

SCIENTIFIC PAPER COMPETITION – INDONESIA

Title of Paper : A Prototype of The Ideal Restaurant to Shift Consumers from Junk

Food to Healthy Eating Habit In Order to Prevent Obesity as a

Predisposing Factor of Type 2 Diabetes Mellitus

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ABSTRACT

Background

Type 2 diabetes mellitus is increasingly observed among children, and adolescents. The International Diabetes Foundation (IDF) says, "Diabetes and obesity are the biggest public health challenge of the 21st century". Of the people diagnosed with type 2 diabetes, about 80 to 90 percent are also diagnosed as obese. This fact provides an interesting clue to the link between diabetes and obesity, where high calories intake as the result of eating junk food will lead to obesity and this will increase insulin resistance and ended up as type 2 diabetes mellitus.

Material and Methods

This study combined survey and literature review. We surveyed 100 random samples of junk food consumers directly at fast food restaurants in Makassar, South Celebes, Indonesia. The aim of this study is to know whether consumers choose junkfood restaurants because of the taste or facilities, and consumers' reasons on why they choose junkfood restaurants rather than healthier one based on price, serving time, place, availability, and facilities. Those data converted to charts and accompanied by several explanations, then we search for several theories and previous researches about what goods about healthier ideal restaurant. At the end, we try to analyze and combine between what consumers want (based on our survey) and what theories stated (based on our literature review) to get the prototype.

Results

Around half of our respondents (53,8%) believe the price of junkfood is affordable enough which around Rp20.000,00 to Rp40.000,00. 50% respondents stated they only spend 5-15 minutes in average to get their food served. 83,3% respondents love junkfood restaurants in public places. 89,7% respondents choose junkfood restaurant due to the convenience such as free Wi-fi service, and they can also get extra souvenirs from the food they buy. But more respondents (64,1%) stated souvenir is not something they can get based on the food they choose in the restaurant. 94,9% respondents satisfied with the parking space of junkfood restaurant. In the poin of availability, respondents agreed that an ideal restaurant should be 24 hours available.

Conclusion

Consumers choose junkfood restaurant rather than healthier one is more because of proper facilities and good services provided compare to the taste. What they love from facilities, which also becoming the prototype of ideal restaurant to change their habit are TEFA which stands for Tolerable prices, Easily reached location, Fast serving time and Additional services (Wi-fi, toys, parking space and 24 hours availability).

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A Prototype of The Ideal Restaurant to Shift Consumers from JunkFood to Healthy Eating Habit In Order to Prevent Obesity as a Predisposing Factor of Type 2 Diabetes Mellitus

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a metabolic disease characterized by sustained hyperglycemia. People with T2DM are at elevated risk for a number of serious health problems including cardiovascular disease, premature death, blindness, kidney failure, amputations, fractures, frailty, depression, and cognitive decline (Goff, 2007). The cause of diabetes mellitus is poorly understood. Changes in diet and life style due to rapid economic development are foremost among the principle drivers of diabetes in developing and developed country (Mohan, V., 2004; 468-474).

Type 2 Diabetes Mellitus develops through abnormal insulin action and insulin secretion. Diabetes is diagnosed with blood glucose levels over 126mg/dL with a fasting blood glucose test and with levels over 200 mg/dL with an oral glucose tolerance test. The burdens of the disease with its dangerous complications include a seriously increased need for amputations and a higher risk for heart attack, stroke, retinopathy, and nephropathy.

The most important lifestyle changes relate to changes in dietary habits and physical activity and diabetes risk, particularly in younger individuals, is associated with the development of obesity and particularly central obesity (Cockram, C.S., 2000). The predisposing factors of type 2 Diabetes Mellitus consists of non modifiable and modifiable factors. One of non modifiable factor is genetic, a number of lifestyle factors, including obesity, lack of physical activity, poor diet, stress, and others are known to be important to the development of type 2 Diabetes Mellitus (Williams textbook of Endocrinology, 12th edition, 1371-1435). Although both diabetes and obesity risk factors are often associated with race, age, and family history, it is becoming more and more clear that the conveniences of modern life also contribute to the development of both diseases. For example, sedentary lifestyles and the popularity of high fat, high energy diets and convenient foods are known to lead to obesity.

Obesity can lead to T2DM. Of the people diagnosed with T2DM, about 80 to 90 percent are obese. This fact provides an interesting clue to the link between diabetes and obesity. Understanding what causes the two diseases will hopefully allow us to prevent diabetes in the future.

Being overweight places extra stress on body in a variety of ways, including the body's ability to maintain proper blood glucose levels through insulin resistance. If people already have diabetes, this means we will need to take even more insulin to get sugar into our cells. And if people don't have diabetes, the prolonged effects of the insulin resistance can eventually cause the T2DM. (Hussain, A., et al., 2010)

Related to the ideal restaurant to Shift Consumers from Junkfood, we have to know that food quality and food type are identified as significant variables in consumers' restaurant choice, the restaurant's atmosphere and its style can become differential elements in consumers' ultimate decision to patronise one restaurant over another. Thus, in many cases, patrons' sense perception may precede or complement the culinary delights they anticipate to enjoy at the establishment. Consequently, the view that restauranters are right to compete primarily on style appears to be appropriate in some hospitality / restaurant scenarios.

In this context, contemporary consumer behaviour research discusses, that consumers' purchase decisions are not only motivated by their direct responses to tangible products or services. In fact, elements that include music, styles, designed, services, scent as well as others may influence such responses. With regard to these aspects, Milliman (1986) pointed out that in some cases the place, or more specifically its atmosphere, is more influential than the product itself in the purchase decision. For businesses, and more precisely those in the restaurant sector, knowledge about these aspects can assist in the process of consumer segmentation. Atmospheric impact is therefore a reminder that product and service components may not always be at the core of consumers' decisions to engage in buyer – seller relationships or in purchasing experiences. This outcome is further demonstrated in a study within a lodging environment, where Countryman and Jang (2006) identified lighting, style and especially colour as the most relevant atmospheric elements that their study's participants associated with their overall impressions of the restaurant.

Once the decision to visit a particular restaurant is made, the overall value of the experience may also be created or judged. In this regard, Hansen (2005) found that the element of harmony during dining experiences was achieved through '... a balanced physical appearance in the meal, such as food and wine in combination with the interior of the restaurant ... physical structure and artefacts'. According to Finkelstein (1989, in Auty, 1992), many restaurateurs appear to have accepted that the establishment's atmosphere can be as important as – or even more important than – the food component. However, subsequent research by Clark and Wood (1999) disputes this notion; moreover, Clark and Wood found that food-related elements (quality, range or type) were the most determinant. Although other researchers seem to be in agreement with Clark and Wood, they note that a restaurant's atmosphere, ambience, design and other elements need to be paid attention to as interest in them is increasing among consumers.

Cortisol Regulation and Dysregulation: A Potentially Influential Contribution to Obesity & Diabetes

It's the 21st century and "junk food" has gone global. For better or for worse (mostly worse), junk food is now available all over the world. We see it most everywhere we go. Of course, junk food is also readily available at restaurant chains across the country in the form of French fries, chicken nuggets, shakes, soda, etc. Not only are most fast foods not terribly healthy, one study indicates that there may be something about fast food that actually encourages gorging.

In the study, from the Children's Hospital in Boston, [teens](#) age 13-17 were given three types of fast-food meals (all including chicken nuggets, French fries, and cola). In one meal, the teens were served a lot of food at once. In another, a lot of food was served at the same time, but in smaller portions. And in the third test meal, a lot of food was served, but in smaller portions over 15-minute intervals.

The researchers found that it didn't seem to matter how much food was served, the teens still took in about half of their daily calorie needs in that one meal. The researchers suggested that certain factors inherent to fast food might promote overeating: It's low in fiber, it's high in palatability (that is, it tastes good), it offers a high number of calories in a small volume, it's high in fat, it's high in sugar in liquid form, so, it can lead to overeating syndrome and cause obesity. So, how did obesity can lead to T2DM? it takes a role played by cortisol regulation and dysregulation.

A direct relationship between diabetes and cortisol concentration has not been fully established, and many studies show a range of results. Circulating levels of cortisol are determined by the metabolism of cortisol, by the rate of its secretion from the adrenal cortex, and by the receptor sensitivity to cortisol. Therefore, cortisol may be increased by various mechanisms, which include impaired metabolism, stress, and conversion of cortisone to cortisol. Although some studies have illustrated that type 2 diabetics do not have higher levels of ACTH or hypothalamic-pituitary-adrenal (HPA) axis activity than normal individuals, other studies have alternatively illustrated that cortisol levels are increased in diabetics by the risk factors: such as emotional or physical chronic stressors, advanced age, and adverse childhood stressors. These stressors, or others such as smoking, alcohol, depression, or dysphoria, may contribute to abnormal HPA axis activity. If the HPA axis activity is increased, excess cortisol may be secreted and correlated with insulin resistance, visceral obesity, and dyslipidemia.

So, how did the cortisol, and lifestyle factors lead the T2DMs? That occurs when the Lifestyle Factors (Stress, Excess caloric intake, Low physical activity) affect HPA activity and increases cortisol in the body, after that, the higher cortisol in adipose tissue (visceral fat) have been correlated with excess hepatic glucose production and lower levels of glucose removal. (Abdominal adiposity is a strong predictor of type 2 diabetes, may be an indication of dysfunctional adipose tissue. Abdominal adiposity is often accompanied by metabolic disturbances, including insulin resistance, hypertriglyceridemia, hyperinsulinemia, glucose intolerance, hypertension, reduced levels of HDL, increased small and dense LDL, glucose intolerance, and hypertension). After that, Adipose tissue is exposed to an increased cortisol concentration when there is a rise in 11β -HSD1 action. Because there is a constant supply of cortisone in the plasma, well-regulated target tissues may adjust cortisol concentrations through this conversion mechanism. Under some conditions in vitro, 11β -HSD1 may increase the conversion of cortisol to cortisone, but the extent of this dehydrogenase activity in the body is unknown. After that, increased cortisol to liver through portal vein was occurred. Because the liver is a major target for glucocorticoids, the effects on the liver leading to insulin resistance likely affect the entire body. This is likely because the liver is responsible for most of the glucose overproduction involved in type 2 diabetes. The glucose overproduction contributes to hepatic insulin resistance and eventually insulin resistance throughout the body and Type 2 Diabetes Mellitus successfully occurred. In obese individuals, though 11β -HSD1 expression is typically increased in adipose tissue, many studies show that its expression is usually decreased in the liver. (Liebman, Tracey, 2001)

In this modern era, people tend to be more selective in choosing foods. We assume that taste is not only priority but also facilities play a big role. Therefore is really important to make a research about whether facility really play a big role, and what factors are involved, so in the end we can create an ideal restaurant to shift consumers' mindset from junk food restaurant to healthy eating habits in order to prevent obesity as a predisposing factor of type 2 diabetes mellitus. This study also aims to give wider perspective for government and any stakeholders that willing to create a healthy restaurant for society and more information to restaurant owners regarding what their consumers really want.

Material and Methods

Fast food has becoming a very popular food worldwide. What we mean by fast food is a typical of fast food chains where most junk food served, which has so many counters in public places although standing for one brand.

In this study, we combine survey and literature review. We do two sections of random sampling survey to 100 junk food consumers directly at fast food restaurants in Makassar, South Celebes, Indonesia to get some data to support this study.

These were two part of this study. The first section aims to know the consumer knowledge on junk food. In this section, we also had one question as our exclusion criteria. So, we are going to exclude the consumers for the next section if they choose junk food because of the taste, because we are going to only focus on facility for the next section.

The second section is the focus of our study. This section aims to know consumers' reasons on why they choose junk food restaurants rather than healthier one based on certain aspects, which are price, serving time, place, availability, and facilities. Those data then converted to certain charts and accompanied by several explanations. After finishing all survey results, then we try to search for several theories and previous researches about what goods about ideal restaurant based on aspects that we put on our survey. At the end of this research, we try to analyze and combine between what consumers want (based on our survey) and what theories stated (based on our literature review) to get the prototype of ideal restaurant to shift consumers from junk food to healthy eating habit in order to prevent obesity as a predisposing factor of type 2 diabetes mellitus.

Results

Based on survey that had done on September 7th 2013 at several fast food chain restaurants in Makassar, South Celebes, Indonesia with 100 respondents who later been restricted into 78 samples after exclusion criteria, then here are the results of first section of our survey regarding general information about consumers' habit in the form of charts as shown below:

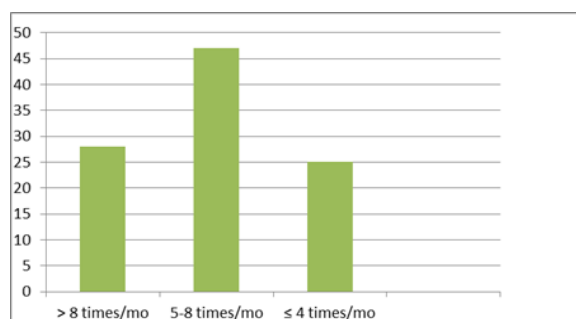


Chart 3.1 Frequency of junk food consumption per month

Chart 3.1 above shows us that most of our respondents, as many as 47 persons (47%), consume fast food approximately 5-8 times in a month; 28 persons (28%) consume even more than 8 times a month; and only 25 persons (25%) consume 4 times a month or less.

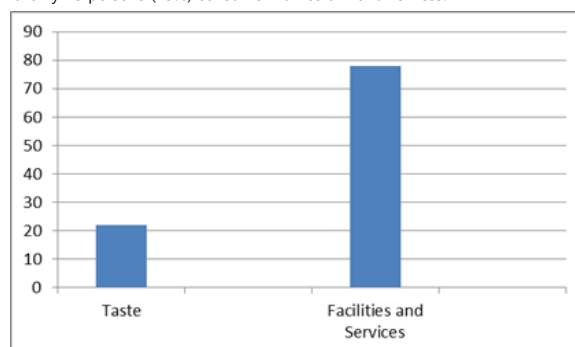


Chart 3.2 Reasons to choose junk food rather than the healthier one

Chart 3.2 above shows us that the main reason consumers choose junk food rather than the healthier food is better facilities and services (78%). The rest of them are due to the taste (22%). Due to the highly subjectivity of taste in individual, taste, as one of the reason consumers choose junk food, were excluded. So, our next questions and study will not including the consumers who choose junk food due to the taste.

After the first section, then we exclude 22 of our respondents for the next section, because they does not fullfil our criteria of inclusion. Then we come with 78 consumers that chose junk food because of facilities and services provided. This section will focus on respondents' opinion about junk food restaurant facilities and services that make them choose junk food restaurants rather than the healthier one. Here are the results:

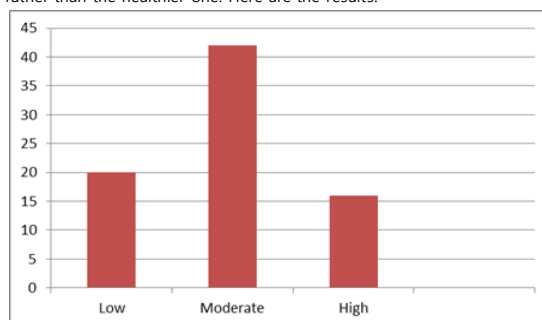


Chart 3.3 Price

Chart 3.3 above shows as that most of our respondents (53,8%) stated that the price of junk food is affordable enough. The rest of them stated that the price of junk food is very affordable (25,6%), and for less respondents (20,5%) the price is barely affordable.

