longer use or dependent on substance, comorbid of physical illness, higher BMI, higher body weight are predictor of developing metabolic syndrome. [68]

Substance abuse also has a negative association with employment outcome. Studies have shown those with substance issue were less likely to be able to hold a job compared to those patients with schizophrenia without substance issues. Due to the complexity of substance usage in schizophrenia patients, there is literature looking into relationships between substance abuse/dependence and metabolic syndrome. Vermani et al. 2007 proposed a few theories that leads to metabolic syndrome among drug abuse.[69] . They found those who are taking substance are significantly non-compliance to treatment among diabetics, therefore leading to higher rates of diabetes complications. Not only that, the literature also noticed that nutrition education, i.e. eating better and healthier among substance abusers can promotes better treatment outcomes.[69] The same articles also examined the theory that cognitive deficits plays a role especially among those abusing methamphetamine, and also metabolic activities per se. Both cognitive

deficits and metabolic abnormalities lead to nutritional problems.[69]. Not only that, some authors also found oral health issues in meth abuser[69,70], results in poor oral hygiene, poor chewing mechanism, xerostomia, more rampant caries and excessive tooth wear, all leads to poorer digestion and hence nutrition absorption and subsequently leads to metabolic syndrome. Virmani et al. also found substance dependence might lead to cell damage, cell excitotoxicity, energy producing abnormalities and lower the anti-oxidant potential of the cells which might be the pathogenesis of metabolic syndrome among substance abuser.

Most of the literatures conclude methamphetamine use leads to losing weight. In the history, methamphetamine initially design and use in World War II to allow soldiers to stay awake for fight. However, in 1950's, it is commonly use in treatment of depression and in diet pills for obesity.[71] However, in the research conducted, investigator found those patients with schizophrenia and comorbid substance abuse (mainly methamphetamine and marijuana) are associated with metabolic syndrome. Why is it so? There are hypothesis why a person with substance use disorder are related to metabolic syndrome.

Methamphetamine use can be divided into stages. After taking the substance, the user will go into "rush" stage follow by "high" stage, which typically lasted 4-16 hour. After that, he or she will enter into tweaking stage where they will feel emptiness and dysphoria. During this stage, most of them will need take more substance to maintain "high stage. After that, they will enter into crash phase in which typically lasted 1 to 3 days. During this period, body epinephrine depleted and body uses the "crash" period to replenish its supply. According to Zorrick T et al. methamphetamine withdrawal can be divided into acute phase (7-10days) and sub-acute phase (can last 2 to 3 weeks). During the acute withdrawal stage, abusers will have increase in appetite, hyperphagia on top of

craving for methamphetamine. [72] Not only that, research had found during this time, the user will have mood symptoms especially depressive symptoms. It is hypothesis, to overcome the depressed mood, they will crave for "happy" food, which are high in glucose, and carbohydrate therefore indirectly lead to metabolic syndrome. On top of that, due to the stimulant property, during methamphetamine intake, patients will have reduce appetite, loss of weight and malnutrition (as body go into a deprive stage, from main nutrition), either from poor oral intake or from its complications to the health especially oral health, which also known as "meth mouth"[67] which subsequently leads to malnutrition. During the withdrawal stage, the body will try replenishing the starvation stage by eating more than he or she used to eat which will indirectly leads to metabolic syndrome.

There are also evidence from research that for patients who has been using methamphetamine for long, there are changes in both α2-adrenoceptor and β-adrenoceptor, which are correlated with homeostasis of food intake: 24-h mean β-adrenoceptor (which act on lateral hypothalamus) binding is reduced and α2-adrenoceptor (which binds to medial hypothalamus) binding is increased upon methamphetamine withdrawal, which explain the feeding patterns during withdrawal, i.e. rebound feeding occurs.[73]

Another reason why patient with schizophrenia and co-morbid substance abuse are associated with metabolic syndrome is those with co-morbid substance, they tends to neglect their health. They might care-less to their physical health, eat less healthy, smokes and neglect self-health. This leads to high risk to develop physical illnesses, example dyslipidaemia and diabetes therefore contribute to occurrence of metabolic syndrome.

