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失智症早期篩檢偵測工具效度及成本效益之統計評估

Statistical Evaluation of Validity and Cost-effectiveness of Two Screening Tools for Early Detection of Dementia

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中文摘要

研究背景

隨著老年人口逐漸增加同時，失智症也有同時增加的趨勢，因此考慮一個符合有效益且有效率的社區型失智症篩檢是非常重要的。在此之前，我們需要一系列的研究，包括流行病學關於失智症早期偵測的認知程度，社區失智症篩檢可行工具的效度，和以社區為基礎的失智症篩檢計畫的經濟評估，及發展出一系列以理論為基礎的統計方法。

研究目的

本論文研究目的有三：(1) 利用一新的估計盛行率/發生率比率為基礎的統計回歸模型，來測量早期偵測，對於失智症發生的平均時間的影響(2)利用一貝氏臨床推理模型，來評估同時合併認知功能檢測(MMSE)及訊息提供問卷(AD8)二種篩檢工具，是否會加社區失智症篩檢診斷的精確度 (3)利用馬可夫決策分析模型，評估社區失智症篩檢中，其不同篩檢模的成本效益分析

研究材料及方法

利用 2000-2003 年期間，全民健保費用申報的大型資料庫，我們分析出 65 歲以上有失智症病人，且符合 ICD-9-CM 編碼為 290, 290.40, 331.0 者，共 99,609 位。另一資料庫來自 2013 年社區主動型篩檢，65 歲以上參與者共 183 位。我們收集關於年紀、性別、及就醫地點等相關訊息。利用貝氏方法估出盛行率與發生率比率，來反映一般民眾對於失智症的認知程度。使用貝氏以盛行率/發生率比率為基礎的統計回歸模型，來做盛行率與發生率比率的校正，用此反映對失智症的認知程度。第二部分，在 AD8 及 MMSE 的效度評估研究中，我們針對 2013 年台南社區整合型篩檢計畫，50 歲以上民眾，評估 AD8 及 MMSE 二種篩檢工具其單獨使用、或平行檢定、或序列檢定，其效度使否有差異? 利用受試者工作特徵曲線(ROC)來探討 AD8 及 MMSE 在失智症及輕度認知功能缺損的預測功能。在缺乏黃金診斷標準下，利用一貝氏臨床推理模型來估計不同失智症篩檢工具模

式的效度。第三部分，架構一馬可夫決策分析模型，來模擬有做失智症社區篩檢的族群其 10 年成本及效益，並比較不同篩檢工具，包括 AD8、MMSE、平行檢定、序列檢定，與無篩檢的族群的成本及效益分析。我們使用一五階段馬可夫模型來模擬失智症進展，利用已發表的國內外文獻所提供參數(轉移機率、各階段所需醫療費用及照顧費用)。效益部分以品質調整人年命 (QALY)來測量，並含 3%每年折扣率，並估出增加成本效用比 (ICUR)。利用 500 次蒙特卡羅模擬，得到從整體社會觀點畫出的分散成本效益面、及接受曲線，此指標可以顯示在不同付費意願閥值下，可以產生符合成本效益的百分比。

結果

失智症盛行率、發生率在健保資料庫(被動性篩檢組)估計值分別為 2.91%及 1.83%。利用盛行率/發生率比率為基礎的統計回歸模型估計校正區域後，得到，被動性篩檢中，65 歲以上老人盛行率對發生率的比率，男性從在 65-79 歲族群 1.20(1.15-1,24)到 90 歲以上族群 3,27 (3.13-3.41)。盛行率/發生率比率發現，65 歲以上老人盛行率對發生率的比率在地理區域北區最高，東區最低。被動性篩檢組，校正年紀、性別、區域對失智症影響後，發現盛行率對發生率的比率 65-79 歲族群 1.45(1.43-1.47) 到 80 歲以上族群 1.64 (1.61-1.66)。參與社區失智症篩檢組 (主動性篩檢組)，發現其盛行率對發生率的比率 65-79 歲族群 4.23(2.68-6.69) 到 80 歲以上族群 4.77 (3.02-7.54)。

AD8 單獨使用對失智症敏感度及特異度分別為 64.71% 及 87.89%，MMSE 單獨使用在校正教育程度的情況，對失智症敏感度及特異度分別為 41.18% 及 84.50% 。兩種篩檢工具合併使用，平行檢定的敏感度及特異度分別為 88.89% 及 70.16% ，序列檢定的敏感度及特異度分別為 50% 及 93.02%。AD8 單獨使用對失智症+輕度認知功能障礙，敏感度及特異度分別為 25.74% 及 90.70%。所有篩檢模式，對於輕度認知功能障礙的敏感度，除了切點切在 26 分以外 ，其他組模式皆顯示敏感度較差，特異度尚可。利用受試者工作特曲線 (ROC) 來探討 AD8 及 MMSE 在失智症及輕度認知功能缺損的預測功能。結果發現合併 AD8 和 MMSE (平

行檢定組)的 曲線下面積(AUC)為 82.3% (75.1%-89.4%)產生比 AD8 (AUC=73.3% (60.7%-85.9%))單獨使用或 MMSE (AUC=77.4 %(67.6%-87.3%)單獨使用或系列檢定(AUC= 67.6% (53.4%-81.8%))更好的預測功能。利用貝氏分析方法，可得到平行檢定提高敏感度(97.2%)相較於 MMSE (82.2%)或 AD8 單獨使用(84.1%)；序列檢定提高特異度度(96.8％) 相較於 MMSE (86.1%)或 AD8 (77.1%)單獨使用。關於經濟評估結果如下：只考慮篩檢及醫療支出的直接成本，則成本效用比 (ICUR)在 AD8、MMSE、平行檢定、序列檢定中分別為每一人年為美金 401.4、457.7、409.8、499.2 元。同時考慮間接成本，在分散成本效益面評估為大約 80％的模擬值在第四象限（顯性）。由四種篩檢模式中可知，如果政府願意付費閥值到達美金 20000 元，則可以得到 88-94%成本效益。如果，只考直接成本，評估為大約 40％的模擬值在第四象限(顯性),當願意付費閥值到達美金 20000 元，則可以得到 93-99%成本效益。

結論

從預防由失智症造成失能和死亡的臨床方面來看，我們的研究，藉由根據所估計盛行率/發生率比率在社區篩檢模式(主動性偵測) 相較於健保照護體系(被動性偵測) 較高，已證實在一般健保照護體系，失智症的認知程度偏低。合併使用 AD8 和 MMSE 在社區失智症篩檢，可提高工具敏感度。最後，使用 AD8 和 MMSE 在社區失智症篩檢 是符合成本效益的：相較於無篩檢組幾乎接近省錢的。最符合成本效益的是合併使用 AD8 和 MMSE 的平行檢定模式。我們的研究結果可應用於健康照護政策評估，及其他有興趣於發展社區失智症篩檢的計畫，進而減少失智症照護的支出。從方法學的角度，我們發展出三種創新方法，包括(1) 估計盛行率/發生率比率為基礎的統計回歸模型。(2) 利用貝氏臨床推理模型來估計不同失智症篩檢工具模式的效度。 (3) 馬可夫決策分析模型，評估社區失智症篩檢中結合 AD8 和 MMSE 的成本效益分析。

關鍵字 ： 失智症、篩檢、敏感度、特異度、成本效益

Abstract

Background

As there is an increasing trend in the morbidity of dementia when aging population has been increasing, considering an effective and efficient community based dementia screening programs is of paramount important. Before doing so a series of studies would be required to embrace various aspects including epidemiological assessment related to awareness of early detection of dementia, the validity of feasible screening tool for community-based screening for dementia, and economic evaluation of community-based screening program with the development of a series of theoretically-sound statistical methods.

Aims

This thesis aimed to (1) quantify the impact of early detection related to awareness on the average duration of disease based on the measurement of the ratio of prevalence to incidence of dementia with a newly proposed P/I-ratio-based statistical regression model; (2) assess the validity of the accuracy of the early detection of dementia with cognitive test (MMSE) and informant questionnaire (AD8) alone and particularly in the combination applied to a community-based dementia screening with Bayesian clinical reasoning model; and (3) perform cost-effectiveness of community-based dementia screening program with various screening strategies proposed in the second aim with the Markov decision tree model.

Materials and Methods

By using a large-scale, claimed data of the National Health Insurance (NHI) database between 2000 and 2003 in Taiwan, we identified 99,609 patients age over 65 years with dementia (ICD-9-CM code 290, 290.40, and 331.0). The other data source included a total of 183 subjects aged over 65 years participating in an active dementia survey conducted in 2013. Information on age, gender, and geographic areas were also collected. Bayesian P/I-ratio-based statistical regression method was used to estimate the adjusted prevalence/incidence (P/I) ratios of dementia to reflect the awareness of dementia. For the validity of AD8 and MMSE as well as the combination of the two tools in the parallel and the serial mode, we applied the two screening tools simultaneously in a community-based screening program for dementia to 282 Tainan residents aged over 50 years in 2013. Receiver operating characteristic curves (ROC) were applied to explore the performance of different screen modalities for prediction of MCI or dementia. Bayesian clinical reasoning method was used to estimate the performance of screening modalities in the absence of golden-standard diagnosis.