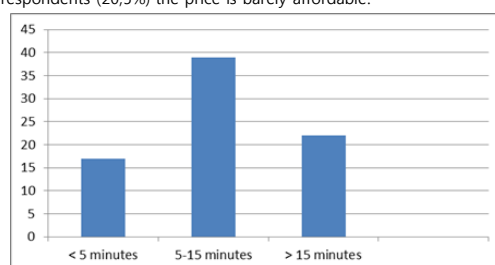


Chart 3.4 Serving time

Chart 3.4 above is about serving time, one of the reason people choose junk food, because they could spend less time to get the food. As much as 50% stated that they could spend only 5-15 minutes in average, much lesser than time they need to spend to get their other food served. As much as 28,2% stated that the serving time is more than 15 minutes. And even 21,7% stated that they could spend less than 5 minutes to get their food served.

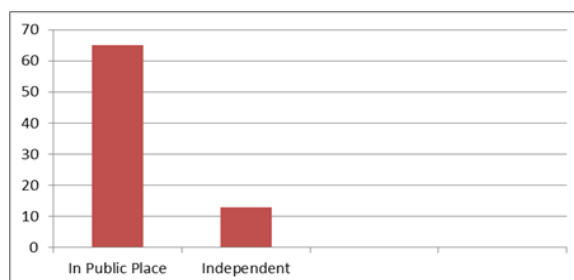


Chart 3.5 above shows us the comparison between consumers who choose junk food restaurants placed in public places and independent restaurants placed outside public places. Most of the respondents (83,3%) go to the junk food restaurants in public places, such as malls, airport, schools, hospitals, and others. The rest of them (16,7%) choose the restaurant outside the public places.

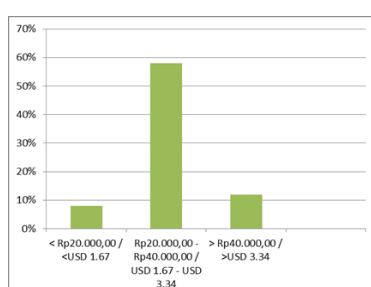


Chart 3.6 Money spent

Chart 3.6 above shows us that most of our respondents (74,4%) spent approximately Rp20.000,00 to Rp40.000,00 (USD 1.67 to USD 3.34) for junk food, which they considered it as affordable enough. The rest of the respondents spent less than Rp20.000,00 (less than USD 1.67) (10,3%) and a little bit more spent more than Rp40.000,00 (more than USD 3.34) (15,4%).

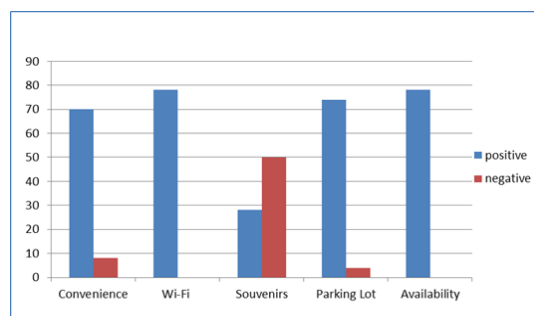


Chart 3.7 Facilities

Chart 3.7 above explains the consumers' opinions regarding point of facilities of junk food restaurant.

Most of our respondents (89,7%) stated that they choose junk food restaurant due to the convenience, and only the rest of them (10,2%) stated conversely. All of our respondents agreed that every junk food restaurant facilitated by free Wi-Fi service, which makes them choose to go to junk food restaurant, to get food and free Wi-Fi. As much as 39,9% of our respondents stated that one of the reasons they choose junk food restaurant to get food is because they also can get extra souvenirs from the food they buy. But more respondents (64,1%) stated that souvenir is not something they can get based on the food they choose in the restaurant. Most of our respondents (94,9%) stated that they are satisfied with the parking lot of junk food restaurant, as one of the facilities the restaurants serve. And only a very few of the rest of our respondents (5,1%) stated conversely. In the point of restaurant availability, all of our respondents are satisfied by junk food restaurant, because those restaurants are available in most time. There are even many junk food restaurants which are available for 24 hours a day in town.

Discussion

This study focused on price, serving time, location, money spent, and facilities to propose a better concept of an ideal health restaurant.

First is about the price of the junk food. Our survey shows that most junk food consumers believe that the average price of fast food is affordable enough. It explains us enough why many people have no problem in spending their money for junk food. Most consumers, represented by our respondents, spend approximately Rp20.000,00 to Rp40.000,00 (USD 1.67 to USD 3.34) to get their fast food. With that amount of money, the consumers can enjoy a bunch of food they love. The declining real price of food and the relative low cost and convenience of energy dense food, in particular, are hypothesized as key contributors to overweight (Lakdawalla and Philipson, 2002; Cutler et al., 2003; Drewnowski and Darmon, 2005).

On the point of serving time, junk food spend time approximately 5 to 15 minutes to serve their food. Here, we can conclude that 5-15 minutes to serve food is the tolerable time for the consumer to get their food served. This is one of the criteria that we want to encourage to the healthier restaurant with longer time of serving.

Location is also the reason people choose junk food restaurant. Most of junk food restaurants in town, especially in Makassar, South Celebes, Indonesia, are located in public places and only a very few of them located as an independent building. This is related to the fact that people choose junk food because they can also get those food while they do their other activities in those public places, such as at school, the airport, malls, and others.

The last criteria of the restaurant consist of five subpoints, which are convenience, free Wi-Fi service, souvenirs, parking lot, and availability of the junk food restaurant. In most of those points, except souvenirs, most consumers are satisfied by the facilities provided by the restaurant. They feel comfortable with the standard design of the restaurants to spend their time with their friends or family to eat delicious those energy dense food. They also choose junk food restaurant because they surely can get free Wi-Fi service, to do their assignment for example, or simply to do online surfing to spend their time. Souvenirs did not significantly impact the high rate consumption of junk food. Most of junk food restaurants only provide souvenirs for kids, and adult consumers do not see that as a weak point of junk food restaurant, so they do not see any reason to stop getting fast food. A proper parking lot is also a determine factor of a success restaurant, including junk food restaurant. Most of the consumers feel satisfied by the proper parking lot the junk food restaurants provide. A proper parking lot here is a good parking lot, in size and security. People tend to choose restaurants or any other public places with good security for their vehicle. Last subpoint is about the availability of the restaurant. Junk food restaurant are chosen more than any other restaurant because they serve consumers more often than other restaurants do. Some of them even available for 24 hours a day. So when people starve for food in the middle of the night, the restaurant that can serve them food is much more likely to be fast food restaurant. According to the research, there are greater numbers of available total restaurant, including fast food, to be significantly associated with higher adult obesity (Chou et al., 2004).

Based on our study, fast food chains actually serve people everything good, except the fundamental one, which is the nutrition value of the food. Several studies have examined associations between junk food consumption and energy and nutrient intake and weight outcomes. Junk food consumption has been associated with higher total energy intake and higher intake of fat, saturated fat, carbohydrates, sugar, and carbonated soft drinks and lower intake of micronutrients and fruit and vegetables (Lin et al., 1999; Binkley et al., 2000; French et al., 2000, 2001; Paeratakul et al., 2003; Bowman et al., 2004; Bowman and Vinyard, 2004; Befort et al., 2006). To solve this kind of problem in order to create an ideal restaurant, we have two choices of actions; either solve the nutritional problem in fast food chains or create a healthier restaurant with fast food chains facilities. We clearly can not apply the first choice, because all those fast food chains are private business, not the part of governmental entity. Those kinds of energy dense food are their signature product which defines them. So, the other way we can propose is a healthier restaurant with at least exactly same facilities as fast food chains provide (relatively low cost, tolerable serving time, good location, convenience, free Wi-Fi service, proper parking lot, and great availability).

This prototype of restaurant will involve some specific job disciplines in running it. Firstly, to maintain the nutritional value and balance of the food, the restaurant needs a nutritionist or clinical nutrition doctor. Secondly, the restaurant certainly needs great chefs to serve (relatively) delicious food for everybody in an efficient time of serving. And the last but surely not the least, the restaurant needs professional waiters/waitresses, great cleaning service and security in order to support the convenience and security of the restaurant. Restaurant with healthier food and good facilities actually grows more nowadays. The problem is those restaurant have a barely affordable cost for their food. That is why this is also the problem that the nutritionist and the chefs should solve. They should provide healthier food which cost relatively low. This will be a new concept of a multidisciplinary job which final goal is to shift consumers from junk food to healthy eating habit in order to prevent obesity as a predisposing factor of many kind of diseases, especially type 2 Diabetes Mellitus.

Conclusion

After doing survey and literature review, here we conclude several things,

1. Most of our respondents choosing junk food not because of the taste, but more because of facilities and services provided. So basically, health restaurants that already exist are competitive enough on taste, they only need to repair themselves more on facilities and services.

2. In order to create an ideal restaurant to shift consumers from junk food to healthy eating habit, we need to consider several things as the prototype,

- a. The price of junk food restaurants are mostly considered as moderate, therefore the range of this price could become a consideration in making an ideal restaurant for healthier food.
- b. Serving time that is considered as tolerable for most consumers is approximately 5 to 15 minutes.
- c. Any healthier ideal restaurant should be placed on public places in order to be easily reached, because that is what consumers love the most.
- d. Most consumers spending 20.000 to 40.000 in one visit, therefore it could become considerations for healthier ideal restaurant in putting prices.
- e. There are several facilities that should be considered most to be put whenever healthier ideal restaurant created, which are free Wi-Fi service, good restaurant design, proper parking lot, and available for 24 hours. If it is possible, interesting souvenirs should be provided.

This study has several limitations during the process, therefore we have several suggestions for the next researcher,

1. This study is only ended up with prototypes, so we need the next research project to test the prototype to make sure this prototype is really work to shift consumers from junk food to healthy eating habits.
2. This study is limited to Indonesian consumers. Larger study should be conducted to evaluate the global consumers in order to create the global prototypes.

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SCIENTIFIC PAPER COMPETITION – JAPAN

Title of Paper

The Medical Students' Role to Spread Proper Comprehension on Hikikomori Caused by Schizophrenia

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Background

Today in the world, mental health is becoming a big problem. In Japan, mental health is also a remarkable problem. There are many social problems caused by various psychotic disorders. Social withdrawal of young people is among them, and it is named "hikikomori" by a Japanese psychologist in 1990.

We have 2 purposes in this paper. The first purpose is to discuss how we can support patients with hikikomori caused by schizophrenia, as a medical student. The second purpose is to share the result of this study with Asian medical students, and to promote their understandings on this symptom -hikikomori-, so that students can deal with a patient when they encounter.

Material and Methods

On discussing this subject, we used reliable statistic researches and studies as systematic review. We interviewed 2 experts to incorporate their professional opinions. We also conducted a survey by using a questionnaire to medical students.

Results

There are 2 reasons of increasing the number of hikikomori; too fond parents and Confucianism. And various difficulties exist in coping with hikikomori caused by schizophrenia in Japan as following; take them to them along to a hospital, letting them continue to take medicines. Moreover, there is a prejudice to the people with mental illness from society, and it makes the patients hard to return to society. The effective treatment for the patients has 3 steps; (1) to find hikikomori from schizophrenia as soon as possible, (2) to see a psychiatrist, (3) to get proper rehabilitation to have chance to get a new job.

Conclusion

In conclusion, to overcome difficulties, it is important to utilize 3 facts; A) Patients and their family have to know management steps: early detection, encouragement of treatment and social rehabilitation, B) Medical staffs have to accept them as patients and acquire the infrastructures for treatments, knowledge, and clinical skills for the middle to long-term medical supports, C) Society and governments have to resolve the prevalent prejudice against mental disorders.

For medical students, we suggest 3 elements which can contribute to the patients; 1) to attend the lectures which actual patients attend and know the facts that aren't usually described in the textbooks, 2) to work as a volunteer member to support the patients and their family as counselors and mental friends, 3) to establish a non-profit organizations to do continuous grass-roots supports with the existing organizations propagating us.

(394 words)

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The Medical Students' Role to Spread Proper Comprehension on Hikikomori Caused by Schizophrenia

Region: Japan

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INTRODUCTION

Today, about 13% of the burden of disease has been attributed to neuropsychiatric disorders around the world, mostly due to the chronically disabling nature of depression and other common mental disorders, alcohol-use and substance-use disorders, and psychoses. It is estimated that 450 million people are suffered from such mental disorders all over the world. The estimates have drawn attention to the importance of mental health for WHO. In 2012, WHO reported Global Mental Health Action Plan from 2013 to 2020, and they insists on "no health without mental health".

Japan also has many problems in mental health. In Japan, sociocultural environment which surrounds us have greatly changed through defeat in the World War II, rapid economic growth, and present virtual communication era. Due to the significant change, many social problems have arisen caused by various psychotic disorders. Social withdrawal of young people is one of the problems.

In 1970, some scientists started to notice this social withdrawal in Japan. After a decade, the withdrawal became a serious problem, because not only the number of youth increased but also it remained for a long time. And Saito, a Japanese psychologist and critic, created the word 'hikikomori' in 1990 for the first time. He defined hikikomori as "A state that has become a problem by the late twenties, that involves cooping oneself up in one's own home and not participating in society for six months or longer, but that does not seem to have another psychological problem as its principal source."

According to the survey, conducted by Japanese Cabinet Office in February 2010, the number of hikikomori is estimated at 696,000.²⁾ And approximately more than 50% of the people still remained as hikikomori and grew old to their 30s.³⁾

There are 3 types of hikikomori. In the first group, people clearly have a mental disease (schizophrenia, depression, panic disorder, neurosis), and the disease makes them stay indoors. In the second group, people have a developmental disorder (mental disabilities or pervasive developmental disorder) and, the disorder makes them stay indoors. In the third group, people stay indoors without remarkable mental diseases and developmental disabilities. (Figure 1)

In Japanese psychiatric field, most of the hikikomori cases, with which health care providers deal, are the first group: people clearly have a mental disease (schizophrenia, depression, panic disorder, neurosis). And those cases, for example cases in their acute stage of schizophrenia and cases of people who lost their interests to outside, tend to be improved with medical cares.⁴⁾

Schizophrenia is a chronic, severe, and disabling brain disorder which has affected people throughout history. People with the disorder may hear auditory hallucinations. They may believe other people are reading their own minds, controlling their thoughts, or plotting to harm them. This can terrify the mental patients and make them withdrawn or extremely agitated. As a result, some of them become hikikomori, but it is difficult to know whether the hikikomori is caused by schizophrenia or not. Therefore, hikikomori caused by the disease is diagnosed with the symptoms such as a hallucination and a delusion. In schizophrenia treatment, pharmacotherapy is very important. Many symptoms of schizophrenia are relieved with it; however, most people who are suffered from this disease have to cope with those symptoms throughout their lives to return to society.