In the current research, the number of schizophrenia patient with comorbid substance abuse/dependent is much less compare to other previous studies. This is because substance abusers tend to be non-compliance and non-adherent to treatment and follow up.[74,75] Therefore they are likely to be not regular in follow up and therefore easily lost to follow up[45] Not only that, according to the self-medicating hypothesis, they might prefer using substance rather than seeking treatment due to poor insight.

Another reason why they are more frequent defaulters, according to Peter Buckley [45] was substance abuse Schizophrenia patients are likely to develop side effects with antipsychotics. That might lead to defaulters.

8.3 DUP AND CHANGE IN FBS:

Duration of untreated psychosis (DUP) is always an area of interest as it is strongly associated with the outcome of the illness. Research has shown the longer the DUP, the poorer the outcome and therefore early intervention is highly recommended. There is a growing recognition that the DUP may have a major impact both in immediate recovery rates [67] and also on long-term outcomes and disability.[76]

Compton MT. found that groups of patients with poorer insight had longer duration of untreated psychosis (DUP)[39]. With poor insight, the patients tend to non-comply to medications as well.[77] This explaineds the finding from the research that the patients with longer DUP have less increase in FBS after 10 years. It is because those patients with shorter DUP have relatively better insight. Therefore they comply with medications and unfortunately leading to more change in FBS levels.

Not only that, Luciane Carniel Wagner (2011) also found chronic schizophrenia patients are incapable with managing their life therefore problem with managing their treatment and also identify their mental and physical problems[77]. This can contribute to poor self-awareness and eventually leads to poor FBS control.

Another point can explain about the DUP and change in FBS is those with longer DUP, are likely to have poorer prognosis. Accoring to Meredith G Haris [78], shorter DUP is associated with better social and occupational functioning and quality of life. In other words, those with longer DUP has poorer social occupational functioning i.e. they might not able to hold a job and might fall into lower socioeconomic group. They might suffer for hunger and malnutrition. While those with better outcome, has better chance of better food leading to difference in change of FBS levels.

8.4 EDUCATION LEVEL AND CHANGE IN FBS:

One of the findings from the above research is education level is inversely related to change in blood glucose level. Higher education did not equal to better understanding about the illness or side effects. On top of that, schizophrenia is a major mental illness that affect the cognitive functions, which can affect their overall executive function and hence less understanding of the risk[77]. They might not comply with physical activities or diet control to prevent glucose control leading to more change in FBS.

Another explanation is, those with higher education, will have better understanding the impact of the non-compliance with medications to the illness (relapse schizophrenia). Therefore more change in FBS.

Chronic schizophrenia tends to lead to a lack of self-autonomy. According to Shapiro[79], who quotes that autonomy is particularly extreme lacking in schizophrenia, similiar to what other authors said (Goldstein, Angyal, Bleuler, Kraeplin, Jung). Luciane Carniel Wagner (2011)[77] concludes that patients with schozophrenia generally have problems with autonomy, in regards during symptomatic or not. They have problems in rationalizing and making decisions of pros and cons for themselves or others. They might be highly dependent on their caretakers including their adherence to their medications. The author also found these patients had not only no freedom to make their own decisions, they also reported not feeling motivated and not capable to perform any decision making[77].

Self-perceived of autonomy support is proven to lead to better compliance and better glucose control in a diabetic groups[80]. With increased perception of autonomy, motivation will increase ($P<0.05$) and hence compliance will increase as well ($P<0.05$) [80] With generally lack of autonomy among schizophrenia patients, the awareness and control of blood glucose will be less.

Stress plays an important part in blood glucose level and control. According to the American Diabetes Association (ADA), people with stress are tends to eat more, exercise less and may not take good care of themselves. They might not plan for good meals. Not only that, stress, both physically and emotionally, can lead to an increase in stress hormones (epinephrine and cortisol), which will then directly increase blood glucose levels. It is hypothesized that those with higher educations might have a more stressful job, or face more stress that leads to more changes in FBS after 10 years. However, in current research, author has no information of stress level among the cohort.