The Markov decision analysis was conducted to investigate the cost-utility of

community-based screening of dementia over a 10-year period to compare different screening tools (AD8, MMSE, parallel and serial test of the two) with no screening. We used a five-state Markov model to simulate the progression of dementia. Disease transition probabilities and costs of different stages were extracted from literatures. The main outcome measure was cost per quality-adjusted life-year gained with a 3% annual discount rate. The scattered cost-effectiveness plane (CE plane) and acceptability curve are presented given a 500 Monte Carlo simulated samples.

Results

The prevalence and incidence rate of dementia based on passive survey were estimated as 2.91% and 1.83 %, respectively. The results with the application of Bayesian P/I-ratio-based statistical regression model show the adjusted P/I ratio increased from 1.20 (1.15-1.24) for 70-74 age group to 3.27 (3.13-3.41) for 90+ age group in males. The P/I ratio was the highest in northern area the lowest in eastern area. After controlling for age, gender, and geographic area, the adjusted P/I ratio increased from 1.45 (1.43-1.47) for 65-79 age group to1.64 (1.61-1.66) for 80+ age group through passive detection method (health insurance system). The corresponding figures increased from 4.23 (2.68-6.69) for 65-79 age group to 4.77 (3.02-7.54) for 80+ age group in active community-based survey. The sensitivity and specificity of the sole use of AD8 in dementia screening were 64.71% and 87.89%. The sensitivity and specificity of the sole use of MMSE in dementia with adjustment for education level were 41.18% and 84.50%. The combination of AD8 with MMSE in parallel mode yielded 88.89% of sensitivity and 70.16% of specificity. The combination of AD8 with MMSE in serial mode yielded 50.00% of sensitivity and 93.02% of specificity. The estimates of sensitivity and specificity of using AD8 test alone for MCI plus dementia were 25.74% and 90.70%. All the estimates of sensitivity for all the modes except the MMSE with 26 of cutoff for detecting MCI were poor and the specificity was moderate. By combining prior information derived from the results of previous studies with Bayesian approach, the results show the parallel mode had higher sensitivity (97.2%) than either MMSE (82.2%) or AD8 (84.1%) alone . Besides, the serial test had higher specificity (96.8 %) than AD8 (77.1%) or MMSE (86.1%) alone. ROC curve showed that the combination of MMSE and AD8 in the parallel mode (AUC=82.3% (75.1%-89.4%)) produced a more accurate prediction of dementia than the use of AD8 (AUC=73.3% (60.7%-85.9%)) and MMSE (AUC=77.4 %(67.6%-87.3%) alone and also the serial mode (AUC= 67.6% (53.4%-81.8%)). Regarding economic evaluation, if only direct cost on screening and medical expenditure were considered, the ICURs for AD8, MMSE, parallel test, and sequential test were $401.4, $457.7, $409.8, and $499.2 per QALY gained, respectively. The scatted CE plane suggested that around 80% simulated sit in fourth

quadrant (dominant) when indirect cost was considered. The probability of being cost-effective was 88-94% given willingness-to-pay (WTP) at $20,000 for the four screening scenario. The corresponding figures for being dominant and cost-effective at WTP at $20,000 when only direct cost taking into account were 40% and 93-99%, respectively.

Conclusions

From the practical aspect of prevention of disability and death from dementia, low awareness of dementia has been ascertained in routine health insurance health care system as the P/I ratio of community-based survey (active detection method) was greater than that of health insurance heath care system (passive detection method). The combination tests of MMSE and AD8 could improve diagnostic accuracy in the community dementia screening. Community-based screening for dementia with AD8 and MMSE is more cost-effective and almost near cost-saving compared with no screening program. The most economic screening strategy is the parallel mode of combining AD8 with MMSE in comparison with other modes.

From the methodological viewpoint, there are three novelties of the methodological development here, including a P/I-ratio-based regression model, the application of Bayesian model for multiple detection modalities, and the development Markov cycle decision tree model for economic evaluation of population-based screening program with AD8 in combination with MMSE. The empirical data together with the development of theoretically-sound statistical method provides a new insight into how to conduct an effective and efficient community-based screening for dementia.

Key word: Dementia, screening, sensitivity, specificity, cost-effectiveness

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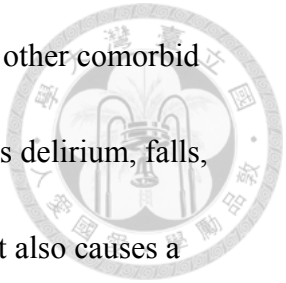
Chapter 1：Introduction

1.1 Background

1.1.1 Disease Burden and Social Significance

Several population-based studies indicate that 3% to 11% of persons over age 65 years and 25% to 47% of those over 85 suffer from dementia. In 1997, the number of people with Alzheimer's disease in the United States was estimated to be 2.32 million, more than 90% of whom were age 60 years and older. Alzheimer's disease is considered the 8th leading cause of death in persons over the age of 65 and is 11th overall in the United States. Median survival estimates of people with dementia ranges between 5.0 and 9.3 years after diagnosis. A recent study found the median survival time, adjusting for date of onset, was around 3.3 years [1]. The previous study has addressed the natural history of dementia from mild, through moderate, and to severe AD, taking a long natural course[2] . The short median survival time leaves much improvement of early detection through awareness and screening to be desired. Dementia causes a high burden of suffering for patients and their families. For patients, it leads to cognitive and functional deterioration, behavioral complications, increased use of



health and social services, complicated clinical management of other comorbid conditions, and increased risk for medical complications such as delirium, falls, motor vehicle crashes, incontinence, fractures, and infections. It also causes a heavy burden for society including family members and health caregivers.

In addition to disease burden imposed to society and sufferings resulting from dementia imposed to individual and caregiver, enormous resources, i.e. annual societal cost of dementia amounting to approximately $100 billion, are also required for both health care and related costs and lost wages for patients and family caregivers. Given an increasing trend in disease burden, sufferings of patient and caregivers, and economic concerns, it is therefore worthwhile to call for a study to embrace these various aspects from epidemiological assessment, screening and early detection, and economic evaluation of population-based screening program.

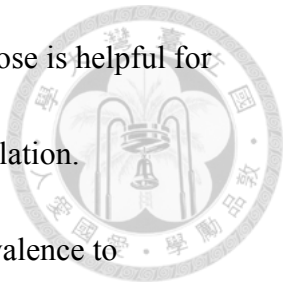
1.1.2 Implications and usefulness of epidemiological profiles of Alzheimer's disease and dementia

Dementia is a syndrome of decline in memory and at least one other cognitive domain such as language, visual-spatial, or executive function sufficient to interfere with social or occupational functioning in an alert person [3].

Multiple diseases can cause the syndrome of dementia. The majority of people with dementia have neurodegenerative disease or cerebrovascular ischemia as the underlying cause. Between 60% and 70% of people with the dementia syndrome have Alzheimer's disease; about 20% to 30% have vascular or mixed vascular and Alzheimer's disease causes. A small fraction of people have other causes such as Lowy body dementia, frontal dementia, Parkinson's disease, hypothyroidism, and vitamin B 12 deficiency [4, 5].

Based on numerous descriptive epidemiological studies, prevalence of dementia shows considerable variations among different countries for persons aged 65 and older, ranging from 1.8-10.5%[6,7, 8] . The variation of incidence across countries still exists but seems smaller than that of prevalence. Incidence is a fundamental measurement related to the etiology of the disease, whereas prevalence reflects disease burden affected by a constellation of factors including active detection, awareness, and quality of care for patients diagnosed as dementia. Accordingly, the ratio of prevalence to incidence, indicating the average duration of dementia, can be used for an indicator for patient's awareness of dementia if both estimates can be provided.

To gain a better understanding of awareness of dementia would be beneficial to patients and also provides an insight into early diagnosis and



treatment of dementia. Developing an indicator for such a purpose is helpful for the reflection of the extent of awareness in the underlying population.

To sum up, the combined both figures in terms of ratio of prevalence to incidence ratio (P/I) provide a good indicator for awareness of detecting dementia and health care quality for treating dementia patients. It is postulated that higher P/I ratio was attributed to the earlier diagnosis through active detection based on community-based active survey.

Few studies have used this indicator for achieving this goal because it requires a large population-based data to estimate prevalence and the continued follow-up over time to estimate incidence in the same study. Moreover, none of study was focused on the development of statistical regression model for quantifying the impact of early detection on the average duration of disease based on the measurement of P /me ratio. My current empirical finding with the application of the P/I-ratio-based regression model here found a low awareness of our routine health insurance system in the diagnosis of dementia in contrast to active community-based survey. This forms the first part of my thesis.

1.1.3 Screening of dementia

Routine history and physical examinations do not readily diagnose dementia

during clinic or physician visits. Numerous studies in western countries indicate low identification of dementia by primary care physicians[9-16]. More than 50% of patients with dementia have never been diagnosed by a physician[17-19]. This argument together with our low P/I ratio derived from routine health insurance system raises the notion of whether effective screening tests should be provided to identify people with dementia at an early stage, thus allowing the possibility of earlier intervention.