We have 2 purposes in this paper. The first purpose is to discuss how we can support patients with hikikomori caused by schizophrenia, as a medical student. The second purpose is to share the result of this study with Asian medical students, and to promote their understandings on this symptom -hikikomori-, so that students can deal with a patient when they encounter.

MATERIAL & METHODS

To incorporate experts' opinion, we interviewed Professor Tamaki Saito, M.D., Department of Psychiatry at Tsukuba University, and also visit 'Sakai-shi kokoro no kenkou center', a government agency of Sakai city, which offers consulting service for mentally challenged person. We interviewed Dr. Masayuki Morikawa, M.D., Designated Psychiatrist, and Mitsuyasu Iwata, clinical psychologist. To know the extent of understanding of schizophrenia and hikikomori and to enlighten medical students, we also sent out questionnaires to medical students, and after that, we let them read the explanation.

RESULTS

We carried out KII and made systematic review and know the following results.

We sent the same questionnaires, and classified the results under chronological order and standpoints. We classified under chronological order into three division: early detection, encouragement to treat, rehabilitation, and classified as standpoints into three division: patient, medical staff, society.

[General Remarks]

Before indicating classified results, we would like to mention contents that cannot be classified as general remarks.

a) Etiology and Pathology of Schizophrenia

There are various hypotheses about schizophrenia, but the definitive cause of schizophrenia doesn't make clear. However, various facts have been founded by research of psychiatry for about 30 years. As patient's condition, the following has been clarified: chemically disorder of dopamine and glutamic acid in the central nervous system among the patients suffered from schizophrenia, histopathologically disorder of neural development in fetal stage, and malfunction of a frontal lobe. As a cause of schizophrenia, 3 hypotheses are advocated: dopamine hypothesis, glutamate hypothesis, and neurodevelopmental disorder hypothesis.

Dopamine hypothesis is the hypothesis that hallucination and delusion with schizophrenia are caused by excess of dopamine. One of the evidences of this hypothesis is that some wake amine (ex. amphetamine and methamphetamine) promotes release of dopamine and cause hallucination or other symptoms like schizophrenia. Furthermore, many psychotropics, drugs for schizophrenia, act as dopamine-accepter blocker. This supports dopamine hypothesis. The hypothesis is said to be the most popular one.

Glutamate hypothesis was made by the fact that abusers of phencyclidine which once appeared in society showed symptoms similar to positive and negative symptoms of schizophrenia, and phencyclidine works depress glutamatergic neuron. A decline of glutamic acid causes negative symptoms (ex. loss of motivation) that aren't caused by excess of dopamine like positive symptoms. Thus glutamate hypothesis fit in the characteristics of schizophrenia, so it has become the most predominant next to dopamine hypothesis.

Neurodevelopmental disorder hypothesis: Usually, if nerve cells happen to die in patient's brain, gliosis will happen. However, there is not gliosis in the brain of the people with schizophrenia in spite of structural disorders of frontal lobe or hippocampus. Therefore these structural disorders are thought to have existed since fetal period. Generally, Brains have layer structure but some survey says that the patients with schizophrenia don't have the ability to make these characteristic structures. In unborn baby's brain, nerve cells are born in the deep and move to surface, it called migration. So some says schizophrenia is caused by disorder of migration.

In 1995, as a result of several studies, specific protein called Reelin was discovered and found that it plays important role in migration. This protein decreases with schizophrenia. In addition, some genes which have connection with schizophrenia are identified and it also has connection with neurodevelopment.

To sum up, schizophrenia is thought that an accumulation of two hits. First hit is occurred in fetal period, for example disorder of layer structure caused by failure of Reelin. This is preparing period. Secondly, disorder of sexual maturation or neurotransmitter happen after first hit, then schizophrenia happen. Lately these two step hypothesis appeared.

b) Current Situation of hikikomori in Japan

In Japan, hikikomori has been getting major problem recently. Thirty percentage of hikikomori is also suffered from schizophrenia or depression. Therefore, it is important to judge whether they have mental disorder or not if you consult hikikomori people. If they have mental disorder, you should primarily treat the disease with some medicines.

c) 3 types of hikikomori

It is said that there are three reasons why hikikomori are increasing. Firstly, people tend to be hikikomori more than be homeless in Japan because parents depend on a child and parents doesn't turn a child out. Secondly, even if a child is hikikomori, the family can make a living because Japanese living standard is high. Thirdly, on the other hand the number of people who get hikikomori is 30,000, the number of people who recover from hikikomori is only thousands. (Figure 1)

d) Why is hikikomori increasing in Japan?

The doctors list up the following 2 reasons as factors of increasing number of hikikomori especially in Japan.

- Too fondparents

Japanese parents are too fond for their children. If their children are staying home long time, they will feed and take care of them. So children with hikikomori or schizophrenia sometimes have little difficulty in their lives.

- Confucianism

Some specialists say that the Confucianism countries, such as China, Japan, and Korea, have a characteristic of deeply considering and helping other people, which is called "jin (仁)" in Confucianism. This characteristic also makes excessive supports from parents to people with hikikomori.

e) Management Steps from Early Detection to Treatment and Rehabilitation

According to the guideline by Ministry of Health, Labor and Welfare (MHLW) in Japan, treatment for hikikomori caused by schizophrenia is conducted step-by-step: early detection, primary medication, maintenance therapy and occupational therapy. All the domestic medical and welfare services are under this guideline. We write about the details of each step as follows. (Figure 2)

[Discovering hikikomori from schizophrenia]

a) How do patients access to the consulting services for hikikomori?

On the first medical examination for patients with schizophrenia, they are accompanied with their parents in many cases. Parents try to take their offspring to see a doctor when parents notice odd behavior and condition. Such parents think their offspring may be suffered from a kind of mental disorders before seeing a doctor. In this field, it is too difficult to take them to a doctor and a hospital. In Japan, health care entities tend to promote outreach activities. However, they patients don't have any insights. So, they reject being outreached by medical staff. It is better cases that patients are brought to see a doctor. Critically-ill patients who really need treatment, tend to reject treatment.

[Treatment (Primary Medication) (Acute Phase)]

There is no clear division between treatment and rehabilitation of hikikomori with schizophrenia. However, as a matter of convenience, we discuss about the period of first drug therapy in this chapter and will discuss maintenance therapy in next chapter.

The most important point is how to have patients continue to take medicine. We try to suppress the problems which could happen in a relapse phase. For example, there are some papers saying that patients who are dosed one and a quarter quantity of medications for schizophrenia preserve their symptoms as the early phase. The level of personal quality of patients who have multiple relapses may go down.

The patients with borderline personality disorder tend to take a large amount of medicines. We can't deny the possibilities that patients with schizophrenia do like former because some of them attempt suicide. Rather, the problem is that they don't take medicines neatly due to no insights.

The points to be careful in the communication among people who use consulting services

People who use consulting services have lost desire and themselves. Therefore we firstly consider recovering that status. To do that, we should protect their self-esteem. Concretely, we evaluate "that a person himself or herself come to a facility" (because the hikikomori need much energy to go out of where they are and we can do new approaches by that). Moreover, it is important to admire what users can do and what they are good at. However, we have to tell people who have mental disease (especially developmental disorder and so on). This is difficult point in communicating with them.

[Rehabilitation (Maintenance Therapy, Occupational Therapy, Social Skills Training (SST)) (Chronic Phase)]

a) The Importance of Group Work

Second step is a group work. In a group work, the patient communicates with the people of about same age. Final step is the support of starting at work.

b) Cooperation among Medical Institutions, Schools and Workplaces

At the consulting service in Sakai city, Osaka, they cooperate very well before the users are getting labored (because of their supporting systems). However, they don't coordinate very well after their employment. So, they leave the employment to 'Supporting Station for the Youngsters,' which usually copes with problems relating to the employment of NEET in Japan. At this stage, some corporations employ the people, who are identified as NEET, hikikomori or the handicapped as a trial. If the suspect do well in the workplace, they can be employed as a regular.

Like this, there are cases that go well. However, now there are actually few places which play roles as middle between 'laboratory' and 'typical office.' They are let do only easy tasks (for example: packing into envelopes) at laboratory many patients are employed. On the other hand, people only do complicated tasks at typical office. Therefore these middle places are needed.

c) Important Support from the Family in the Rehabilitation

The treatment of hikikomori includes three steps. First, you take the hikikomori out of home. It is significant for the family to visit support center for hikikomori, and learn how to communicate with the hikikomori. It is impossible for the family to persuade the hikikomori to go out owing to his pride. It is effective that the family say a word to the hikikomori before going to the support center because the hikikomori feel a debt to the family.

Considering the high prevalence of 'hikikomori' in the men, opposite to in women, Japanese women who are home often call themselves 'a domestic helper.' So, it is too difficult to distinguish a female hikikomori from 'a domestic helper.' Eventually, the prevalence of hikikomori in men is getting higher compared with that of women relatively.

d) Stigma for Hikikomori in Society

Though lecture meetings about mental disorder are held, there is prejudice and discrimination against mental disorder. For example, people dislike to establish a workshop where people with mental disorder work. In addition, patients can't recover from hikikomori for a long time because parents don't consult with others about the situation of their child for fear of prejudice. After 10 years, hikikomori people will receive pension even though they don't work at all in their life. Although the society requires that people work, there are few employments. Becoming irregular employments grow the hikikomori.

Though their families totally recognize the symptoms of mental disorders in patients, they don't want to accept such facts, or they fear being labeled by surroundings. As a result, they stubbornly don't go to see a doctor and they try to make it at home.

The prejudices for patients with mental disorders decline compared with the past, but it is natural that general people fear those who have hallucinations and rack remarks. To such a not understandable people's face, it is difficult for general people to take them up.

[Result of Questionnaire]

After the KII, we made the following questionnaire. We sent out the questionnaire on mails and SNS, and got 100 answers. Table 1 and Figure 3 show the detail of the answers. The appropriate answer of Q1, 2, 4 and 8 is correct, and that of the rest or Q3, 5, 6, 7 and 9 is incorrect.

Questionnaire for Medical Students

This questionnaire is supposed to survey the consciousness among medical students about schizophrenia. Please choose Correct or Incorrect.

- Q1. Anyone has the risk to contract.
- Q2. One out of a hundred people can contract in their life.
- Q3. The patients recognize themselves as patients of schizophrenia.
- Q4. The patients and their family want to talk with those who have the same situation.
- Q5. There is little prejudice against the workshops at which the patients with schizophrenia work.
- Q6. It doesn't matter whether patients' family cooperate with their medications.
- Q7. It is enough to continue the medications since their symptoms disappear.
- Q8. It is important for the patients to join the treatment course.
- Q9. The social barrier doesn't prevent patients from their social re-integration and employment seeking.

DISCUSSION

In this section, we discuss how we can support patients as a medical student. We suppose treatment cycle that to find hikikomori from schizophrenia as soon as possible first, and second treat in hospital, finally rehabilitation to get back local community. This treatment cycle from finding to rehabilitation is important, especially early finding.

[From the view point of Patient and their Neighbor]

To find hikikomori as soon as possible, when you feel not good or you find your friends are not usual, please consult doctor without any reserve.

To gain correct knowledge and the place where you can consult make treatment better and comfortable environment for patient's family to live. We suppose making patient's community and participation to it are also good.

[From the view point of Government and Society]

We should do enlightenment activity to share the correct information with who needs it.

We should try to decrease discrimination and prejudice presenting in society, for example to hold lecture event for public.

In education field, teachers also have to know the correct knowledge about hikikomori.

Administration is said dividing vertically into divisions which have little cooperation, but we need to organize comprehensive support system which involves doctors and patients to provide better services.

[From the view point of Medical Staffs]

All doctors have to know about mental disease and the place to consult. These knowledge leads early findings, better treatment and enhancement of patient's QOL.

[Medical Students]

What is the role of medical students and citizens? As a medical student, we can't do medical activity because we don't have doctor's license, so we should approach the phase of early findings and rehabilitation.

a) Mental-friend

Medical students and co-medical students can be mental-friends who play and talk with people with hikikomori in volunteer work. Mental-friends support their rehabilitation. If your neighbor hesitates to go to school, your role is to help them and introduce them to appropriate health service. You should tell them "If you have some trouble now, how about consult together?" than "You have a mental illness and should see a doctor."

b) Take Part in the Activities of NPO

As another way of support, we can participate in the camp for truancy as a volunteer.

In addition to join the camp, our attendance on lectures of mental illness including schizophrenia or hikikomori also makes big meanings in improvement of health service.

c) Discussion of the Questionnaire

Judging from the result of questionnaire, we can see lack of understanding of schizophrenia in some aspects among medical students. It means that educating people is necessary in order to discover schizophrenia early and to treat that smoothly. After answering the questionnaire, medical students read the explanation about the schizophrenia, so we were able to educate one hundred medical students.

[Summary of Discussion]

There are various problems in every part: medical experts, patients, society and administration. But the common problem is that everyone doesn't understand schizophrenia and hikikomori well. The conclusion of this section is that correct understanding is the most important thing in support of schizophrenia and hikikomori. (Figure 4)

CONCLUSION

In this paper, we have focused on the patients with schizophrenia withdrawing from societies, and stated what we, medical students, can(could) do for those patients. We have two objectives to write this paper: first, to describe the present situation about schizophrenia: one of the most critical diseases in Japan. Second, to share the information on social supports, medical treatments, and what we can do as the medical students.

According to the statements above, in the points of A) patients and their family, B) medical staff, and C) society and government, you can see that various difficulties exist in coping with hikikomori caused by schizophrenia. To overcome those difficulties, referring to RESULTS or DISCUSSION, it is very important to utilize not only the autonomies by every three of them but also mutual aids among them, and then cooperate as team. Moreover, as medical students, we concluded that we may find clues to resolve these problems by getting appropriate knowledge on mental disorders including schizophrenia, cultivating better understandings about them, and enlightening the surrounding people based on what we learn. Specifically, Japanese people, who are ignorant about mental disorders strongly, tend to prejudice against mental patients.

So, A) patients and their family have to notice that most mental disorders can be convalescent if detected early at proper places, and if patients accept medications and mental therapies,

B) Medical staffs have to accept them as extant, and acquire the infrastructures for treatments, knowledge, and clinical skills, to enable the establishments of the middle- to long-term medical supports,

C) Society and governments have to resolve the prevalent prejudice against mental disorders among the fields with which they don't cooperate intensively, such as the educational sites and the local communities by enlightening the ignorance. And society must NOT deem the mental disorders and patients as the target of the prejudice. Moreover, the society is required to establish the comprehensive supporting systems to achieve the post MDGs for regarding mental disorders and the curable diseases similar to other somatic diseases.

For the above descriptions, consequently, there are two fields that we, medical students, can take part in.

1) As early detections, we need to attend lectures which are held by actual patients and to know the facts that aren't usually described in textbooks. While we often focus on knowledge as medical practitioners, we have to appropriately know what patients and their family really want, and then propagate the information not only to medical students but also to people who are ignorant of it.