Another point can be considered is that the higher education group might have better socioeconomic background, therefore more luxurious food. Hence they have better dietary intake compare to those less fortunate. With better dietary intake, the chance to have higher level of glucose, therefore more change in FBS after 10 years. Besides that, compared with well-to-do families (higher education group), complications from chronic illness means they need more care and more money. Hence they are more careful and pay more attention to the illness, therefore have less FBS changes. Besides with the easily available fast food, people with better socioeconomic background might have more food access to those foods.

However, this area needs more future research with better study design and follow up.

8.5 PHYSICAL ACTIVITY AND BLOOD PRESSURE CHANGES:

Another finding from the research is high physical activity (moderate to vigorous activity) leads to higher change in blood pressure after 10 years. The author hypothesizes few possibilities.

The group of patients who practice high levels of activities might not control their diet as strict as others. Due to their active life-style, psychologically they might not control their diet as strict. They might consume more fat or sodium, which will then lead to change in blood pressure.

There is another possibility that due to their own risk factors, they pay more attention to their health and go for regular check ups. There is a possibility that due to their high risk, the doctor adviced them to exercise more therefore they promote more regular and high physical activity. Besides that, the treating psychiatrist might be regularly psychoeducating this group to promote healthy life-style.

Another findings gathered different types of physical activity are associated with change in blood pressure. [81] During normal exercise, blood pressure increases exponentially and with rest of 10-20 minutes, the blood pressure return to normal. However, with more vigorous exercise, the increment of blood pressure is much higher and also needed longer durations of rest before the pressure returns to normal again (30-40minutes). During the blood pressure measurement on follow up, there might be a possibility author did not let the subjects rest enough before taking the measurement.

There is literature examine change in diastolic blood pressure (DBP) and also serum cholesterol and insulin resistant level shows those with higher cholesterol and insulin resistance, even during low level of exercise or gender exercise (mild exercise), there was increase in diastolic blood pressure.[82] the hypothesis is those with high cholesterol will have impaired achetylcholine (for vessels relaxation). Cholesterol deposition in blood vessels will directly affect the elasticity of the vessels. Both factors are the reason

there is more change in DBP during exercise. Author felt the higher physical activity group hypothetically are more active and less blood cholesterol while those less exercise group are more sedentary and more dyslipideamia. Therefore the group has more change in DBP compare to higher activity group. Author was not able to draw that conclusion from the research conducted because lack of blood component at baseline and also at current, not all subjects agree for blood taking. However, it might provide a new area to explore for future research.

However, author concludes that this area need future research.

9. Strengths and Weaknesses of the Research:

9.1 Strengths:

This is the first long-term outcome study (10 years) conducted in Malaysia. Based on NMHR registry, author is able to identify most of the subjects and analyze them. For those who defaulted, author tried to contact them and give them new appointments.

The National Mental Health Registry of Schizophrenia (NMHR) had registered 394 first onset schizophrenia 10 years ago from GHKL and prospectively followed up on them to date. Not only that, the registry also provide better understanding and more clinical meaningful data.

The main subjects of the research are from General Hospital Kuala Lumpur, which is the biggest government hospital in Klang Valley (KL). The subjects represents the population in Kuala Lumpur. This provides a good catch man area, which represent general population of Kuala Lumpur. Therefore the outcome is able to apply to general population.

Because of the presence of the national mental health registry of schizophrenia and clinical practice guidelines, the author managed to identify those with the metabolic syndrome, including those with dyslipaemia and insulin resistant. On top of that, from the research conducted, author is able to find the associated factors or even causative factors for the populations.

9.2 Weakness:

There are lots of confounding factors for metabolic syndrome. One of the major confounding factors is dietary intake. Diet plays a big role in metabolic syndrome. Excessive intake and even nutrition deficiency can lead to the syndrome. As mentioned before, iron deficiency, vitamin B, folate, Vitamin D are associated with metabolic syndrome. [28–32,70] In this research, author did not look into this. It will be good to look into this in future research.