Most screening tests for dementia can be divided into cognitive tests of patients and functional assessments using both patients and other informants. Cognitive tests, the primary screening approach that researchers have investigated, include the Mini-Mental Status Examination (MMSE). MMSE was developed and considered as screening tools more than 30 years ago since 1975. Since that time it has been widely used in early detection of dementia. However, it requires intensive training to investigators and is too lengthy for use in general practice. The MMSE often renders signs of detection insensitive, particularly in high education individuals.

Among other available cognitive testing strategies, the Clock-Drawing Test (CDT)[20], which can take less than 1 minute to administer, has the best potential for meeting these criteria . The small number of methodologically sound studies regarding other clinically relevant cognitive tests limits our ability to evaluate them adequately.

Some informant-based functional tests, such as the Functional Activities Questionnaire (FAQ),[21] the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE),[22] and the Instrumental Activities of Daily Living (IADL) Questionnaire,[23] have been used for early diagnosis of dementia. These instruments offer everyday relevance, acceptability by subjects, adaptability to various types of patients, administrative ease, longitudinal perspective, and cross-cultural portability. The primary limitations of these tests are that not all patients have caregivers and that some functions (e.g., cognition) are not tested.[24] Most importantly, few methodologically sound studies regarding the accuracy of these questionnaires have been completed. In recent years, a brief informant interview with eight-item (AD8) to detect dementia was developed to make the measurement simple and also improve the performance of early detection. However, whether AD8 can be used for population-based screening for dementia is still unclear because the validity of the accuracy of early diagnosis of dementia has been barely addressed albeit its application to clinical patients has been proven[25, 26]. In addition, since AD8 and MMSE have played each unique role in detection and diagnosis of dementia how to combine AD8 with MMSE as a set of screening tool for dementia is of great interest to health decision-makers who are involved in population-based screening for dementia. The comparison of different combinations of screening modalities (parallel,

serial, AD8 alone, and MMSE alone) based on both AD8 and MMSE is therefore worthy of being investigated. This is the second part of my thesis.

1.1.4 Cost-effectiveness analysis of screening for dementia

As mentioned earlier, the economic and social burden caused by dementia is a grave health care problem in Taiwan. Screening and early detection of dementia is therefore proposed. Besides the evaluation of the validity of screening tools in the second part, it is also indispensable to conduct an economic appraisal of different screening strategies, as indicated in the second part, of community-based screening for dementia as screening often demands enormous costs at initial period but accrues the benefit of reducing enormous cost spent in caring for severe dementia as a result of delayed diagnosis in the absence of an effective community-based screening program[27]. The implementation of an nationwide opportunistic screening program for dementia can be cost-effective depending on disease severity, treatment effect, costs by disease stage, ages of the participants, and the societal willingness to pay (WTP)[28] . Above all things, improving access to more effective therapies The third part of my thesis is therefore focused on cost-effectiveness analysis of community-based screening for dementia by various modalities in combination of AD8 with

1.2 Aims

By collecting empirical data including a large population-registry health insurance claim data and a community-based dementia screening data, and relevant parameters from literature review, the objectives of thesis in pursuant to the rationales mentioned above are composed of the following three parts.

Part I

The first part was to elucidate the epidemiologic profiles of dementia including age, gender, area-specific prevalence and the corresponding incidence rate of dementia and prevalence/incidence ratio of dementia in Taiwan and also to develop a P/I-ratio-based statistical regression model to compare the effect size of P/I ratio from active (community-based) survey with that from passive health insurance system to indicate the extent of low awareness (underdiagnosis) of dementia after controlling for age, gender, and geographic variation.

Part II

Through a community-based screening for dementia, the second part is to assess the validity of accuracy of early detection of dementia with different instruments including cognitive test (MMSE), informant questionnaire (AD8) and

combined test (MMSE and AD8). We also applied a Bayesian estimation method to assess the validity of various combinations of screening modalities with the incorporation of prior information from literature in conjunction with the likelihood data derived from a community-based study.

Part III

Based on the parameters of the sensitivity and specificity obtained from the second part together with the relevant parameters including the transition probabilities, the efficacy of treatment, and costs on medical aspect and social aspect, a series of probability cost effectiveness analysis of community-based dementia screening programs with various comparisons were conducted from a societal perspective in Taiwan.

Chapter 2：Literature Review

2.1 Epidemiology of dementia

2.1.1 Prevalence and incidence of dementia

Dementia is one of the most distressing and burdensome mental health problems in the old population. Many studies have been conducted on the prevalence of dementia and its subtypes worldwide. The prevalence of dementia increase steadily with age , roughly double every 5 years [29] .The prevalence of dementia in persons aged 65 and older has been reported to be 3.6% to 10.3% in Western countries, 1.8%to 4.6% in china [6, 30], 3.7% to 6.7% in Japan [7], and 9.5% to 10.8% in Korea [8] since the mid-1980s. Several previous studies have shown that the prevalence of dementia in Taiwan is between 1.7% and 4.3% in adults aged 65 and older.[31] [32, 33] These variations among the reported prevalence may depend on methodological differences such as case finding procedures and the characteristics of the population sample. The diagnostic threshold used to justify a diagnosis of dementia may also contribute considerably to the variations. On the other hand, ethnic differences might exist and they may be due to racial genetic factors, shared cultural practices, or common environmental factors. Incidence is a fundamental measurement related to the etiology of the disease, whereas prevalence better reflects disease burden and it is useful for the planning of

the provision of health care services. The incidence of dementia may vary from country to country. Based on the incidence of dementia in different studies, the annual incidence of dementia in the elderly people aged 65 years or older ranged from 12.8 to 20.3 per 1000 person year. 12.8 ‰ of the annual incidence of dementia among those aged 65 and older in Taiwan was found based on 2915 community cohort with one year follow-up study. The incidence in Taiwan is slightly lower than 13.1 per 1000 person years of incidence in European and also lower than 14.6 per 1000 person years in USA.

2.1.2 Risk factor of dementia

D Dementia is more prevalent in women than in men. This difference is explained by the greater life expectancy and by a high survival rate of women with dementia compared with same age men with dementia. A meta-analysis of European studies by the EURODEM incidence research group showed that women had a greater risk of developing dementia[34] (odds ratio=1.2). More recently, results from a large prospective incidence study in the United Kingdom also showed an increased risk for women [35](odd ratio=1.6).

Early-onset dementia is more common in individuals with a family history of dementia. The apolipoprotein E (APOE) gene is a risk for Alzheimer's disease. APOE has three major alleles, ε2, ε3, and ε4, leading to six common APOE genotype.

The risk of dementia is higher in heterozygous ε4 allele, and is higher still in those who are homozygous for ε4. A ε2 allele has been linked with a reduced risk of dementia. The effect of APOE depends on a variety of other factors, including age and ethnicity. APOE allele distribution varies across the world. The ε4 is lowest in southern European, the Middle East, and North Africa[36]. Stroke , Parkinson disease, and poor self-perceived health were all found to be indicator for dementia[35]. Vascular risk factors are also commonly associated with an increase in the risk of Alzheimer's disease[37].

Prospective studies have found that moderate intake of alcohol (especially wine) is associated with having of dementia risk.

A systematic review found consistent evidence that diabetes both in midlife and later life is a risk factor for both Alzheimer's disease and dementia in general[38]. Effective control of diabetes may reduce this risk. The relationship between single traumatic head injury and dementia id unclear[39]. A meta-analysis of incidence studies in Europe by the European Community concerted action on the epidemiology and prevention of dementia (EURODEM) group found there was a lacking of increase in dementia risk with a reported history of head trauma[40].

2.2 Types of Dementia

Dementias can be classified in a variety of ways and are often grouped by what they have in common, such as what part of the brain is affected, or whether they worsen over time (progressive dementias).Some dementias, such as those caused by a reaction to medications or an infection, are reversible with treatment.

Types of dementias that worsen over time (progressive dementias) include:

2.2.1 Progressive dementias

2.2.1.1 Alzheimer’s disease

In people age 65 and older, Alzheimer's disease is the most common cause of dementia, around 60% in all types of dementia. People generally may develop symptoms after age 60, but some people may have early-onset forms of the disease, often as the result of a defective gene.

Although in most cases the exact cause of Alzheimer's disease isn't known, plaques and tangles are often found in the brains of people with Alzheimer's. Plaques are clumps of a protein called beta-amyloid, and tangles are fibrous tangles made up of tau protein. Certain genetic factors also may make it more likely that people will develop Alzheimer's.

Alzheimer's disease usually progresses slowly over seven to 10 years. Your cognitive abilities slowly decline. Eventually, the affected areas of your brain don't work

properly, including parts of your brain that control memory, language, judgment and spatial abilities.

2.2.1.2 Lowy body dementia

Lowy body dementia affects approximately 10 to 22 percent of people with dementia, making it one of the most common types of dementia. Lowy body dementia becomes more common with age. Lowy bodies are abnormal clumps of protein that have been found in the brains of people with Lowy body dementia, Alzheimer's disease and Parkinson's disease. Lowy body dementia symptoms are similar to symptoms of Alzheimer's disease. Its unique features include fluctuations between confusion and clear thinking (lucidity), visual hallucinations, and tremor and rigidity (Parkinsonism). People with Lowy body dementia often have a condition called rapid eye movement (REM) sleep behavior disorder that involves acting out dreams.