2) As the way of re-integration into societies, we can work as volunteer counselors to support patients and their family.

Furthermore, as one of possibilities, we can establish non-profit organizations to do continuous grass-roots supports with the existing organizations which propagate us. We concluded that above two of them can be of some help for the patients with mental disorders, not limited to the patients of schizophrenia with hikikomori. Hikikomori is the complicated and delicate problem which includes cultural, historic and social backgrounds, like Japanese relatively high economic condition in which was achieved through the rapid economic growth. Additionally, it naturally follows from some papers related to hikikomori that this problem spreads worldwide gradually. It is our pleasure if you go by the existing supporting systems and the continuous activities as far as we can describe above, and they can be of some help for you.

(3,729 words)

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Figures and Tables

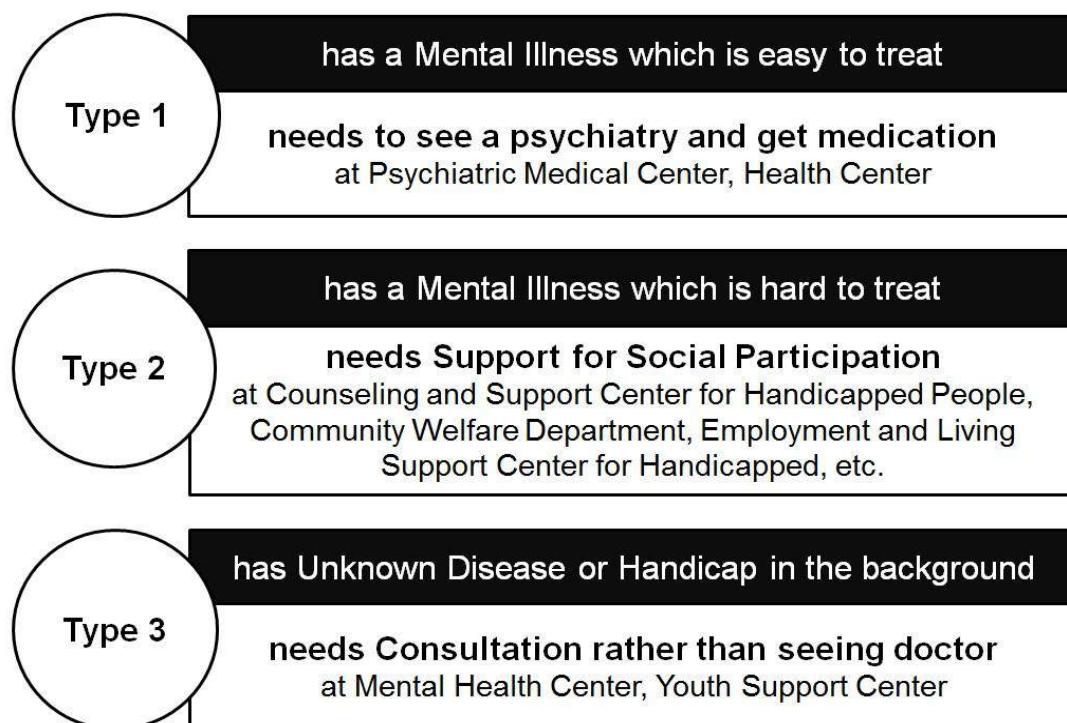


Figure 1: 3 Types of Hikikomori

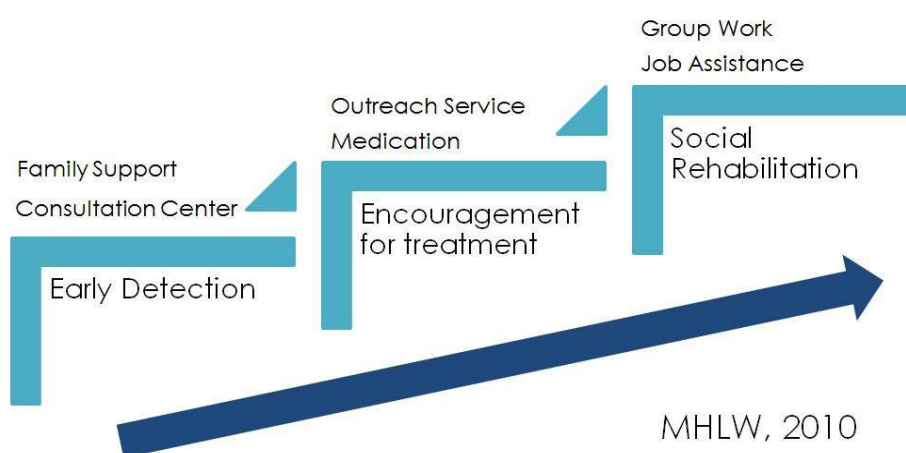


Figure 2: Management Steps from Early Detection to Treatment and Rehabilitation

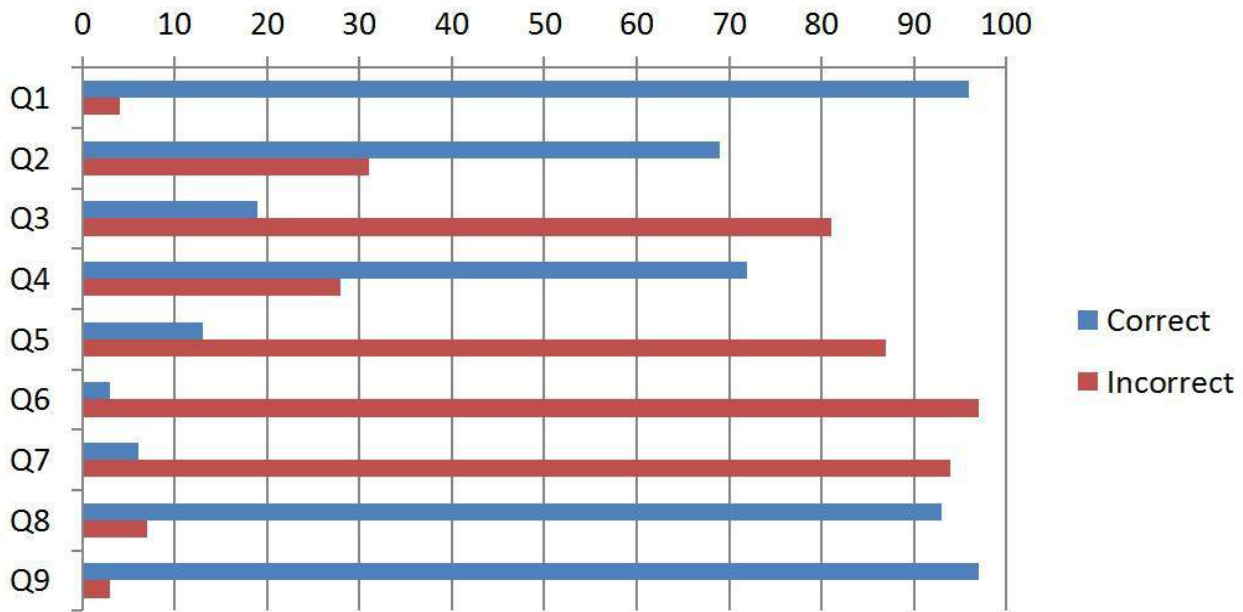


Figure 3: The Result of Questionnaire for Medical Students

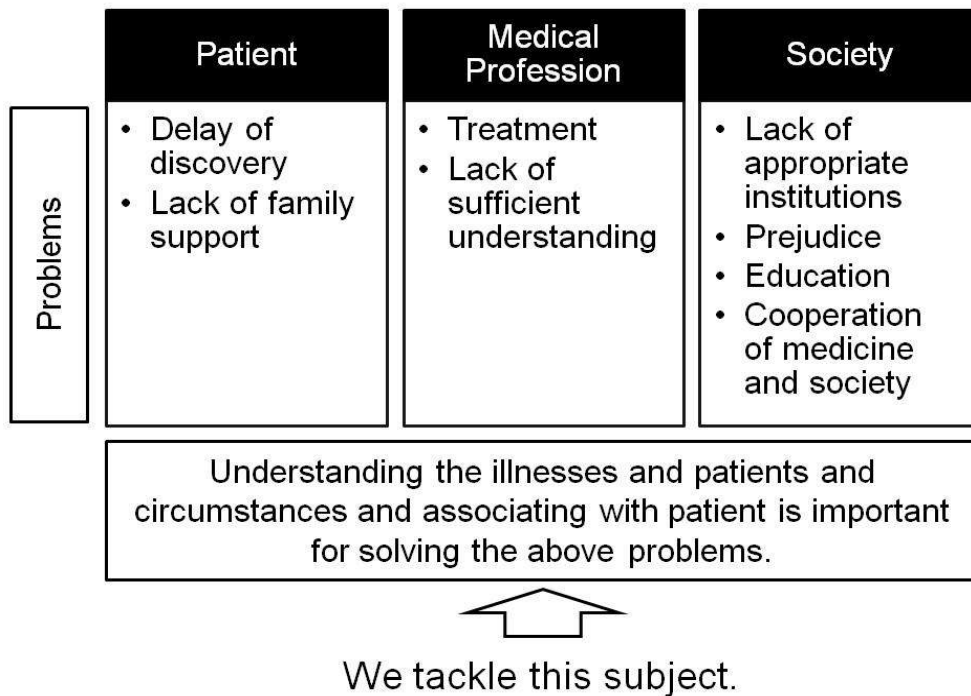


Figure 4: Summary of Problems

Table 1: The Result of Questionnaire for Medical Students

	Correct	Incorrect
Q1	96	4
Q2	69	31
Q3	19	81
Q4	72	28
Q5	13	87
Q6	3	97
Q7	6	94
Q8	93	7
Q9	97	3

N=100

SCIENTIFIC PAPER COMPETITION – KOREA

Title

**A New Perspective of Tuberculosis as a Chronic Disease
– Prevalence, Strategy, and Risk Factors in Korea**

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Abstract

Backgrounds

Tuberculosis causes many problems not only as an infective entity but also as a chronic disease.

Especially with the emergence of MDR-TB, control and prevention of tuberculosis become one of the primary concerns of the government.

Materials & Methods

We review articles and statistical data about latency and resistance control programs for tuberculosis.

Next, we systematically review and meta-analyze retrospective / prospective cohort articles about risk factors affecting mortality due to tuberculosis, according to PRISMA Guideline posed by Cochrane group.

Results

Tuberculosis incidence was bimodal, for 20th and over 80th. Latent tuberculosis was most at 40th. MDR-TB was increasing, with higher incidence with those infected. We classified risk factors as a subgroup; Chronic Diseases (end-stage renal disease, renal disease, COPD, chronic bronchitis, diabetes mellitus, hypertension and coronary artery disease) OR=4.42, 95% CI=[3.22, 6.07]; Social Determinants (aging, malnutrition, and daily alcohol intake) OR=2.57, 95% CI=[1.51, 4.38]; Cancer OR=3.90, 95% CI=[2.68, 5.66], and Nonspecified (HIV, immunosuppression, and steroid) OR=3.50, 95% CI=[2.70, 4.54]

Conclusion

We found that tuberculosis is one of the main concerns for chronic disease control program. Latent tuberculosis was most at 40's and MDR-TB was increasing in Korea. Control and prevention guideline for tuberculosis was well established. Analyzed risk factors were all statistically significant so that controlling these risk factors could lead to the better prognosis for tuberculosis management.

Full Paper

A New Perspective of Tuberculosis as a Chronic Disease – Prevalence, Strategy, and Risk Factors in Korea

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Introduction

M.tuberculosis, one of the oldest infectious agents as we know, has gone through the human history, not only affecting human behavior and development of medicine but adapting itself to the environment coexisting with human.

Tuberculosis is a communicable chronic disease. Infection of *M.tuberculosis* occurs by encountering those who were infected. After the exposure, tuberculosis infiltrates into the body, finding its niche. After the long-standing competition between immune system and *M.tuberculosis*, most of those infected are healed – But sometime *M.tuberculosis* wins and infection occurs, developing into active tuberculosis. Active tuberculosis presents with pulmonary symptoms in most case, but those who have other co-morbidities can undergo tuberculosis in quite different ways. Extra-pulmonary manifestations include peritonitis, pleurisy, lymphadenitis, skeletal abnormalities, CNS tuberculosis etc. After the successful recovery from the active phase, *M.tuberculosis* may be eradicated from the body or become dormant in its niche – This phase is called “latent”. When the host immunity becomes weaker, reactivation occurs. Reactivation usually undergoes in more severe ways, leaving host more sequelae. Sometimes re-infection occurs for those who has been cured from *M.tuberculosis* infection. In a nutshell, latency of *M.tuberculosis* infection is the source of chronicity and reactivation and re-infection is the process of its chronicity.

Epidemiologic model for tuberculosis requires three variables; pathogen, host and environment with three levels for prevention; before the infection, for the infection control and for rehabilitation. Integrated approach is the most important strategies for tuberculosis control and systematic approach deals with the needs. Currently no single model of approach is established and there are number of things we the future medical participants to engage and solve.

According to the WHO, global burden of tuberculosis has been decreasing since 2000, both in incidence and mortality. But in some area, tuberculosis manifests as an endemic, especially South Africa, East Asia and India (WHO, 2013) (Figure 1). Also, tuberculosis manifestation usually correlates with low socio-economic status posing greater problems. Thus, WHO set up strategies for tuberculosis control, namely DOTS strategy (mid-1990s) and Stop TB program (2006-2015) for controlling drug resistance and eradicating tuberculosis. Stop TB program is based on the epidemiologic model suggesting detection at least 70% of new TB cases and achievement treatment success over 85% (WHO, 2013). But with emergent MDR-TB and economic crisis, the result remains inconclusive. Korea is one of the countries tuberculosis hasn't been eradicated, so CDC allocates independent department for AIDS/Tuberculosis, surveying data and controlling tuberculosis epidemics.

We will review some articles and Korean statistical data for controlling tuberculosis manifestation, focusing on the latency control and drug resistance management. We proceed to the proposal for the tuberculosis control based on SEIR models. Also we will systematically review and meta-analyze some of the published articles about risk factors contributing tuberculosis mortality. Assembling these results will lead to the question of where we are in the tuberculosis eradication strategy and what should we do to prevent tuberculosis epidemic.



Figure 1. (Left) Estimated Tuberculosis Incidence Rate, 2011 (Right) Notified cases of MDR-TB as a percentage of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2011 (Adapted from WHO, 2013)

Materials & Methods

Tuberculosis chronicity in Korea & Worlds – A Comparison

We have contacted with Centers for Disease Control and Korea National Tuberculosis Association by e-mail, and gathered statistics from Korean Statistical Information service, WHO Global TB Report 2013. Also we review the brief portrait of the tuberculosis condition in Korea with guideline issued from CDC.

Also, using data obtained from WHO, we analyze the global trend of TB recurrence focusing on mechanism of latency. Supplement articles are gathered from PubMed Database.

Meta-analysis on the risk factors contributing tuberculosis mortality

2.1. Information Sources & Search Methods

Articles were identified by searching accessible electronic sources. This searching was applied to PubMed and using MeSH terms with keywords. The last search was run on 9 November 2013. The keyword terms to search were attached to appendix.