The drop out rate is relatively high. Although the author had tried to trace as many as possible, there are still subjects to whom no record or contact available. The amount can be reduced if there is a better tracing system.

There is a possibility of recall bias. With the duration of 10 years, there will be recall problem and leading to bias. On top of that, the questionnaire of IPAQ examines the physical activity for the past 1 week. That does not guaranty the person is having the same amount of physical activity before this. Therefore research might not represent the true picture of the cohort. The cohort might be under-reporting their physical activity as well.

Another limitation is some of the information is not measured during baseline. For example, blood result, waist circumference variables are not available at baseline. This is because during the formation of registry, metabolic syndrome was not their main emphasis of outcome. Therefore this piece of information was not recorded. The physical activity was not measured at the beginning too.

About compliance, both at baseline and current, is not being assessed. Adherence to treatment can influent the outcome measured especially those with atypical antipsychotics. This will be one of the confounders too.

The sample size of substance abuser group is relatively small were to compare to other studies conducted. ECA study reported as high as 50% of patients with Schizophrenia has life-time substance abuse risk. NMHR 2008 also reported 20% of patients with Schizophrenia had comorbidity and out of them, substance abuse is the highest (80%). The author assumes those with comorbid substance might be lost to follow up but are not able to analyze the reasons. Due to the small subject pool, the author has difficulty to analyze the subgroup of each substance with metabolic syndrome.

A better defaulter-tracing system is much needed to prevent the drop out in future.

Another limitation of this study is assessment of co-morbidity. The author did not apply or use any scale or instrument to assess the presence of co-morbidity. Author only interview and based on medical record. This can miss the undiagnosed subjects. It is important in future to conduct a structured way with scale or instrument to assess comorbidity.

10. Conclusion:

Metabolic syndrome is on the rise more so in patients with Schizophrenia. The author found 36.2% of the cohort had metabolic syndrome after 10 years. The rate is much higher compare to other countries in Asia, for example, prevalence of Metabolic syndrome in China is 9.8%; Indian recorded 24.9%; Korea, Hong Kong, Taiwan and Thailand recorded 13.1%, 13.4%, 16.4% and 15% respectively. [83–87]Among patients with Schizophrenia, the prevalence of other Asian country, although generally increase, Malaysia still has the highest prevalence. For example, Japan only recorded prevalence of 27.5% ;India registered 33.5%; Thailand reported 22.8% only. This is further evidence by recent report [88] in Lancet about Malaysian is the highest overweight and obese country in Asia. In view of its importance, management of the syndrome, primary prevention and secondary prevention are equally important. It should be in the plan for the management.

Primary prevention: Aim is to reduce or delay the onset of type 2 diabetes and also onset of cardiovascular disease. There are many ways to prevent the onset of the syndrome, and IDF[21] recommendations those in high-risk group, should reduce their calorie intake, restriction to 20-25kcal/kg body weight[89] (Malaysia DM CPG). Another significant way to prevent the syndrome is to reduce the weight for 5-10% especially during 1st years. Studied had shown by reduce the weight, there will be a reduction of risk, or at least, delaying the onset of the metabolic syndrome. (IDF) Physical activity needs to be increased, to at least 150 mins/week[89] and change in dietary composition. [21]i.e. reduce and control carbohydrates (preferably whole grain), fruits,,vegetables, legumes and low fat or skimmed milk

While secondary prevention's aim is to prevent complications. Drug therapy and non-pharmacological therapy are both equally important. Therefore pharmacological

treatment for each component of metabolic syndrome (i.e. dyslipidaemia, insulin resistance, high blood pressure, high glucose level) are needed especially in those with higher risk factors in order to lower the individual risk associated with each component will hence reduce the overall impact on CVD and diabetes risk.

For the individual metabolic parameters, all SBP, DBP, BMI and FBS are significantly increased from baseline. ($p<0.001$).

Substance abuse is associated with metabolic syndrome after adjusting for physical activity and intramuscular flupethixol depot. This is an important finding as it will influent the management of the disease.

In the research conducted, the dropout rate is relatively high (117 out of 394). Theis can influence the outcome. Therefore a better tracing system is much needed.

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