2.2.1.3 Vascular dementia

Vascular dementia, the second most common type of dementia, around 20% in all types of dementia, occurs as a result of brain damage due to reduced or blocked blood flow in blood vessels leading to your brain. Blood vessel problems may be caused by stroke, infection of a heart valve (endocarditis) or other blood vessel (vascular) conditions. Symptoms usually start suddenly and often occur in people with high blood pressure or people who have had strokes or heart attacks in the past.

Several different types of vascular dementia exist, and the types have different causes and symptoms. Alzheimer's disease and other dementias also may be present at the same time as this dementia.

2.2.1.4 Frontotemporal dementia

This less common cause of dementia tends to occur at a younger age than does Alzheimer's disease, generally between the ages of 40 and 65.

This is a group of diseases characterized by the breakdown (degeneration) of nerve cells in the frontal and temporal lobes of the brain, the areas generally associated with personality, behavior and language. Signs and symptoms of fronto-temporal dementia can include inappropriate behaviors, language problems, difficulty with thinking and concentration, and movement problems. As with other dementias, the cause isn't known, although in some cases this dementia is related to certain genetic mutations.

2.2.2 Reversed type of dementia

Some causes of dementia or dementia-like symptoms can be reversed. Your doctor may identify and treat these causes:

2.2.2.1 Infections and immune disorders

Dementia can result from fever or other side effects of your body's attempt to fight off an infection. People may develop dementia or thinking difficulties if they have brain infections like meningitis and encephalitis, untreated syphilis, Lyme

disease, or conditions that cause a completely compromised immune system, such as leukemia. Conditions such as multiple sclerosis that arise from the body's immune system attacking nerve cells also can cause dementia.

2.2.2.2 Metabolic problems and endocrine abnormalities

People with thyroid problems, too little sugar in the bloodstream (hypoglycemia), too low or too high amounts of sodium or calcium, or an impaired ability to absorb vitamin B-12 may develop dementia or other personality changes.

2.2.2.3 Nutritional deficiencies

Dementia symptoms can occur as a result of not drinking enough liquids (dehydration); not having enough thiamine (vitamin B-1), a condition common in people with chronic alcoholism; and not having enough vitamins B-6 and B-12 in your diet.

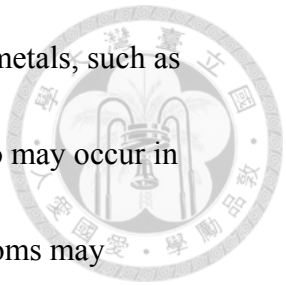
2.2.2.4 Reactions to medications

Dementia may occur as a reaction to a single medication or because of an interaction of several medications.

2.2.2.5 Subdural hematomas

Subdural hematomas are caused by bleeding between the surface of the brain and the covering over the brain. They can cause symptoms similar to dementia.

2.2.2.6 Poisoning



Dementia symptoms can occur as a result of exposure to heavy metals, such as lead, and other poisons, such as pesticides. Dementia symptoms also may occur in some people who have abused alcohol or recreational drugs. Symptoms may disappear after treatment, but in some cases symptoms may still be present after treatment.

2.2.2.7 Brain tumors

Dementia rarely can result from damage caused by a brain tumor.

2.2.2.8 Anoxia

This condition, also called hypoxia, occurs when organ tissues aren't getting enough oxygen. Anoxia may occur due to severe asthma, heart attack, carbon monoxide poisoning or other causes.

2.2.2.9 Heart and lung problems

Brain can't survive without oxygen. Dementia symptoms may occur in people with chronic lung problems or a heart condition that deprives the brain of the oxygen it needs.

2.2.2.10 Normal-pressure hydrocephalus

Sometimes people have normal-pressure hydrocephalus, a condition caused by enlarged ventricles in the brain. This condition can cause walking problems, urinary difficulty and memory loss. Shunt surgery, which delivers cerebrospinal fluid from

the head to the abdomen or heart, may help these symptoms.

2.3 Common cause of dementia

Alzheimer's disease accounts for most cases of dementia in North America (50–85%)[4, 5], with an additional 10–20% attributed to vascular ("multi-infarct") dementia. The relative importance of vascular dementias is higher in populations where hypertension and stroke are more common (Asians, African Americans, persons over 85) [41-43].Other important causes of dementia include alcoholism, Parkinson's disease, metabolic disorders (vitamin B12 deficiency, hypothyroidism), central nervous system infections (e.g., HIV, neurosyphilis), intracranial lesions, and other illnesses [4, 44].

2.4 Diagnosis of dementia and MCI

According to the National Institute on Aging and the Alzheimer's Association(NIAA), criteria for all-cause dementia and for AD dementia in 2011[45],dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that : 1. Interfere with the ability to function at work or at usual activities; and 2. Represent a decline from previous levels of functioning and performing; and 3. Are not explained by delirium or major psychiatric disorder; 4. Cognitive impairment is detected and diagnosed through a combination of (1)

history-taking from the patient and a knowledgeable informant and (2)an objective cognitive assessment, either a “bedside” mental status examination or neuropsychological testing. 5. The cognitive or behavioral impairment involves a minimum of two of the following domains: (a) impaired ability to acquire and remember new information. (b) Impaired reasoning and handling of complex tasks, poor judgment. (c) Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.(d) Impaired language functions (speaking, reading, writing).(e) Changes in personality, behavior, or comportment–symptoms.

MCI was often diagnosed, based on the criteria recommended by the NIA-AA[46],

as below : (1) Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (2) Objective evidence of Impairment in one or more cognitive domains, typically including memory (3)Preservation of independence in functional abilities (4) Not demented

2.5 Early detection of dementia

Most persons with dementia remain undiagnosed by their primary care physicians. Prospective longitudinal studies demonstrate serious deficiencies in the healthcare system's ability to recognize dementia. Most dementia remains unrecognized in the primary care setting. Persons with mild dementia are more likely to go unrecognized by physicians and family (over 90%) than persons with moderate to severe dementia (over 70%); however, those with early disease are best treated with available medications[47-49]. Family members often under-recognize cognitive decline in elders (over 50%). Many elderly live alone and have limited contact with distant relatives. Under-recognition of dementia is a serious, unsolved healthcare problem despite multiple expert panels that have discussed recommendations on dementia screening.

2.5.1 Instruments of neuropsychological measurements in dementia screening

2.5.1.1 Cognitive test: Mini-Mental Status Examination (MMSE)

The Mini-Mental Status Examination (MMSE) is the best-studied instrument for screening for cognitive impairment. The Agency for Health Care Policy and Research (AHCPR) supported a systematic review and meta-analysis of studies (published primarily before 1994) that evaluated the MMSE for screening.[50]

The AHCPR panel used mean effect size as the measure of effectiveness, as described by Hasselblad and Hedges.[51] The mean effect size for discrimination between patients with and without dementia was 1.78. This effect size corresponds to an equivalent sensitivity and specificity of 84% and a sensitivity of approximately 75%, for a fixed specificity of 90%.Studies from 1994 to 2001 have had 2 usual orientations when evaluating the MMSE: primary investigations into its validity when adjusting for either cultural or educational factors (or both) and secondary investigations that compare the performance of newer screening tools to that of the MMSE. Table 2 compares the finding of 5 MMSE studies.[52] Excluding the Wilder et al. study (evaluating specificity levels for 90% sensitivity), the MMSE sensitivity (71% to 92%) and specificity (77 % to 96%) fell into a moderate range and the percentage of falsely classified individuals (false negatives and false positives as a percentage of the total number of tested individuals) ranged from 4% to 18%.The primary factors determining the rate of false diagnoses are likely to be related to cut-off values and the overall percentage of individuals with dementia in each study. Folstein et al., in 1975, documented that the MMSE is a reliable instrument.[53] Two decades later, McDowell et al. provided additional reliability data that confirmed the earlier findings.[52]

The accuracy of the MMSE depends upon a person's age and educational level: using an arbitrary cut-point may potentially lead to more false-positives among older

people with lower educational levels, and more false-negatives among younger people with higher educational levels.

2.5.1.2 The informant-based tests：AD8 Questionnaires

The AD8 is a brief informant-based questionnaire developed by Washington University in St Louis. It is a screening tool with 8 questions to reliably differentiate no demented from demented individuals even at the very mild stage.[26, 54] The AD8 is sensitive to the earliest signs of cognitive change as reported by an informant. The AD8 is highly correlated with gold standard, the CDR, as well as performance on brief objective measures such as the MMSE.

The AD8 test the subjective cognitive abilities in memory, temporal orientation, judgment, and function. The score on AD8 was range from 0 to 8. It is sensitive to the earliest signs of cognitive change as reported by an informant[26]. The cut points of AD8 for distinguishing dementia cases was greater than 2. The sensitivity of AD8 for dementia ranges from 68% to 95.9%, and the specificity ranges from 78.1% to 90%[25, 26, 55]

2.5.2 Accuracy and reliability of early detection instruments in dementia

The goals of any screening test are to separate people with a high probability of having the disease from those with a low probability and to presumptively identify

unrecognized disease. Diagnostic confirmation is generally required. An effective screening test should be inexpensive, and its characteristics should include reliability, sensitivity, specificity, social acceptability, safety, and brevity.