2.2. Eligibility Criteria

Design was limited to cohort study described clearly. Length of study period was limited at least 1 year. The articles in English were only included. Participants of any age with TB were analyzed regarding latent or chronic TB. No limitation on area, ethnicity and source of subject. We search articles for treatment and preventive control of TB. Risk factors should be independently analyzed and present with HR, 95% CI. Only articles with clear description on control group are included. We only restrict the outcome as mortality and relapse. Data on cure rate or prognosis is gathered together but only included if it concerns about TB latency.

Eligibility assessment was done by 3 steps, and all steps were independently reviewed by 3 authors. First screening process was done by the types of study design, the types of population and language criteria. Second screening process was done by the types of interventions and comparator. Third screening process was done by the types of outcomes. These processes were plotted with PRISMA flow diagrams (Figure 2, 3). Although the PRISMA flow diagrams were conducted by divided as therapy and prevention part, finally included studies were 6 after adjusting for duplicates. Thus 6 articles were analyzed to synthesis in this systematic review.

Conducting the analysis of PRISMA flow diagrams and forest plot of risk factors were done by Review Manager 5.2 software. PRISMA flow diagrams were employed to select articles for systematic review. Forest plot was employed to synthesis the results, where confounding factors are considered and used to analyze the results.

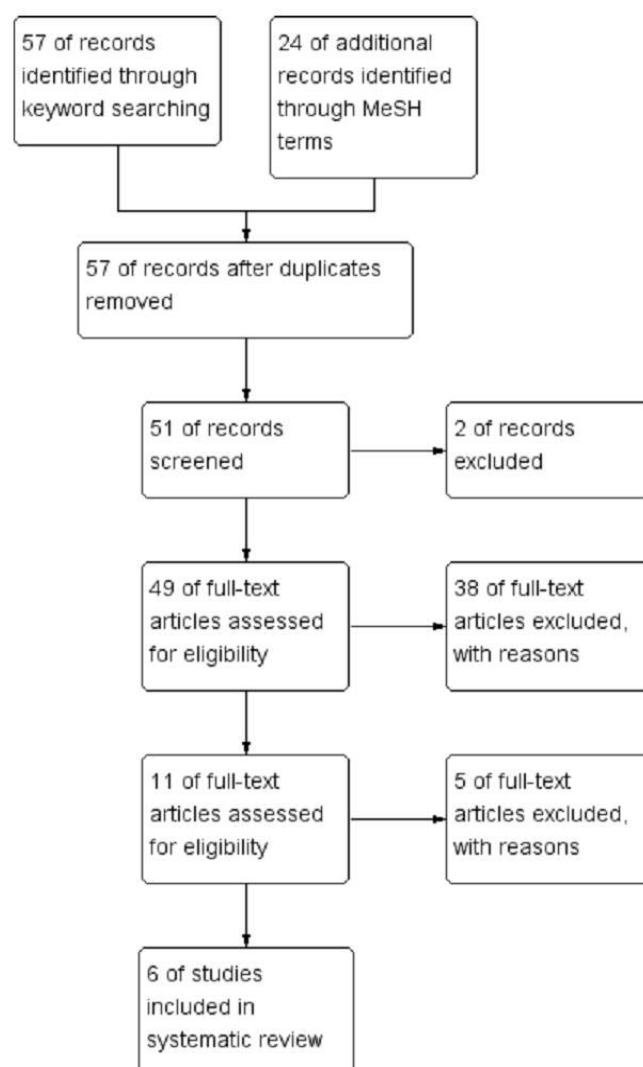


Figure 2. PRISMA flow diagram of study selection - Therapy part

In therapy part, how TB treatment affected on mortality was the purpose, which reflected on hazard ratio with respect to no TB incidence. The search of PubMed and MeSH terms provided a 57, 24 articles, respectively. After adjusting for duplicates 57 remained. By the first screening the abstracts, 6 studies were discarded by study design and population criteria, and 2 additional studies were discarded because full text of the study was not be feasibly translated into English (Spanish, Japanese). The full text of the remaining 49 studies were examined in more detail. By the second screening process, it appeared that 38 studies did not meet the inclusion criteria as described. By the third screening process, 6 studies met the inclusion criteria and were included in the systematic review.

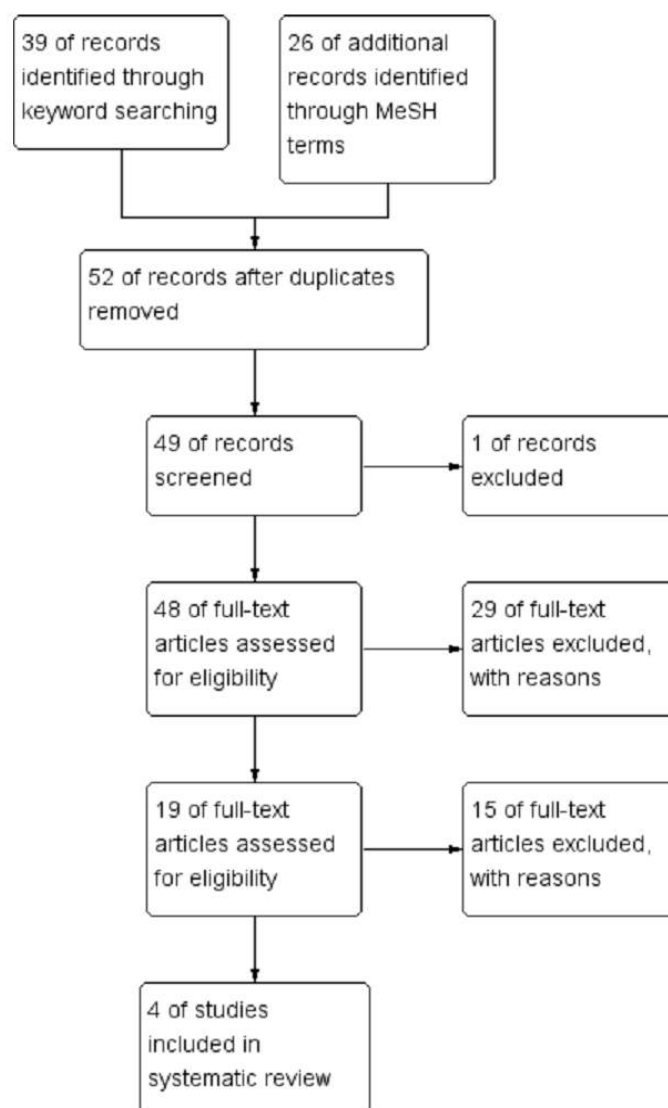


Figure 3. PRISMA flow diagram of study selection - Prevention part

In prevention part, how TB prevention affected on mortality was the purpose, which reflected on hazard ratio with respect to no TB incidence. The search of PubMed and MeSH terms provided a 39, 26 articles, respectively. After adjusting for duplicates 52 remained. By the first screening the abstracts, 3 studies were discarded by study design and population criteria, and 1 additional studies were discarded because full text of the study was not be feasibly translated into English (Japanese). The full text of the remaining 48 studies were examined in more detail. By the second screening process, it appeared that 29 studies did not meet the inclusion criteria as described. By the third screening process, 4 studies met the inclusion criteria and were included in the systematic review.

Result

Tuberculosis chronicity& Strategy in Korea

There was not enough data about latent tuberculosis in Korea, so we indirectly measured TB chronicity by New TB subtracting from the sum of MDR-TB and Total TB as an overview.

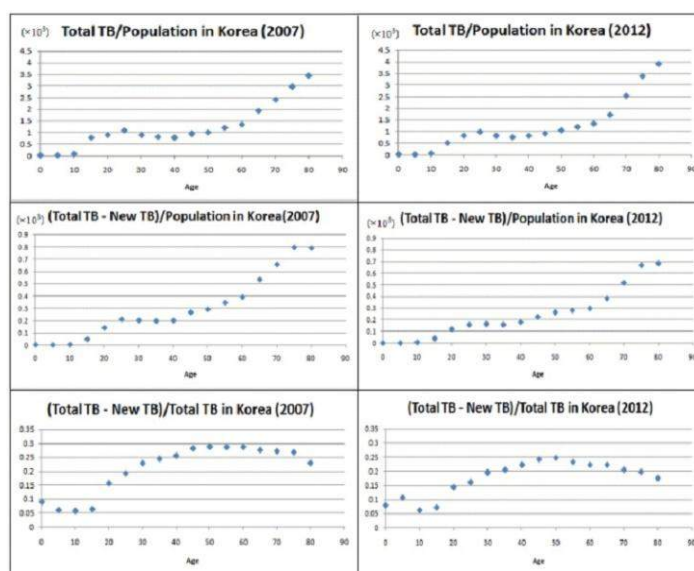


Figure 4. Tuberculosis investigation in Korea.

The data showing various statistics and the incidence of tuberculosis in Korea was obtained from 2012 annals of tuberculosis report, which was measured by cross-sectional method from 2012.1.1 to 2012.12.31. The ratio of TB or (Total TB - New TB) in Korea peaked at age near 20 and 80, as shown in the upper four graphs. In addition, the peaks appeared at age near 50 from the remaining two graphs.

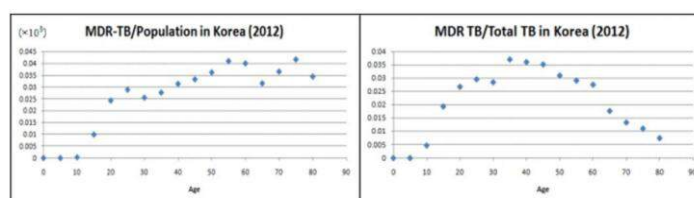


Figure 5. MDR TB in Korea.

Figure 5 shows the statistics of MDR-TB in Korea. This data is from 2012 annals of tuberculosis report, and is measured by cross-sectional method from 2012.1.1 to 2012.12.31. The data shows the incidence of the tuberculosis. From the left graph at Figure 5, we can find that the graph of ratio of MDR-TB in Korea shows peaks at age near 20, 55, and 75. In addition, from the right graph, the peak appears at age near 35.

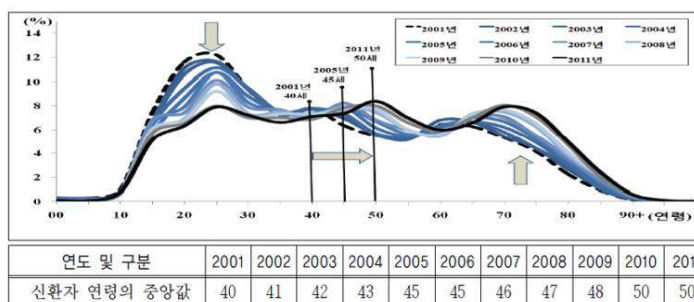


Figure 6. TB in Korea.

Figure 6 shows the change of new TB in Korea from 2001 to 2011. This data is from 2013 National Tuberculosis Control Guideline.

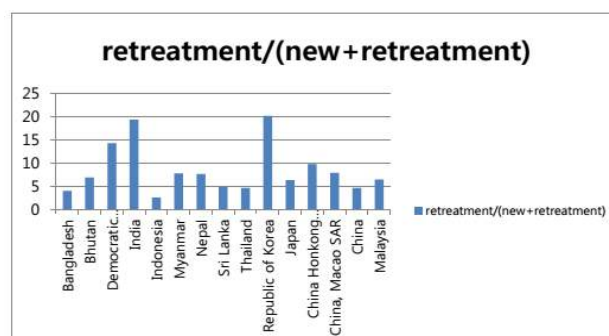


Figure 7. The rate of retreatment among total treatment of TB(new and retreatment combined)

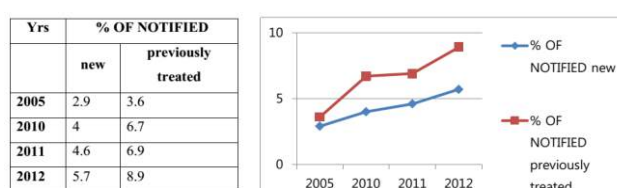


Figure 8. The rate of patients with MDR-TB is rapidly increasing around the world, especially in Korea, posing threat to further latency of TB

year	new	relapse	previous treatment failed	return to treatment after stop	latent Bacillus	transferred	other
2001	34123	6742	500	914	6	3517	280
2002	32010	6270	429	772	24	3302	233
2003	30687	5693	359	713	48	2834	166
2004	31503	5691	405	803	98	2917	318
2005	35269	5891	393	711	133	1914	2688
2006	35361	5558	281	773	90	1833	2388
2007	34710	5403	314	784	56	1742	2588
2008	34157	5227	289	734	60	1607	2100
2009	35845	5624	309	896	51	1775	2802
2010	36305	5637	267	949	23	1918	3002
2011	39557	5844	206	1165	55	2149	1515
2012	39545	5215	121	836	25	1553	2237

Table 1. The number of patients classified by TB treatment history in Korea

Because there were no suitable parameter for tuberculosis latency and no direct survey on TB latency were found, we use MDR TB and Total TB – New TB to indirectly see the overview of latent TB in Korea. We guess the reason for the peak shown at age 20 and 80 at the graph of tuberculosis in Korea (Figure 4) is that at age near 20, the social activity increases dramatically so that people are more likely to be exposed to tuberculosis. In addition, at age near 80, since the immune system weakens as people get older, the higher the age, the higher the risk of the tuberculosis. Though not conclusive, the cause for the peak shown at age near 40 at the graph of latent tuberculosis in Korea (Figure 4) maybe due to the long social activities. In addition, many people at the age near 40 is the householder in the family, so they may be unwilling to get proper treatment, and chances are, this may also contribute to the high latent rate at the age 40. In Korea the rate of patients being treated again are far higher than other countries in Asia. Some of other Asian countries that have high retreatment rate are North Korea and India, where the rate is over 10% (Figure 7).

We will review the management of latent TB in Korea. For the diagnosis of latency, there are two methods – TST (Tuberculin Skin Test) and IGRA (Interferon-Gamma Releasing Assay). TST is done by Mendel-Mantoux test, which applies PPDSC5-10mm under the elbow. The test is defined positive, after 48-72 hours, when the following conditions are satisfied :

1. the wheal is bigger than 10mm from the primary inspection
2. the wheal is bigger than 5mm for the infants who did not get BCG yet
3. the wheal is bigger than 15mm for 5 to 17 year old teenagers who have not contacted with tuberculosis patients and got TST by chance.

For IGRA test, it is not applied for the age under 5. In addition, except for the children 5-18 years of age in juvenile tuberculosis, IGRA test is not used alone.

1. BCG vaccination after the age of 1
2. If he/she has received BCG vaccination

The treatment starts unless TB is MDR. In case of MDR-TB, patient isolation enforced and regimen determined by his/her condition. Before the treatment, the following examination must occur;

1. Liver function test except for children with no history of liver disease
2. If RIF is included in the treatment, CBC should be performed before it.