Researchers and practitioners in this clinical area have traditionally divided screening tests into cognitive tests and functional assessment. Most screening tests have been evaluated in studies with small sample sizes, and the populations of patients on whom screening instruments have been tested have varied greatly, making it difficult to determine the overall performance of screening tests for dementia. The best evidence is available for a cognitive test—the Mini-Mental Status Examination (MMSE)—from studies in primary care settings that used standardized diagnostic instruments (e.g., the DSM-IV) as a "gold standard." Depending upon the cut point used for an abnormal test, the sensitivity of MMSE for dementia ranges from 71% to 92%, and the specificity ranges from 56% to 96%[52, 56]. The predictive value of a positive test, in a population with 10% prevalence of dementia, may range from 15% to 72%.[57] A drawback of MMSE is that its accuracy depends upon age, education, and ethnicity of the individual; it is most accurate for whites with at least a high school education. Other cognitive screening tests, such as the Short Portable Mental Status Questionnaire, Clock Drawing Test, Modified MMSE, Mini-Cog, Hopkins Verbal Learning Test, and the 7-minute screen are promising, but have not

been adequately evaluated in primary care settings.

Some informant-based functional tests, such as the Functional Activities Questionnaire (FAQ), the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), and the Instrumental Activities of Daily Living (IADL) Questionnaire, have also been tested. [58] The sensitivity and specificity of FAQ is reported to be 90%. The functional test instruments offer the advantages of "everyday relevance," acceptability by subjects, adaptability to various types of patients, administrative ease, longitudinal perspective, and cross-cultural portability. The primary limitations of these tests are that not all patients have caregivers and that some functions (e.g., cognition) are not tested. Most important, few methodologically sound studies regarding the accuracy of these questionnaires in primary care settings have been completed. Testing for genetic mutations may eventually prove useful in screening individuals at risk for Alzheimer's disease. There are, however, limited population-based data regarding the absolute risk of dementia among individuals having a positive genetic test. Thus the potential benefits and harms of testing for an individual patient are uncertain. Finally, the ethical issues in genetic testing for dementia are unresolved.

2.5.3 The benefit of early detection in dementia

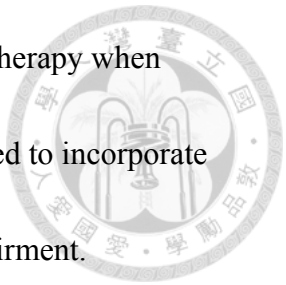
Persons who screen positive are referred to their local physician for follow-up along with the results of the testing. Previous studies demonstrate that over 60% of individuals with positive screens seek follow-up care. [59, 60] Studies show that 10-20% of individuals will score positive during a routine screening. The percentage of expected positive screening depends upon the age of the screening population, the location, and multiple other variables.

Early identification of at-risk patients provides multiple benefits to the individual, the family, and society. For the affected individual, identification of early stage dementia allows early aggressive use of available treatments. Early stage patients can be offered support groups to diminish the psychological impact of the disorder. Moreover, the total medical care for this individual can be adjusted to meet the needs of a cognitively impaired patient. Issues such as patient education, self-medication, compliance, and hospital care can be adjusted to meet the needs of a mildly demented person who is at risk for common complications such as delirium and depression. The early identification of dementia supports individual patient rights and self-determination. Most mildly impaired patients are capable of charting the future course of their care and making substantial decisions on issues like end-of-life care, resuscitation, disposition of wealth, etc. Informing at-risk patients about abnormal

screening does not produce hardship or harm to the patient or family caregiver.[61]

About one-third of elders live by themselves and these individuals are at risk for accidents, injuries, exploitation, and other adverse outcomes. Early identification allows safeguards and home assistance to assure continued maximization of home placement. Family caregivers derive multiple benefits from early identification. Early identification may reduce the burden of later life decision-making on issues like resuscitation, disposition of wealth, etc. as families can solicit the opinion of the patient while still competent.

Screening and early identification may benefit society by protecting individuals and reducing costs of healthcare. Unrecognized dementia can increase the likelihood of avoidable complications such as delirium, adverse drug reactions, noncompliance, etc. These complications can reduce the autonomy of the patient. Enhancing compliance and protecting demented patients has obvious financial benefits to the healthcare system. Adverse outcomes from screening programs are rarely reported by available literature or experienced by community providers. Published studies on screening for community-based elders demonstrate effectiveness and acceptance [62]. Screening programs detect possible impairment in 10-20% of screened individuals [60.] Patient and family satisfaction has been reported as high based on published studies and experience by AFA membership.



The benefits to citizens are clear. Patients can receive available therapy when identified and diagnosed. The healthcare management can be adjusted to incorporate treatment strategies that accommodate a person with cognitive impairment. Home-based support systems can be adjusted to maximize home placement for this person. Safeguards can be taken to prevent avoidable complications such as delirium during hospitalization. In persons with dementia, advanced directives can be discussed that incorporate the wishes of the individuals and reduces the burden of surrogate decision making for the family. Available treatments for Alzheimer's disease and other forms of dementia are most helpful in the early stages of illness. Early identification allows optimal therapy with available and emerging medications.

For persons with a normal screen, this intervention provides a valuable opportunity to promote cognitive wellness and successful aging. A simple, direct, cognitive wellness message can be presented to these individuals that may reduce their likelihood for developing dementia at a later age. The emotional boost from a normal dementia screen can be used as an opportunity to discuss basic, preventive interventions such as compliance with anti-hypertensive, responsible drinking, intellectual stimulation and other recommendations that may further protect a patient's cognitive function [63].

Presently, there is no national policy on dementia screening. Despite the acceptable accuracy of screens as well as the availability of medications for early stage disease,

there is no public health policy on assessing for dementia. The present Medicare screening and prevention program does not include cognitive function. Local organizations are left to create their own programs without assistance or guidance. A national system of dementia screening will require several years for development and implementation. A flexible array of services and instruments will be required. A policy executed today would only be fully available in the field several years from now. Scientists and researchers are trained to accept treatment strategies that incorporate evidence-based practices. Although, this conceptual model is the gold standard, this strategy has significant limitations that are rarely emphasized by the scientific community. Mass scale public health interventions are tested over a multi-decade period. Researchers are generally preoccupied with conclusive scientific data and the promotion of research. In contrast, public systems must use a pragmatic approach, i.e., “best possible solution”. To date, national policy has been dominated by expert opinions provided by clinical and basic science researchers. The failure of the “magic bullet” approach warrants an alternative strategy that incorporates interventions to limit the impact of this public health problem. No professional organization contends that undiagnosed, unprepared, uninformed patients with dementia are preferable to individuals with accurate diagnoses and appropriate, early interventions.

2.6 Cost-effectiveness analysis of dementia

The essential part for the cost-effectiveness analysis is to understand the disease course. As dementia involves different disease states and death, the multi-state Markov model can be used to depict the disease course. In this section, we also reviewed literatures for the disease burden of dementia and the evidence regarding the efficacy of a memory screening test. Finally, the empirical findings of cost-effectiveness analysis of dementia screening from two studies were described.

2.6.1 Multi-state Markov models

Multi-state Markov models are often used to depict the evolution of disease progress over time.

Let $\{X_t, t >= 0\}$ (data realization) be a discrete random variable with state space $\Omega = \{1, 2\ldots.. m.\}$ representing a stochastic process of disease. In clinical practice, data realization involves a series of successive observations where disease would progress to severe stages and/or an 'absorbing' state, often death, and may regress to mild stages. The possible states of disease and/or death constitute the state space,Ω.

For example, one could develop a five-state Markov model to define the dementia-related status in a community with X_t of state space $\Omega = \{0, 1, 2, 3, 4\}$, where

- 0=normal,
- 1=mild dementia,
- 2=moderate dementia,
- 3=severe dementia, and
- 4=death.

Suppose one subject has the disease history of

Normal, Normal, Mild, Mild, Mild, Severe, Death

at seven distinct time (t=0, 1, 6). The joint probability of disease history for this subject can be expressed as

$$Pr\{X_0 = 0, X_1 = 0, X_2 = 1, X_3 = 1, X_4 = 1, X_5 = 3, X_6 = 4\} \quad (1)$$

Due to sequential order by time of the observation, equation (1) can be written as

$$\begin{aligned} &Pr\{X_6 = 4 | X_5 = 3, X_4 = 1, X_3 = 1, X_2 = 1, X_1 = 0, X_0 = 0\} \\ &\quad \times Pr\{X_5 = 3 | X_4 = 1, X_3 = 1, X_2 = 1, X_1 = 0, X_0 = 0\} \\ &\quad \times Pr\{X_4 = 1 | X_3 = 1, X_2 = 1, X_1 = 0, X_0 = 0\} \\ &\quad \times Pr\{X_3 = 1 | X_2 = 1, X_1 = 0, X_0 = 0\} \times Pr\{X_2 = 1 | X_1 = 0, X_0 = 0\} \\ &\quad \times Pr\{X_1 = 0 | X_0 = 0\} \times Pr\{X_0 = 0\} \end{aligned} \quad (2)$$

The Markov assumption suggests that given the knowledge of a present state, say X_t, the outcome in the future (X_{t+1}, X_{t+2}, …) is no longer dependent on the past (X_0, X_1, …, X_{t-1}) [64]. Equation (2) can then be simplified as

$$Pr\{X_6 = 4|\, X_5 = 3\} \times Pr\{X_5 = 3|\, X_4 = 1\} \times Pr\{X_4 = 1|\, X_3 = 1\}$$
$$\times Pr\{X_3 = 1|\, X_2 = 1\} \times Pr\{X_2 = 1|\, X_1 = 0\} \times Pr\{X_1 = 0|\, X_0 = 0\}$$
$$\times Pr\{X_0 = 0\} \qquad (3)$$

For each X_t we denote the absolute probability by

$$Pr\{X_t = x_t\} = \pi_{x_t}$$

And for each pair of random variables, X_α and X_β, $\alpha < \beta$, the conditional probability is

$$Pr\{X_\beta = x_\beta | X_\alpha = x_\alpha\} = P_{x_\alpha, x_\beta}$$

with the conditions that $\sum_{x_t \in \Omega} \pi_{x_t} = 1$, and $\sum_{x_\beta \in \Omega} P_{x_\alpha, x_\beta} = 1$.

Thus, equation (3) can be written as

$$\pi_0 P_{00} P_{01} P_{11} P_{11} P_{13} P_{34} \qquad (4)$$

Namely, a Markov model can be completely determined by the initial absolute probability distribution (π_{x_0}) and the transition probabilities (P_{x_α,x_β}).

A Markov model is called **homogeneous** with respect to time if the transition probabilities (P_{x_α,x_β}) are independent of time α,β and is **non-homogeneous** with respect to time if the transition probabilities (P_{x_α,x_β}) are function of time α,β. For the ease to the presentation, the transition probabilities can be arranged in the form of a square matrix. For example, the probabilities of all possible transitions for the abovementioned 5-state dementia example can be described in

$$\mathbf{P} = \begin{array}{c} \\ 0\ (\text{Normal}) \\ 1\ (\text{Mild}) \\ 2\ (\text{Moderate}) \\ 3\ (\text{Severe}) \\ 4\ (\text{Death}) \end{array} \begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} P_{00} & P_{01} & P_{02} & P_{03} & P_{04} \\ P_{10} & P_{11} & P_{12} & P_{13} & P_{14} \\ P_{20} & P_{21} & P_{22} & P_{23} & P_{24} \\ P_{30} & P_{31} & P_{32} & P_{33} & P_{34} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} \end{array} \qquad (5)$$

The final row in **P** of (0 0 0 0 1) is for the absorbing state, death. Transition probabilities can be modified according to the clinical plausibility. For example, if dementia is impossible to reverse to normal (dementia-free), then P_{k0}=0 for k=1, 2, 3, and 4. If severe state of dementia is believed not to recover, then P_{3l}=0 for k=0, 1, and 2.

The Markov model can also be classified as **discrete-time** and **continuous-time** Markov model if one concerned the one-step transition probabilities given data realizations are in regular time intervals or instantaneous transition rate

where data realizations could be given in regular or irregular intervals, respectively. For the former, parameters of interests are π_{x_0} andP_{x_α,x_β}, whereas the latter is described by π_{x_0} and instantaneous transition rates between states, $X_t(=i)$ and $X_{t+\Delta}(=j)$

$$\nu_{ij} = \lim_{\Delta\to 0} \frac{P_{x_t,x_{t+\Delta}}(t,t+\Delta)}{\Delta} \quad (6)$$

Where$\nu_{ii} = -\sum_{j\neq i} \nu_{ij}$.

For the continuous time Markov model, the transition probability matrix, **P**, is a function of instantaneous transition rates, which can also be expressed in matrix form. Take again the abovementioned 5-state dementia as an example, in which we do not allow regression from any state of dementia to normal, and regression from severe dementia to any earlier states, and treat death as an absorbing state. Its transition intensity matrix **Q** can be expressed as

$$\mathbf{Q} = \begin{array}{c} \\ \text{0 (Normal)} \\ \text{1 (Mild)} \\ \text{2 (Moderate)} \\ \text{3 (Severe)} \\ \text{4 (Death)} \end{array} \begin{array}{c} \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array} \\ \begin{pmatrix} \nu_{00}=-(\nu_{01}+\nu_{04}) & \nu_{01} & 0 & 0 & \nu_{04} \\ 0 & \nu_{11}=-(\nu_{12}+\nu_{14}) & \nu_{12} & 0 & \nu_{14} \\ 0 & \nu_{21} & \nu_{22}=-(\nu_{21}+\nu_{23}+\nu_{24}) & \nu_{23} & \nu_{24} \\ 0 & 0 & 0 & \nu_{33}=-\nu_{34} & \nu_{34} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \end{array} \quad (7)$$

The derivation of the forward Kolmogorov differential equation gives the solution of transition probability matrix in a time interval, *t*, **P**(*t*) as a function of **Q** subject to **P**(0)=**I**, where **I** denotes a unit matrix [64] [65]as

$$\frac{\partial}{\partial t} P_{ik(\tau,t)} = \sum_j P_{ij(\tau,t)} \nu_{jk}(t), \quad j,k \in \Omega$$

This model, with varying numbers of transient states, has been used in applications to Parkinson's disease [66], type 2 diabetes[67, 68], diabetic retinopathy[69], comorbidity of chronic diseases[70], breast cancer[65, 71, 72], colorectal neoplasia[73], prostate cancer[74], oral pre-malignancy [75], and hepatocellular carcinoma [76]

More general models of this type can be constructed to allow for additional states, representing, for example, periods of treatment, hospital stays or competing causes of death. The Markov assumption, essentially, that the future of the process depends on the current state, and not on the history of the process, would also be more easy to assess if the exact times of transition between the states are known. However, the assumption of homogeneity of transition rates through time and across individuals can be assessed, for discrete time and continuous time Markov models, by modelling transition rates on observed covariates.

Different model assumptions can be made about the dependence of the transition rates on time. These include time homogeneous Markov models (the intensities are constant over time, that is, independent of *t*.[64, 77] and the transition intensities only depend on the history of the process through the current state.[78]) and semi-Markov models (future evolution not only depends on the current state *h*, but also on the entry

time t_h into state. Therefore, we may consider intensity functions of the general form $\alpha_{hj}(t, t - t_h)$ or, as the special homogeneous case $\alpha_{hj}(t - t_h)$.[79])

2.6.2 Decision analysis of dementia

Cadman et al. described five essential characteristics needed for an effective community based disease screening program in 1984[80], including (1) to detect a condition with sufficient societal burden, (2) for which treatment options are available, (3) a reliable screening test is available, (4) for which those who could benefit can be reached, and (5) necessary follow-up interventions and monitoring of compliance can be provided. While these characteristics were originally developed as a guide for infectious disease screening programs, they were easily adapted to non-contagious disease, such as chronic diseases and cancers.

2.6.2.1 Disease burden of dementia: medical cost and drug cost

In 2015, the total worldwide societal cost of dementia, on the basis of a dementia population of 29.3 million persons, was estimated to be US$315.4 billion, including US$105 billion for informal care (33%). Seventy-seven percent of the total costs occurred in the more developed regions, with 46% of the prevalence. [81] In 2010, the estimated total worldwide costs of dementia increased to US$604 billion[82]. About 70% of the costs occurred in Western Europe and North America. In such

high-income regions, costs of informal care and the direct costs of social care contribute similar proportions of total costs, whereas the direct medical costs were much lower. Among them, informal care and direct social care costs each accounted for about 40% of all costs, while direct medical costs accounted for only 16%. In low- and middle-income countries, informal care accounts for the majority of total costs; direct social care costs are negligible.

Epidemiological studies in Taiwan have shown that the prevalence of dementia is approximately between 2% to 8% among people aged 65 and above. Given the projected elderly population as 7.8 million in 2060 arising from 2.5 million in 2010, the number of people with dementia living in the community was estimated to grow from 124,000 in 2010 to 723,000 in 2060. The economic costs for one dementia patient per year varied from 206,311 to 710,737 NT dollars[83]. The financial impacts on the families and society are substantial. The estimated cost of dementia for the total population of Taiwan in 1999 varies from 5.1 billion to 17.6 billion NT dollars depending on the composition of aging population and caring human resources[83]

In Taiwan, as in many other countries, families are the main caregivers to older dementia patients who are no longer able to care for themselves[84]. Such individuals usually require constant supportive care at home or in a nursing home (informal care) to improve their basic and instrumental activities of daily living and medical treatment

(formal care) [85] . The costs of formal and informal care in patients with AD are high and are related to disease severity and the presence of behavioral disturbances.

The annual direct cost of institutional care in Taiwan was significantly higher than community care (464,193 NTD vs. 144,047 NTD, $p<0.001$), but indirect cost was significantly higher in home care than in institute (287,904 NTD vs. 35,665 NTD, $p<0.001$) [86].