The follow-up management of patients after the treatment is as follows; (There is no fee for patients)

1. Latent TB recover or person who is not infected but have contacted with TB patient.
 - a) Chest X-ray examination 3, 9 months after the treatment initiation
 - b) If the X-ray examination held 9 months after the start of the treatment showed new TB patient, enforce a chest X-ray again after the 6, 12 months from that point.
2. Latent TB patient who did not take treatment or stopped the treatment
 - a) Chest X-ray 3, 6, 9, 12 months after the first examination

Medication	The daily dosage The daily dosage / weight 1kg	Dosage period	adaptation	Dosage method
INH(9H)	300mg(maximum) Adult(5mg/kg), Child(5-10mg/kg)	9 months	Fundamental rule	Once a day after the breakfast
RIF(4R)	600mg(maximum) Adult(10mg/kg), Child(10-20mg/kg)	4 months	INH resistance	Once a day, 30 minutes before meal
INH+RIF (3HR)	H(300mg(maximum)) + R(600mg(maximum)) H : Adult(5mg/kg), Child(5-10mg/kg) R : Adult(10mg/kg), Child(10-20mg/kg)	3 months	If only short-term treatment is possible	H : Once a day after the breakfast R : Once a day, 30 minutes before meal

Table 2. National Medication Strategy for Latent Tuberculosis. Adapted from (Korea Center for Disease Control, 2013)

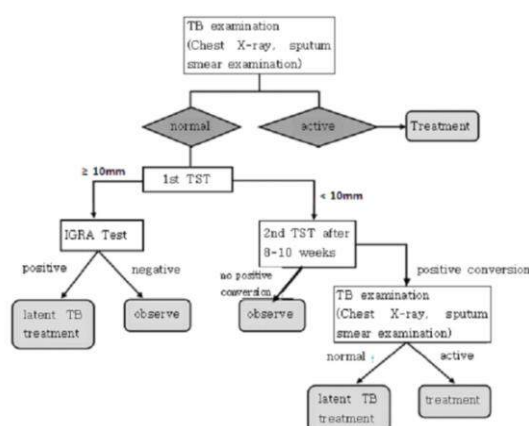


Figure 9. Korean Algorithm for Latent Tuberculosis Management. Adapted from (Korea Center for Disease Control, 2013)

Meta-analysis on the risk factors contributing tuberculosis mortality

Since prevalence of TB and incidence of MDR-TB are posing threat in Korea, there is a need to analyze how TB affects on various factors especially selected from the known risk factor (Marais, Lönnroth, & Lawn, 2013a) as etiology and socio-cultural aspects. For this need, we conducted systematic review to study how magnitude of risk factors exist at the end-point.

2.1. The Results of Individual Studies

All six included articles employed retrospective cohort study designs (Table 3). Three of included articles were studied each cohort in 1990s, whereas others were in 2000s. Since area of 3 cohort groups was overlapped in Maryland or Baltimore in the U.S., there are three cohort nations in included articles (the U.S., China, and Taiwan). The summary and analysis on each cohort group is included in Appendix 2. The study characteristics and risk factors are summarized on Table 4.

2.2. Meta-analysis of the studies

We categorized 14 risk factors selected from 6 papers into 4 categories; 'Chronic Diseases' (ESRD, COPD, chronic bronchitis, DM, hypertension, CAD), 'Social Determinants' (age>60, malnutrition, alcohol), 'Cancer', and 'Nonspecified' (HIV, immunosuppression, steroid).

The analysis concerns the impact of the risk factors on mortality. From each category and in total, the pooled estimates were calculated by random effect method, Mantel-Haenszel model, and presented in a Forest plot (Figure 10). Certain data selected from the papers, that are missing the total number of the Risk Factor(+) group, were automatically excluded from the analysis and the Nonspecified category was excluded as well because the number of data for HIV, steroid, and immunosuppression was insufficient (≤ 3).

The result from the Chronic Disease category is significant (OR=4.42, 95%CI=[3.22, 6.07], $p<0.0001$), so is that of the Social Determinants category (OR=2.57, 95%CI=[1.51, 4.38], $p=0.0005$), and the result from the Cancer category is significant as well (OR=3.90, 95%CI=[2.68, 5.66], $p<0.0001$). The overall estimate of all the selected risk factors, except those of the Non-specified category and the excluded, is significant (OR=3.50, 95%CI=[2.70, 4.54], $p<0.00001$).

Table 3. Summary cohort of included studies evaluating the risk factors in tuberculosis

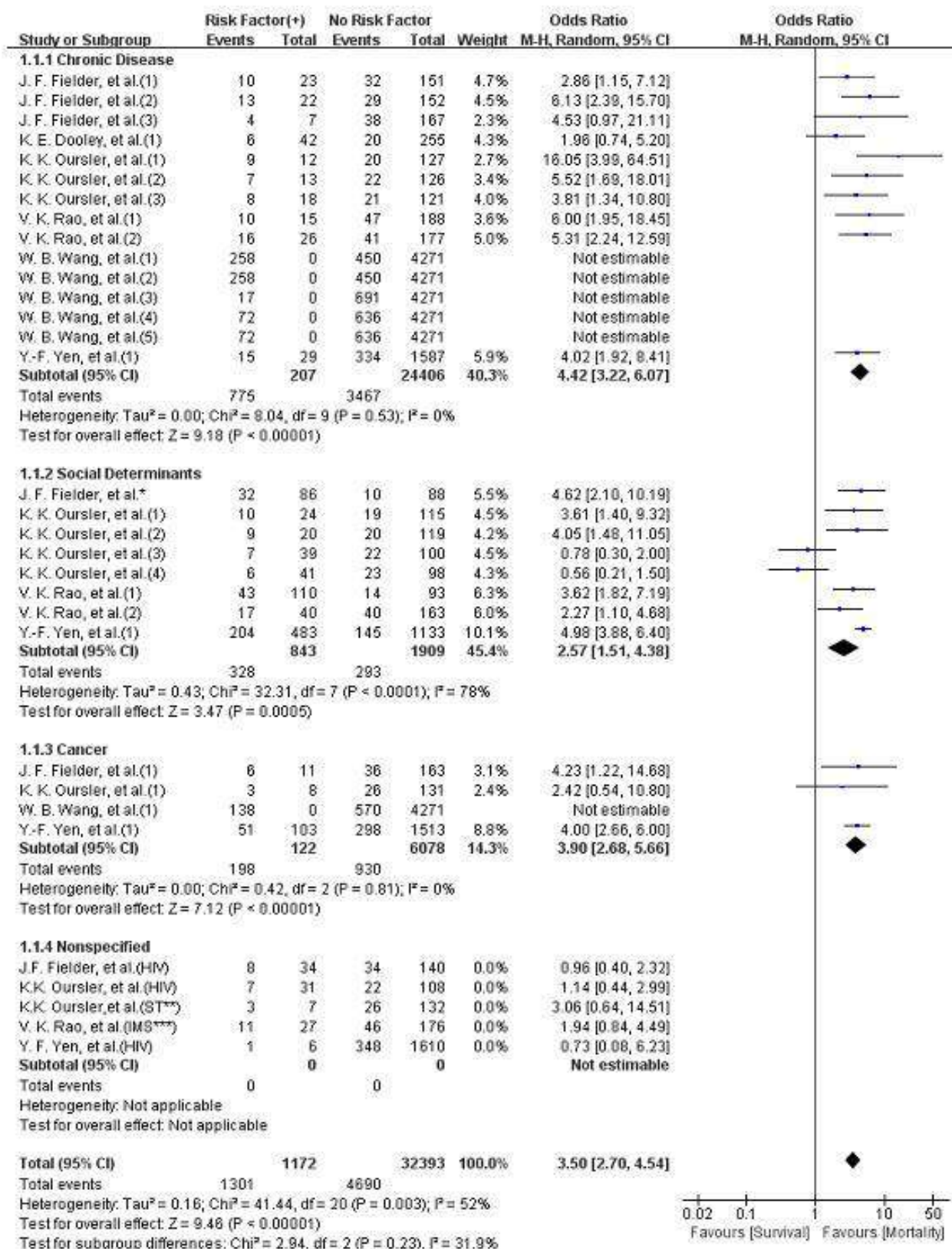
Study Overview			Study Population						Study Object		
Author	Study Design	Study Period	Source of Subject			Number of Subject	Event observed	Number of Events	Diagnosis Modality	Manifestation	Subtype
			Description	Age	Sex						
(Dooley, Tang, Golub, Dorman, & Cronin, 2009)	Retrospective	2004-2005	active TB Johns Hopkins Schools of Public Health and Medicine, Maryland Department of Health and Mental Hygiene, Maryland Hispanic 39(15), Asian 72(21), Black 206(58), White 77(22)	Mean (SD) w/o DM 39.8 (18); w/ DM 56.5 (15)	All F M	297 140 (47) 157 (52)	Mortality DM	26 (8.8) 6/42 (14.3)	culture-confirmed sputum culture conversion	PTB w/o DM 5/20 (25) w/ DM 2/6 (33) EPTB w/o DM 5/20 (25) (CNS, disseminated, pulmonary embolus) w/ DM 1/6 (16) (Miliary)	MDR 0/26 death (0)
(Fielder et al., 2002)	Retrospective	1993-1998	Newly diagnosed PTB Baltimore's Eastern Chest Clinic, Baltimore City Health Department (BCHD), Baltimore Black 133(76)	20+ Median 49 Mean 50.6; death 62; live 47	All F M	174 50 124	Mortality Age ≥ 49 HIV Cancer COPD CAD DM Renal F	42(24) 32/86 (37) 8/34 (24) 6/11 (55) 10/23 (43) 4/7 (57) 13/22 (59) 9/15 (60)	Sputum smear-positive	PTB 174 Concomitant EPTB 24 (14)	MDR 2/174 (1)
(Oursler et al., 2002)	Retrospective	1994-1996	PTB In the RFLP library Baltimore City Health Department(BCHD) Tuberculosis Clinic, Maryland Black 102(73), White 28(20), Other 9(7)	18+ Mean(SD) 52.6 (17.5)	All F M	139 39 100	Mortality Age 61-75 Age 76-90 Weight loss Alcohol HIV Cancer COPD Steroid DM Renal	29 (21) 10/24 (42) 9/20 (45) 7/39 (18) 6/41 (15) 7/31 (23) 3/8 (38) 7/13 (54) 3/7 (43) 8/18 (44) 9/12 (75)	culture-confirmed	PTB only (pts w/ EPTB was excluded from this cohort)	MDR 0 (excluded)
(Rao, Elizabeth, Fraser, & Kollef, 1998)	Retrospective	1988-1996	TB 8 hospitals in Barnes-Jewish-Christian (BJC) Health System, St. Louis, MO, metropolitan area Whites 92(45.3), African-Americans 94(46.3), Other 17(8.4)	Mean(SD) 58.0 (21.4) (range 16-95)	All F M	203 91 112	Mortality Age > 60 Malnutrition Resp. F ESRD Immunosuppression	57/203 (28) 43/110 (39) 17/40 (43) 16/26 (62) 10/15 (67) 11/27 (41)	Culture-positive Acid-fast stain CXR	PTB 27/57 (47.4) EPTB 11/57 (19.3) Both 19/57 (33.3)	1st-R 24 (12) MDR 3 (2)
(Wang et al., 2013)	Retrospective	2004-2008	PTB 4 districts of Shanghai (Yangpu, Pudong, Putuo and Songjiang), China National TB Surveillance System Chinese	Mean 54.5 (range 6-105)	All F M	4271 3173 1098	Mortality Cancer Resp. ds CVD Endocrine, nutrition.	708 138/708 (19) 258/708 (36) 72/708 (10) 17/708 (2)	CXR, Sputum smear, Culture, DST	PTB only	MDR (2.8% of 2368 smear-positive)
(Yen, Yen, & Shih, Deng, 2012)	Retrospective	2007-2008	Adults with PTB Taipei City Hospital, Taipei, Taiwan Tawianese	18+ 18-34 200 (12.4%) 35-49 199 (12.3%) 50-64 292 (18.1%) 65-79 442 (27.4%) ≥80 483 (29.9%)	All F M	1616 502 1114	Mortality Age≥ 80 HIV Malignancy ESRD Past TB MDRTB	349 (22) 204/483 (42) 1/6 (17) 51/103 (50) 15/29 (52) 15/72 (21) 9/20 (45)	Culture-positive	PTB	Total

Abbreviation : DM : Diabetes Mellitus; COPD : Chronic Obstructive Pulmonary Disease; CAD : Coronary Artery Disease; Renal F : Renal Failure; ESRD : End-Stage Renal Disease; Resp. ds : Respiratory Disease; CVD : CardioVascular Disease; Endocrine, nutrition : Endocrine, nutrition, and metabolic disease; RFLP : Restriction Fragment Length Polymorphisms; CXR : Chest X-Ray; DST : Drug Susceptibility Testing; PTB : Pulmonary tuberculosis; EPTB : Extra-Pulmonary tuberculosis; MDR : Multidrug-Resistant; 1st-R : Resistant to First-line antituberculosis agents

Table 4. Summary outcomes of included studies evaluating risk factors in tuberculosis