A pilot study in Taiwan concluded that families with higher accessibility to nursing homes were willing to pay US $174 per month more than caregivers with lower accessibility [87]. Family caregivers aged> 65 years, educated in a high school level or higher, with higher family income and having easy accessibility to nursing home services were likely to attach higher economic value to nursing home placement.

The direct medical costs for outpatients in Taiwan were estimated at US $1.2 million in 2000, US$1.9 million in 2001, and US $2.3 million in 2002; the costs for inpatient care were estimated at US $670,000 in 2000, US $2.4 million in 2001, and US $3.2 million in 2002. The total direct medical costs in Taiwan were estimated at US $1.86 million in 2000, US$4.24 million in 2001, and US $5.48 million in 2002 [88] .

The total cost of dementia to society in the UK is £26.3 billion (with an average cost of £32,250 per person) which can be broken down to £4.3 billion for healthcare,

£10.3 billion for social care (publicly and privately funded), and £11.6 billion for the work of unpaid cares of people with dementia. Unpaid care accounted for three-quarters (74.9%) of the total cost for all people with dementia living in the community.

Although the expenditure on both formal and informal cost was enormous, it has been shown the patients in an earlier stage actually spent less than those in late stage[89]. The annual cost of medical cost increased from mild of US$ 1266 (633-2533), moderate of US$1298 (649-2596), to severe state of US$1586 (793-3173); so as to that of caregiver costs from mild of US$8996 (4498-17992), moderate of US$ 17593 (8797-35187) to severe state of US$24367 (12184-8735). From the cost perspectives, early detection of dementia can benefit patients from less cost given an effective screening tool is available.

2.6.2.2 The effect of a memory screening on the early diagnosis of dementia

Patients with dementia referred by the memory screening program had significantly higher MMSE score (20.8±5.7) than those referred by physicians (18.8±6.6), family/friends (16.8±6.6), or other referral sources (15.3±7.1) [90]. Subjects with AD, referred by the memory screening program, also had a lower reported duration of illness at presentation, and a decreased frequency of psychosis compared with those referred by family/friend and other methods. The memory screening

program referred patients with AD to a memory clinic at an earlier phase of illness compared with traditional methods such as physician referral.

2.6.3 Empirical results of cost-effectiveness analysis of dementia

Community-based dementia screening may be one method that can be used to achieve earlier detection and earlier initiation of therapy, with consequent reduced time spent in more costly higher dementia severity levels[27]. An investigation of cost effectiveness community-based screening study showed that community based dementia screening resulted in a total cost savings benefit over 10 years of US$208.54 or 9.83% savings per patient screened compared to no dementia[27] . Community based dementia screening resulted in an increased time spent in MCI and mild dementia states (155% and 247%, resp.) and reduced total percentage time spent in moderate and severe dementia states (32.4% and 35.2% reductions). Time spent in the normal cognition and death states were not substantially affected by dementia screening.

Although more demand for screening for dementia is envisaged, the cost-effectiveness of opportunistic population screening for dementia at a nationwide level has rare been investigated. In 2010, Korea has implemented “the National Dementia Early Detection Program” (NDEDP) for the aged. This study aims to investigate the cost-effectiveness of the NDEDP of Korea and to explore the

requirements for enhancing its cost-effectiveness[28]. The study showed that the cost per QALY gained ranged from $24,150 to $35,661 depending on the age group. The probability of screening being cost-effective was highest in the group over 75 years old in a wide range of willingness to pay (WTP). The implementation of an opportunistic screening program for dementia can be cost-effective depending on disease severity, treatment effect, costs by disease stage, ages of the participants, and the societal willingness to pay.

Chapter 3： Materials and Methods

3.1 Study samples and design

3.1.1 Part I: Epidemiology of dementia in Taiwan

There are two data sources for estimating prevalence of dementia by different detection methods based on various data sources that are described as follows.

Population-health-insurance-registry cohort of dementia

The first data for estimating prevalence are based on data that are derived from the National Health Insurance (NHI) system in Taiwan initiated since 1995. It has covered more than 99 % of the total population[91]. For the use of research, the NHI database has been utilized as dataset to establish various sets of database for public policy use. However, the NHI dataset can be designed as a longitudinal follow- up cohort including 23 million insured people in Taiwan. The dataset includes information of all medical service, such as ambulatory care claims, inpatient claims and prescription drugs and registry beneficiaries[91].

We collected data on age, gender, location of clinic visit, date of clinic visit and date of diagnosis in population-based cohort study (passive survey). The people with dementia diagnosed before 2000 were excluded. We followed the normal cohort from 2000 to 2003. Most patients with dementia would visit their neurologist at least annually. There were 55882 prevalent cases diagnosed with dementia (ICD-9-CM

code 290,290.40, 331.0) in 2000. Total 99609 incident cases were diagnosed with dementia (ICD-9-CM code 290,290.40, 331.0) between 2000 and 2003.

Community-based screening survey on dementia

To estimate the prevalence of dementia though active screening detection method, three-phase design was conducted. Subjects in this study were derived from a community-based integrated screening program in 2013 in Tainan, the southern area of Taiwan. There were 183 participants who were older than 65 years old were enrolled in our investigation. The procedures of the three-phase study design were composed of three steps：(1) Step1: The AD8[25] screening questionnaire is a brief informant-based measure used by participants (2) Step2: The Chinese versions of the MMSE used by psychologist (3) Step3: The participants were diagnosed with or without dementia by neurologists using the NIA-AA (National Institute on Aging Alzheimer's Association) guideline in 2011. The cut-off point of AD8 was 2 in our study. The MMSE scores were adjusted by education and age. The diagnosis of all-cause of dementia was based on the clinical criteria recommend by the National Institute on Aging Alzheimer's Association (NIA-AA).There were a total of 18 cases diagnosed with dementia (See the Part-II).

Study design for ascertaining incident dementia

In addition to estimating the prevalence of dementia by different detection

methods, we also estimated incidence by identifying a normal cohort after excluding those with preexisting dementia in the year of 2000 based on a population–based health – insurance –registry data. The cohort study design began at year of 2000. We followed the normal cohort free of dementia from 2000 to 2003 to identify newly diagnosed (incident) cases. We used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and prescription codes to identify dementia patients from the NHI database. Total of 99,609 incident cases were diagnosed with dementia (ICD-9-CM code 290,290.40, 331.0). The total follow-up person years were 5,445,586 person years.

We also compared our data with those derived from western countries and other Asia countries. We used age-standardized incidence rate to compare age specific incidence rate of dementia in Taiwan, USA, and European.

3.1.2 Part II：Combination MMSE and Ad8 tests in community-based Screening for dementia

Subjects

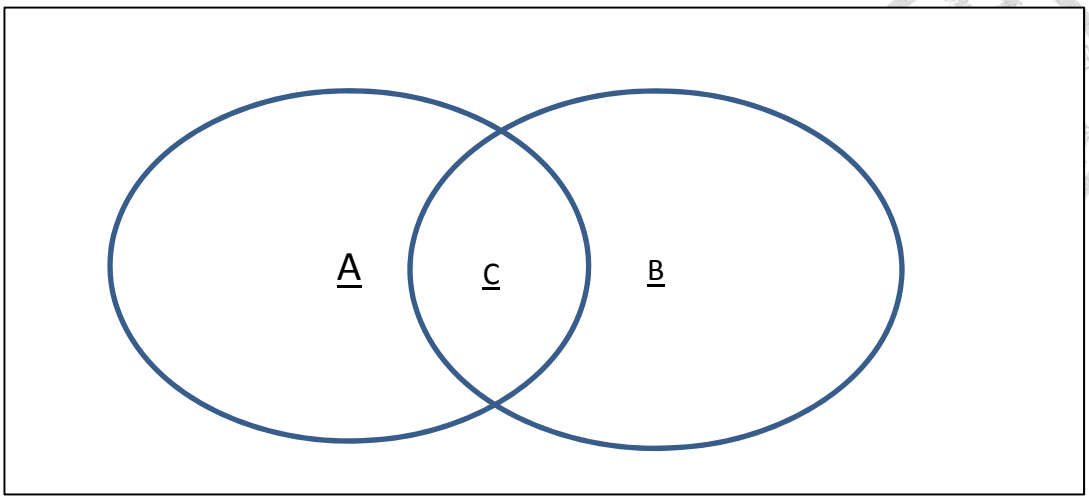
The study was a community-based study. Subjects in this study were derived from a community-based integrated screening program in Tainan, Taiwan. The area is a rural region in Taiwan. The inclusion criteria for the participants were age 50-99 years

old. The exclusion criteria was people with dementia diagnosed before screening.

Study Design

The study design is formed for validation of the accuracy of the early diagnosis of dementia in the community-based screening program, whereby various screening modalities including single test with ADB or MMSE and also dual modality in parallel and sequential mode were tested.