Ref Number	Study Characteristics				P for Trends	Confounding Factors	Comments
	Category		Relative Ratio (95% CI)				
(Dooley et al., 2009)	DM	Yes	6.5 (6/26)	(1.1, 38.0)	0.039	HIV, age, weight, foreign birth	Adjusted HR
(Fielder et al., 2002)	Age	≥ 49 years	4.6 (32/86)	(2.1, 10.2)	<0.001	HIV, Cancer, COPD, CAD, DM, Renal failure	Crude HR, univariate analysis
	HIV	Positive	2.4 (8/34)	(0.8, 7.0)	0.11	Age, Cancer, COPD, CAD, DM, Renal failure	Adjusted HR for age
	Cancer	Yes	2.3 (6/11)	(0.6, 8.1)	0.21	Age, HIV, COPD, CAD, DM, Renal failure	Adjusted HR for age
	COPD	Yes	1.5 (10/23)	(0.6, 4.0)	0.27	Age, HIV, Cancer, CAD, DM, Renal failure	Adjusted HR for age
	Coronary Artery Disease	Yes	2.4 (4/7)	(0.5, 11.6)	0.39	Age, HIV, Cancer, COPD, DM, Renal failure	Adjusted HR for age
	DM	Yes	3.8 (13/22)	(1.4, 10.3)	0.008	Age, HIV, Cancer, COPD, CAD, Renal failure	Adjusted HR for age
	Renal Failure	Yes	5.2 (9/15)	(1.6, 16.9)	0.005	Age, HIV, Cancer, COPD, CAD, DM	Adjusted HR for age
	Age	61-75	4.1 (10/24)	(0.5, 33.5)	0.2	Weight loss, Daily alcohol, HIV, Cancer, COPD, steroid, DM, Renal disease, Injection drugs, Gender, Race	Reference age : 18-60 years
(Oursler et al., 2002)	Age	76-90	4.3 (9/20)	(0.2, 76.6)	0.3	Weight loss, Daily alcohol, HIV, Cancer, COPD, steroid, DM, Renal disease, Injection drugs, Gender, Race	Reference age : 18-60 years
	Weight loss	Yes	1.2 (7/39)	(0.5, 2.9)	0.7	Daily alcohol, HIV, Cancer, COPD, steroid, DM, Renal disease, Injection drugs, Gender, Race	Adjusted HR for age Weight loss was defined by an arbitrary threshold of ≥ 20 pounds.
	Daily alcohol	Yes	1.1 (6/41)	(0.4, 2.9)	0.8	Weight loss, HIV, Cancer, COPD, steroid, DM, Renal disease, Injection drugs, Gender, Race	Adjusted HR for age
	HIV	Yes	2.4 (7/31)	(0.3, 16.8)	0.4	Weight loss, Daily alcohol, Cancer, COPD, steroid, DM, Renal disease, Injection drugs, Gender, Race	Adjusted HR
	Cancer	Yes	0.9 (3/8)	(0.2, 3.4)	0.9	Weight loss, Daily alcohol, HIV, COPD, steroid, DM, Renal disease, Injection drugs, Gender, Race	Adjusted HR for age
	COPD	Yes	6.1 (7/13)	(0.8, 49.8)	0.09	Weight loss, Daily alcohol, HIV, Cancer, steroid, DM, Renal disease, Injection drugs, Gender, Race	Adjusted HR
	Steroid use	Yes	4.2 (3/7)	(1.2, 15.0)	0.03	Weight loss, Daily alcohol, HIV, Cancer, COPD, DM, Renal disease, Injection drugs, Gender, Race	Adjusted HR for age
	DM	Yes	6.7 (8/18)	(1.6, 29.3)	0.01	Weight loss, Daily alcohol, HIV, Cancer, COPD, steroid, Renal disease, Injection drugs, Gender, Race	Adjusted HR
	Renal disease	Yes	9.7 (9/12)	(1.2, 80.3)	0.04	Weight loss, Daily alcohol, HIV, Cancer, COPD, steroid, DM, Injection drugs, Gender, Race	Adjusted HR Renal disease was defined by a serum creatinine level ≥ 2.0 mg/dL
	Age	> 60 years	3.5 (43/57)	(2.4, 5.2)	<0.001	Malnutrition, Respiratory failure, ESRD, Immunosuppression, Dyspnea	
(Rao et al., 1998)	Malnutrition	Yes	3.2 (17/57)	(2.1, 4.9)	0.007	Age, Respiratory failure, ESRD, Immunosuppression, Dyspnea	Adjusted HR Malnutrition as defined by a body weight < 90% of the ideal weight or a recent significant weight loss
	Respiratory F	Yes	6.5 (16/57)	(6.0, 7.0)	<0.001	Age, Malnutrition, ESRD, Immunosuppression, Dyspnea	Adjusted HR Respiratory failure was defined as a Requirement for mechanical ventilation for at least 24 h.
	ESRD	Yes (dialysis)	7.0 (10/57)	(3.7, 13.3)	0.002	Age, Malnutrition, Respiratory failure, Immunosuppression, Dyspnea	Adjusted HR
	Immunosupp	Yes	3.2 (11/57)	(1.6, 5.2)	0.018	Age, Malnutrition, Respiratory failure, ESRD, Dyspnea	Adjusted HR
(Wang et al., 2013)	Cancer	Yes	1.72 (138/708)	(1.10, 2.68)		COPD, Chronic bronchitis, HTN, CAD, DM	Adjusted HR for sex, age, and Tx Hx Data extracted from all-cause of death from TB cohort. The numbers of cause of death were obtained by categories.
	COPD	Yes	1.56 (258/708)	(0.83, 2.92)		Cancer, Chronic bronchitis, HTN, CAD, DM	Adjusted HR for sex, age, and Tx Hx
	Chronic bronchitis	Yes	1.47 (258/708)	(1.05, 2.04)		Cancer, COPD, HTN, CAD, DM	Adjusted HR for sex, age, and Tx Hx
	HTN	Yes	0.77 (72/708)	(0.48, 1.24)		Cancer, COPD, Chronic bronchitis, CAD, DM	Adjusted HR for sex, age, and Tx Hx
	CAD	Yes	1.22 (72/708)	(0.65, 2.28)		Cancer, COPD, Chronic bronchitis, HTN, DM	Adjusted HR for sex, age, and Tx Hx
	DM	Yes	1.09 (17/708)	(0.88, 1.35)		Cancer, COPD, Chronic bronchitis, HTN, CAD	Adjusted HR for sex, age, and Tx Hx
(Yen et al., 2012)	Age	≥ 80 years	1.9 (204/483)	(1.3, 2.6)	<0.001	HIV, Malignancy, ESRD, Past Hx of TB, AFB, CXR, MDRTB, DOT, Gender, Marital status, Education level, Employment	Adjusted HR Reference age : 65-79 years
	HIV	Yes	1.4 (1/6)	(0.1, 15.3)	0.76	Age, Malignancy, ESRD, Past Hx of TB, AFB, CXR, MDRTB, DOT, Gender, Marital status, Education level, Employment	Adjusted HR
	Malignancy	Yes	3.1 (51/103)	(1.9, 5.0)	<0.001	Age, HIV, ESRD, Past Hx of TB, AFB, CXR, MDRTB, DOT, Gender, Marital status, Education level, Employment	Adjusted HR
	ESRD	Yes (dialysis)	2.9 (15/29)	(1.2, 7.4)	0.02	Age, HIV, Malignancy, Past Hx of TB, AFB, CXR, MDRTB, DOT, Gender, Marital status, Education level, Employment	Adjusted HR
	past Hx of TB	Relapse	0.8 (15/72)	(0.4, 1.8)	0.62	Age, HIV, Malignancy, ESRD, AFB, CXR, MDRTB, DOT, Gender, Marital status, Education level, Employment	Adjusted HR
	MDRTB	Yes	22.5 (9/20)	(5.4, 93.6)	<0.001	Age, HIV, Malignancy, ESRD, Past Hx of TB, AFB, CXR, DOT, Gender, Marital status, Education level, Employment	Adjusted HR

Abbreviations DM : Diabetes Mellitus; COPD : Chronic Obstructive Pulmonary Disease; ESRD : End-Stage Renal Disease; HTN : Hypertension;
CAD : Coronary Artery Disease; Past Hx of TB : Past history of tuberculosis; AFB : Acid-fast bacilli stain; CXR : Chest X-Ray; MDRTB : Multidrug-Resistant TB
DOT : Directly Observed Therapy; HR : hazard ratio; Tx Hx : Treatment History



* Age $\geq$ 49 years; ** Steroids; *** Immunosuppression

Figure 10. Summary of Meta-Analysis on Risk Factors contributing to TB Mortality

Recurrence Mechanism & Risk Factors of TB	
With re-infection	Without re-infection
1. Endogenous reactivation of primary infection induced by re-infection. 2. Exogenous re-infection 3. multiple strains	1. Progressive primary tuberculosis due to primary infection 2. Tuberculosis due to endogenous reactivation of primary infection
re-infection (Marais, Lönnroth, & Lawn, 2013a)	without re-infection (Thomas et al., 2005)(Santha et al., 2002)
• Immunosuppressants • Steroids (eg, prednisone, prednisolone, methylprednisolone) • Antimetabolites (eg, methotrexate, azathioprine, leflunomide) • T-cell inhibitors (eg, ciclosporin, tacrolimus) • Alkylating agents (eg, cyclophosphamide, chlorambucil) • Biological agents • Tumour necrosis factor or interleukin 2 blockers (eg, etanercept, infliximab, adalimumab) • Humanised chimaeric monoclonal antibodies (eg, basiliximab, daclizumab, muromonab-CD3, tacrolimus) • Non-steroidal anti-inflammatory drugs (eg, ibuprofen, diclofenac)	• Taking irregular treatment([aOR] 2.5) • Initial drug resistance to isoniazid and/or rifampicin([aOR] 4.8) • Smoking([aOR] 3.1) • Being male([aOR] 3.4) • History of previous treatment([aOR] 2.8) • Alcoholism([aOR] 2.2) • Diagnosis by community survey([aOR] 2.1) • Weight < 35kg ([aOR] 3.8)

Table 5. Recurrence Mechanism & Risk Factors of Tuberculosis

The cause of TB recurrence can be divided into two parts: recurrence with re-infection and without re-infection. According to the study published by C. Chiang and L. Riley (Chiang & Riley, 2005), the factors of each are shown in **Table 5**.

1.1 Recurrence of TB with re-infection

1.1.1. Theoretical prediction of re-infection rate among patients with TB recurrence

According to Williams et al (Bacaër, Ouifki, Pretorius, Wood, & Williams, 2008), the re-infection rate among TB cases was 48% for those who have only TB, and 32% for those who have TB and HIV.

In Korea, the CDC report of 2013 reveals that 0.1% of population has HIV, therefore re-infection rate would be near 48%, rather than 32%. Furthermore, the HIV prevalence rate is currently rising, so it is predicted that the re-infection rate would decrease.

Herrera et al (Herrera, Bosch, Nájera, & Aguilera, 2013) uses SEIR model analyzing long-term dynamics of tuberculosis and latent tuberculosis in semi-closed communities. In the SEIR model as five compartments the five possible routes toward TB infection were applied. If $R_0 > 1$, there is possibility of existing multiple endemic equilibrium states. If $R_0 < 1$, the disease will eventually disappear; however the re-infection could reverse the situation irreversible for eradication. From this article, we see that not only R_0 but the strategies are important for TB control.

1.1.2. Clinical research

Lambert-Lancet (Lambert et al., 2003) reanalyze articles on DNA fingerprintings so that reinfection and relapse could be distinguished—though there remains possible bias on study designs. The paper concludes that if not in such extreme situations like HIV infection, re-infection poses little threat to TB control programs. Study on RFLP analysis (Alland et al., 1994) reveals that recently transmitted tuberculosis accounted for approximately 40% of the incident cases. The result presents that the transmission of tuberculosis contributes substantially to tuberculosis epidemics.

1.2 Recurrence of TB without re-infection

Recurrence of TB without re-infection is due to two different mechanisms.

First, progressive primary tuberculosis due to primary infection—the recurrence resulted from treatment failure or default from the primary infection. There are several risk factors that affect default, failure and death rate among tuberculosis patients. South India Group (Santha et al., 2002) reveals that irregular treatment, history of previous treatment, alcoholism and MDR are the main risk factors for treatment failure. Second, recurrence due to endogenous reactivation of primary infection, namely 'relapse'. This process is different from 'progressive primary tuberculosis due to primary infection' because primary infection had been cured or completed.

2. Pathophysiology of recurrence of TB

In connection with the results of relevant studies we found, some of the risk factors that contribute to TB recurrence are to be analyzed in this part.

According to the study conducted in South India (Thomas et al., 2005), the risk factors investigated as a result were low compliance to the treatment (aOR 2.5; 95% CI 1.4-4.6), initial drug resistance to isoniazid and/or rifampicin (aOR 4.8; 95% CI 2.0-11.6) and smoking (aOR 3.1; 95% CI 1.6-6.0).

Research mainly focusing on recurrence wasn't found, but the risk factors of re-infection can be predicted. HIV infection weakens the immune system to make the patient more vulnerable to secondary infection. Drug resistance and low compliance to the treatment leads to low success rate of TB eradication. During the prolonged treatment process people who contact with the patient, especially in hospitals where endemic reactivation is more plausible, are more likely to be reinfected.

2.1. Low compliance to the treatment.

Several researches have argued that one of the crucial factors of recurrence is low compliance to the treatment process. Taking medicine irregularly induces bacillus to proliferate or drug resistant bacillus to appear.

2.1.1. Reason for irregular treatment

The low compliance of patients can result from several reasons. For instance, Castelnovo et al (Castelnovo, 2010) suggests that patients lost to follow up the treatment due to the distance, money for transport or logistic in referring and transferring patients, other challenges in adhering to treatment are side effects, poor knowledge of the disease and insufficient family support.

The DOTS program requires patient to take medications regularly, therefore self-medication is an important part of treatment. However, self-medication can be distracted by several factors. In Korea, Lee JH et al (Lee & Chang, 2001) describes that 14.8% of the score of compliance in self-medication of the subjects was explained by five variables: Behavioral Intention, Duration of Treatment, Age, Perceived Sensitivity and Perceived Barrier. 8.7% of the score of self-evaluation of self-medication was explained by three variables: Perceived Control, Perceived Sensitivity, and Age.

As analyzed in the result part, recently in Korea there has been emergence of drug resistant bacillus and relatively reduced acknowledgement of TB caused by decrease in number of new and relapse infections. (Figure 8, Table 1) Drug resistant TB makes the duration of treatment longer, and since the prevalence of TB has been decreasing, perceived sensitivity would also go down. Therefore, the tendency of low compliance to treatment is predicted to rise.

2.3. Drug resistance

2.3.1. Effect of drug resistant TB on recurrence of TB

Drug resistant TB, including MDR-TB affects recurrence of TB in several ways.

First, a patient who has MDR-TB is likely to fail treatment. According to study (Santha et al., 2002), MDR-TB patients are 30% more vulnerable to treatment failure. The failure of treatment will eventually lead to recurrence, since the drug resistant bacillus remains in the system and by re-infection or endogenous activity, activation may occur.

Second, due to more complicated treatment program, patients are likely to show low compliance to the treatment. According to Korean group (Lee & Chang, 2001), drug-resistant (DR) group showed less compliance with treatment. DR group showed lesser adherence to treatment than the drug-sensitive group, showing more frequent self-interruption of medication, lower completion rate of treatment and higher failure rate of follow-up than the drug-sensitive group.

Also, R_0 of MDR-TB is higher than drug sensitive TB (approximated as 10-12 by CDC, Korea). Because of the environment patients with MDR-TB have to encounter, e.g. hospital (closer to semi-closed community that Herrera has noted in his research article), re-infection will be more accelerated.

2.3.2. The reason for emergence of drug resistant TB

The Korean Study (Lee & Chang, 2001) assessed the risk factors of drug resistance (DR). The result showed that previously treated tuberculosis is a most important risk factor for DR, along with others such as pulmonary involvement and associated medical illness.

2.4. Treatment history

There were two studies arguing that existence of previous history of TB treatment increases possibility of recurrence.

Korean group (Lee & Chang, 2001) found that for previously treated tuberculosis patients, higher rate of overall DR and MDR, larger number of resistant drugs and more frequent self-interruption of medication were observed than newly diagnosed patients.

The Study at South Africa (Verver et al., 2005) observing recurrence suggests that age-adjusted incidence rate of TB attributable to re-infection after successful treatment was four times that of new TB. From the studies, we could conclude that people who have a history of treatment before, are at a strongly increased risk of developing TB when re-infected.

3. Pathophysiology of the risk factors

3.1. Diabetes Mellitus

Tuberculosis in persons with DM is characterized by elevated frequencies of CD4⁺ Th1 and subset of Th17 cells also expressing IL-10. (Kumar et al., 2013) Natural regulatory T cells, however, decrease and make Th1/Th17 responses too excess to respond to bacterial pathogens. (Zielinski et al., 2012) Thus, people with diabetes show impaired sputum conversion and cure rates on tuberculosis treatment, with increased risk of death and relapse. (Marais, Lönnroth, & Lawn, 2013b)

3.2. Cardiovascular Disease

First of all, heart failure puts our body system under hypoxic condition damaging our body functions. Secondly, vascular diseases such as atherosclerosis impair the immunologic functions of vascular endothelium such as complement modulation, migration of inflammatory cells, and inflammatory mediation. (Fauci, 2008)

3.3. Chronic Kidney Disease

Chronic kidney disease is a set of a variety of primary causes and involves consequent changes in kidney such as hyperfiltration and hypertrophy of the remaining normal nephrons until this adaptation reaches its limit. As the adaptation fails, the kidney functions deteriorate leading to electrolyte imbalance, accumulation of toxic metabolites, and multiple organ failures (Fauci, 2008).

3.4. Respiratory Disease

Chronic lung disease reflects cumulative lung damage and deconditioning, impairing its immune defense against foreign pathogens inhaled. (Marais et al., 2013b) Metabolic adaptation induced by chronic lung disease allows mycobacteria to tune phenotypes in host immunity (Stewart, Robertson, & Young, 2003). Since hypoxia is a key element of the inflammatory response, *M. tuberculosis* in poorly oxygenated lesions consequently evades immune response.

3.5. Age

The problem of the aging process is the overall degeneration of body functions. Although some essential functions are spared during the aging process, many critical degenerative changes make our body vulnerable to multiple comorbidities (Figure 11). In addition, the resting metabolic rate decreases by time, which predisposes our body to an ineffective condition to readily respond to stress such as infections. (Fauci, 2008) (Figure 12.)

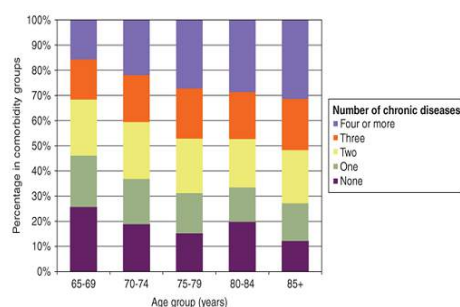


Figure 11. Original source : Prevalence of comorbidity by age group in persons 65 years and older living in the U.S. and enrolled in Medicare parts A and B in 1999. (From JL Wolff et al: *Arch Intern Med* 162:2269, 2002. (Wolff, Starfield, & Anderson, 2002))

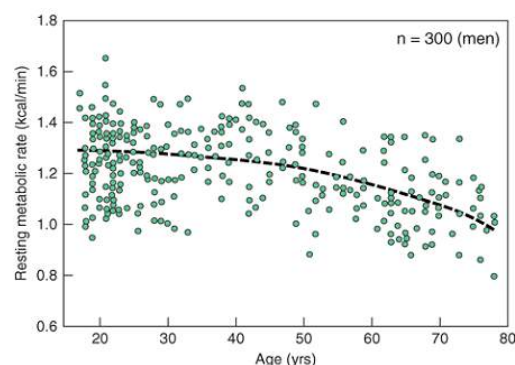


Figure 12. Original source : Changes in resting metabolic rate with aging. [Data from the Baltimore Longitudinal Study of Aging (unpublished).]

3.6. Malnutrition

Malnutrition is a condition that is an inappropriate energy balance. In this condition, body fails to respond to stress, which leads to insufficient production and turnover of proper proteins such as inflammatory cytokines, signaling molecules, and immunologic factors, and the failure of adequate energy facilitation to support the responding process.(Fauci, 2008)Since malnutrition is very common in many parts of the world(Marais et al., 2013b) and contributes to the risk for TB by the result of this review, it is suggested that this risk factor be controlled.

3.7. Alcohol

Alcohol misuse significantly amplified risk of relapse and death during and after TB treatment due to comorbidities, mainly hepatitis C virus and HIV infections, cancer, cardiovascular disease and COPD.(Marais et al., 2013b)Alcohol interferes with the absorption of vitamins and the storage. It also interferes with gluconeogenesis in the liver and fatty acid oxidation, which consequently impairs the counter-regulatory function to respond to stress(Fauci, 2008).

3.8. Cancer

Cancer itself is known to promote reactivation of latent TB(Marais et al., 2013b). In addition, subsequent chemotherapy impairs immune system predisposing our body to a vulnerable condition to various infections.

3.9. HIV

HIV virus replicates inside CD4+ T cells, eventually decreasing the number of the host cell. The CD4+ cells play an important role in immune reactions in activating macrophages, sensitizing B cells, and etc. Thus, the decrease of CD4+ cells eventually leads to AIDS, incapacitating our immune system from eradicating infecting microorganisms.(Fauci, 2008)Although antiretroviral therapy was implemented on HIV-infected patients, risk of metabolic disease is increased that show impaired sputum conversion and increased risk of death.(Marais et al., 2013b)

3.10. Steroid/Immunosuppression

Immunocompromised state is susceptible to either active tuberculosis after infection or reactivation of latent infection due to physiological like very young and elderly people, pathological like malignant disease, therapeutic like immunosuppressive treatment, and chronic disease states.(Marais et al., 2013b)

4. Glimpse on the Trends in Korea

TB infection in Korea has been decreasing since 1950s when WHO TB eradication program was launched. However, with the recurrence occurring and appearance of MDR-TB, drug resistant TB, TB is currently becoming more prevalent.

It is also important to reduce recurrent cases. Recurrence results from either with re-infection or without re-infection. Clinical observation demonstrated that re-infection accounts for less than 40% of recurrence cases, and mathematical models were adopted to give specific numbers. Re-infection is affected by HIV infection and MDR-TB infection. Since in Korea HIV infected patients and MDR-TB which has larger basic reproduction rate(R_0) prevalence is increasing, more effort should be put to control re-infection. More accurate, prompt screening methods should be developed and adopted, and MDR-TB infected patients must be closely supervised, so that they don't infect others and receive full treatment.

Since recurrence of TB is prevalent in Korea, mortality is defined as end-point in analysis with risk factors which contribute common cause of death such as cancer, cardiovascular, respiratory disease, etc (Figure 13). As already mentioned, incidence of TB is related with age, social factors are also categorized.

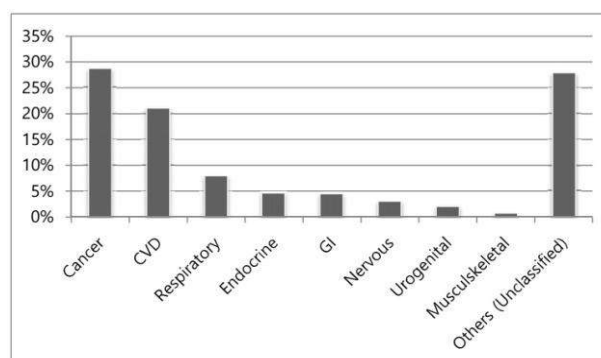


Figure 13. Cause of death in Korea, standardized by gender, age from 2012. (From Statistics Database, Korean Ministry of Health and Welfare)

Of all categories, the OR of the Chronic Disease category showed the highest value. Also, its social and medical importance remains valuable because it reflects the need to control the prevalence and progress of chronic disease, considering that it is becoming more prevalent in Korea. Regarding the common pathophysiology of chronic diseases, associated with progressive metabolic or immunologic adaptation, providing more screening tests and education would possibly control prognosis or even prevalence of chronic disease, consequently contributing to reduction of TB mortality. Second, the significant OR of Social Determinants category reflects the social need to put more effort in improving medical and socioeconomic condition of vulnerable subpopulations, like the elderly, alcohol abusers, and the malnourished. Next, the result reflects the need for more intensive care for cancer patients with TB. Not only with the disease, but also with their chemotherapy is careful assessment required. Although the data of immunosuppression was insufficient for supporting that chemotherapy may contribute to mortality, considerations on its pathophysiology give a glimpse of the possible role of chemotherapy in mortality.

Finally, more studies on the role of HIV, immunosuppression, and steroid use in mortality of TB patients are required. Each has various pathophysiology, especially in a light of affecting the natural history of TB. Immunologic, pharmacologic, and microbiologic aspects should be considered in assessing the effect of the elements of the Non-specified category.

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Appendix 1

–Prevention & Control Strategies

- ("tuberculosis" or "tb") & "cohort" & ("latent" or "chronic") & ("cure" or "prognosis" or "mortality" or "relapse") & ("Prevention" Or "Control" Or "Strategy" Or "Plan")

39 Articles fetched

- ("Latent Tuberculosis/diagnosis"[Mesh] Or "Latent Tuberculosis/prevention and control"[Mesh]) & "cohort" & ("cure" or "prognosis" or "mortality" or "relapse")

4 Articles fetched

- ("Tuberculosis/diagnosis"[Mesh] Or "Tuberculosis/prevention and control"[Mesh]) & "cohort" & ("latent" or "chronic") & ("cure" or "prognosis" or "mortality" or "relapse")

22 Articles fetched

–Treatment & Therapy

- ("tuberculosis" or "tb") & "cohort" & ("latent" or "chronic") & ("cure" or "prognosis" or "mortality" or "relapse") & ("Treatment" Or "Therapy" Or "Regimen" Or "Management")

57 Articles fetched

- ("Latent Tuberculosis/drug therapy"[Mesh] OR "Latent Tuberculosis/therapy"[Mesh]) & "cohort" & ("cure" or "prognosis" or "mortality" or "relapse")

2 Articles fetched

- ("Tuberculosis/drug therapy"[Mesh] OR "Tuberculosis/therapy"[Mesh]) & "cohort" & ("latent" or "chronic") & ("cure" or "prognosis" or "mortality" or "relapse") & ("Treatment" Or "Therapy" Or "Regimen" Or "Management")

22 Articles fetched

Appendix 2

In K. E. Dooley et al, diabetes mellitus (DM) is the risk factor we concerned. This study shows that PTB manifestation was 5 over 20 death without DM and 2 over 6 death with DM, and EPTB manifestations was 5 over 20 death without DM by CNS, disseminated TB, and with pulmonary embolus and 1 over 6 death with DM by miliary TB. There was no multidrug-resistant(MDR)-TB in 26 death. The race composition of this study is various with Hispanic 39 (15%), Asian 72 (21%), Black 206 (58%), and White 77 (22%).

In J. F. Fielder et al, the study was implemented in Baltimore for over 20 years, conducting a retrospective cohort study among all patients with newly diagnosed sputum smear-positive PTB. The risk factor chosen is Age, HIV, Cancer, COPD(chronic obstructive pulmonary disease), DM(diabetes mellitus), and renal failure. The 174 cohort participants of this study all were manifested to PTB, and some 24 participants were concomitantly manifested to EPTB. The race of this study contains Black 133 (76%).

In K. K. Oursler et al, the cohort subjects were included not with EPTB and MDRTB but with culture-confirmed PTB. Also excluded were patients whose age were below than 18. The mean subject age was 52.6 years, and SD was 17.5 years. In this study, age, weight loss, alcohol, HIV, cancer, COPD, and steroid use were selected as risk factors to be analyzed. The race of this study contains Black 102 (73%).

In V. K. Rao et al, the cohort patients of this study were with culture-positive TB. The mean age of patients was 58.0 years, and SD was 21.4 years (range, 16 to 95 years). The total numbers of having risk factors such as age > 60, malnutrition, respiratory failure, ESRD(end-stage-renal-disease), and immunosuppression were 110, 40, 26, 15, and 27, respectively. And the numbers of mortality with respect to each risk factors were 57, 43, 17, 16, 10, and 11, respectively. TB manifestation status were 27 of PTB, 11 of EPTB, and 19 of both PTB and EPTB in 57 death cases. The race of this study consists of Whites 45.3%, African-Americans 46.3%, and 8.4%.

In W. B. Wang et al, the cohort participants of this study were all PTB manifested in China. The mean age of patients was 54.5 with range of 6 to 105. The size of cohort studied in this article was 4271, and the number of mortality cases was 708. This article handled various risk factors such as cancer, COPD, chronic bronchitis, HTN (hypertension), CAD (coronary arterial disease), and DM, however, this article only shows the number of mortality events in categories like 138 of cancer, 258 of respiratory disease, 72 of cardiovascular disease, and 17 of endocrine, nutrition and metabolic diseases. This article included only PTB manifestation.

In Y. F. Yen et al, the cohort participants of this study were adults with PTB whose age were not younger than 18. The number of total participants was 1616, and the number of total mortality cases was 349. The risk factors chosen in this article are Age over 80, HIV, malignancy, ESRD, the numbers of which were 483, 6, 103, and 29 in total cohort participants, respectively. And the numbers of mortality with respect to each risk factor were 204, 1, 51 and 15, respectively. This study included PTB and MDRTB, and also analyzed Past history of TB as a risk factor.

SCIENTIFIC PAPER COMPETITION – MALAYSIA

Abstract

Title of paper: Retinal Nerve Fiber Layer Thickness in Primary Open Angle Glaucoma and Primary Angle Closure Glaucoma

Country: Malaysia

Authors: Lau Kheng Joe, Lee Yee Liong, Tan Jian Liang

Faculty/School of authors: Universiti Sains Malaysia

Background: Systemic illnesses such as hypertension and diabetes mellitus are popularly identified as chronic diseases in our community. However, not much is known about chronic diseases of the eye. Glaucoma is a chronic, irreversible neurodegenerative disease which causes specific patterns of visual field defect. It causes significant visual morbidity which lead to serious impairment in normal daily functioning. It is the second leading cause of blindness worldwide after cataract. The prevalence of glaucoma is expected to increase every year and lead to a substantial public health challenge worldwide. Identification of retinal structural defect using Optical Coherence Tomography (OCT) is important in diagnosing the types of glaucoma at early stage. This is important in preventing further functional defect. The aim of this study was to compare the retinal nerve fiber layer thickness (RNFL) between primary open angle glaucoma (POAG) and primary angle closure glaucoma (PACG).

Materials and method: A cross-sectional study was conducted involving 49 patients with POAG and 31 with PACG. Every patient had undergone ophthalmoscopic examination, IOP measurement, visual acuity measurement, gonioscopic examination, Humphrey Field Analyzer for visual field examination and OCT for evaluation of RNFL thickness. During visual field examination, eyes were classified into severity subgroups using AGIS scoring; mild (1-5), moderate (6-11), severe (12-17), advanced (18-20). The RNFL, Vertical Cup-Disc Ratio (VCDR), rim area, cup volume were recorded from the optical coherence tomography. These parameters were compared between POAG and PACG according to their subgroups (severity).

Results: There was female preponderance among PACG patients. There was significant difference of hypertension between POAG and PACG ($p=0.010$). There was no significant difference of RNFL thickness in the selected eye between POAG and PACG patients ($p=0.200$). However, there was significant difference of VCDR ($p=0.001$), rim area ($p=0.024$) and cup volume ($p=0.012$) for the mild stage glaucoma between POAG and PACG. PACG seems to have a bigger rim area and cup volume compared to POAG.

Conclusion: Detection of early structural changes in glaucoma patients is important to strategize a more effective management plan. OCT is a good tool to evaluate early changes of optic nerve head. PACG seems to have a significant larger rim area and cup volume compared to POAG. Identifying early structural changes can prevent further functional changes in glaucoma patients.

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