A community-based screening for dementia using AD8 in combination with MMSE as the two detection modalities has been conducted simultaneously to target at 282 residents aged over 50 years in Tainan. This design offers an opportunity to evaluate the yield and the performance of screening given AD8 only, MMSE only parallel AD8+MMSE, and sequential AD8+MMSE. The details of study design for comparing different screen modalities are given in following figure. There are four sets in the venn diagram. A set represents the AD8 (+) (AD8 mode). B set represents the MMSE (+) (MMSE mode). C set represents both of positive for AD8 and MMSE (sequential mode). D set represents both of negative for AD8 and MMSE. The parallel mode composed three sets (A, B, and C). The parallel mode could be further extended to parallel (2) mode which composed two sets (A and C) and parallel (3) mode (B - C).



Parallel (1) mode: A+B+C

Parallel (2) mode: A+C

Parallel (3) mode: B+C

Sequential mode: C

Instruments

The Chinese versions of the MMSE and AD8 questionnaire were used. The details of assessing the performance of MMSE and AD8 described as follows. The MMSE is a brief test of mental status. It has been demonstrated to have satisfactory psychometric properties. The score on MMSE was range from 0 to 30 with lower values indicative of greater cognitive impairment. The AD8 is a brief, sensitive screening tool that reliably differentiate between dementia and non-dementia at the very mild stage. The score on AD8 was range from 0 to 8.

Procedures

The procedures of the three-phase study design is composed of three steps: (1) Step1: The AD8 screening questionnaire is a brief informant-based measure used by participants (2) Step2: The Chinese versions of the MMSE used by psychologist (3) Step3: The participants was diagnosed by neurologists using the NIA-AA (National Institute on Aging Alzheimer's Association) guideline in 2011：Criteria for all-cause dementia[92].

Measurements for Cognitive Status

The Mental State Examination result were adjusted by education, defined as a score 24 in literate elders and 15 in illiterate elders[93, 94] . The cut points of AD8 for distinguishing dementia cases was greater than 2.

Diagnosis of dementia and MCI

The diagnosis for all-cause dementia was according to the core clinical criteria recommended by the National Institute on Aging-Alzheimer's Association (NIA-AA)[45]. A brief medical history was taken from the participant by Neurologist. The criteria is as below：Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that: (1) Interfere with the ability to function at work or at usual activities; and (2) Represent a decline from previous levels of functioning and performing; and(3) Are not explained by delirium or major psychiatric disorder; (4) Cognitive impairment is detected and diagnosed through a combination of (a)

history-taking from the patient and a knowledgeable informant and (b) an objective cognitive assessment. (5) The cognitive or behavioral impairment involves a minimum of two of the following domains: (a) memory (b) Executive function (c) Visuospatial function (d) language (e) behavior

MCI was diagnosed, based on the criteria recommended by the NIA-AA[46], as below : (1) Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (2) Objective evidence of Impairment in one or more cognitive domains, typically including memory (3)Preservation of independence in functional abilities (4) Not demented

3.1.3 Part III: Cost-Effectiveness of community-based dementia screening

An analytical Markov decision model was framed with five screening strategies: population-based dementia screening with AD8 test, MMSE test, parallel test, sequential test, and no screening (the natural history model). The target population for Markov model simulated a hypothetical cohort of 10,000 elder people aged 65 in Taiwan.

We used a Markov model to construct the nature course of dementia, comprising the states of normal, mild, moderate, severe and death. We simulated the Markov Model for screening group with 5 years interval. A further 10-year simulation was al performed to evaluate the long-term outcome. Quality-adjusted life years (QALY) as healthy outcome measure were computed. Economic evaluation with probabilistic sensitivity analyses by using a Monte Carlo simulation was performed to calculate the incremental cost-utility ratio (ICER) and to yield cost-utility acceptability curve.

3.2 Methodology

3.2.1 Part I: Epidemiology of dementia in Taiwan

3.2.1.1 Prevalence and Incidence calculation

We began with a cohort that was dementia-free at entry to the study (2000) and followed them up between 2001 and the end of 2003 in order to identify newly diagnosed cases and compute person-years for the underlying population at risk. We first estimated age-gender –specific prevalence based on the cross sectional data in the year of 2000. We also estimated the prevalence of dementia based on a community based survey to represent the prevalence dementia through early screening detection. We estimated the incidence rate of dementia based on the cohort who was dementia-free at entry to the study (2000) and followed them up until the end of 2003. To identify newly diagnosed cases, we compute person-years with the underlying population at risk. The age specific incidence of dementia during the period 2000-2003 was calculated as the number of new cases of dementia divided by the number of person-years at risk given as 5-year age interval starting at age 65 years. The numbers of person-years contributed by each subject who had no dementia is calculated by the time from taking the time between the date of entry and the date of ending .For subjects with dementia the numbers of person-years was calculated by the time from the date of study began and to the date of first diagnosed as dementia. The

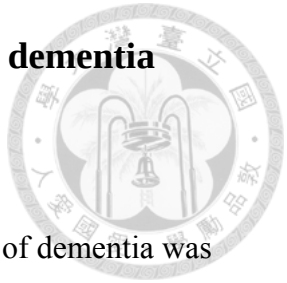
effect of age, gender and geographic areas factors on the incidence of dementia was assessed using a multivariable Poisson regression model. The date of the last follow-up date is used as the endpoint for subjects died or loss to follow-up since dementia status is unknown at the time of death or dropout.

3.2.1.2 Age-standardized incidence rate of dementia

To compare the incidence of dementia, the summary rates should be independent of age. A common way to consider the age structure of a population is to standardize incidence rates for age using an external (standard) population[95]. The age-standardized rate is a summary of the individual age-specific rates using an external population called a standard population. The age-standardized incidence rate is expressed, as is the crude incidence rate, as the number of new cases per 100 000 person-years.

$$\text{Age standardized rate} = \sum_i \frac{d_i w_i}{y_i}$$

Such that i represents each age group, d_i the number of cases in the ith age group, Y_i the population size in the ith age group, and w_i the weight applied for the ith age group, with d_i / y_i being the age-specific rates for each ith category and the sum of w is being equal to 100 000 to express the age-standardized rate per 100 000 person-years. We used World Health Organization (WHO) 2000-2025 standard population.



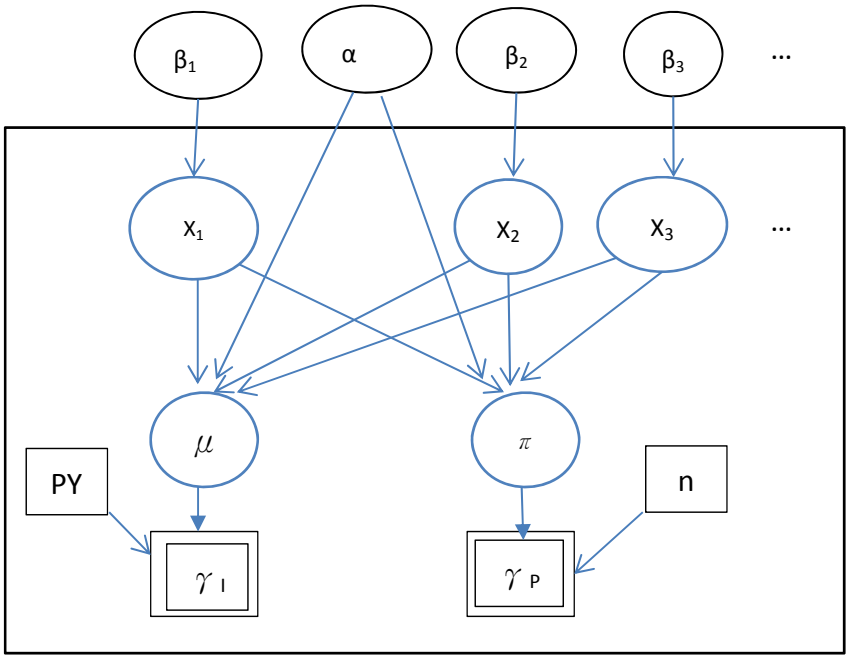
3.2.1.3 The effect of risk factors on the incidence of dementia with Poisson regression model

The independent effect of age and risk factors on the incidence of dementia was assessed using a multivariable Poisson regression model .P-value < 0.05 were considered statistically significant .The date of the last follow-up date is used as the endpoint for subjects who die or drop out since dementia status is unknown at the time of death or dropout.

3.2.1.4 The Prevalence/Incidence (P/I) ratio

The P/I ratio was estimated by using both prevalence figures. For adjusting the P/I ratio for dementia, the Bayesian method was developed for estimating the adjusted P/I ratios. Prevalence follows a Binominal distribution and Incidence follows a Poisson distribution. Following the framework of generalized linear model, the relationship between the P/I ratio and the covariates of interest, e.g. age, gender, and area was regressed through a logarithm link function. We have assessed the interaction terms in Bayesian regression model and strong interaction between age and gender was found. Therefore, the stratified models by gender were conducted in our analysis. For a better understanding of the difference of P/I ratios between passive and active survey, we also developed a Bayesian regression model making allowance for estimating the P/I ratios of two survey methods.

The direct acyclic graphic (DAG) model for estimating the parameters of adjusted P/I ratio is diagrammed as follows



Bayesian direct acyclic graphic model for the regression analysis can be expressed as follows.

$$\log(\frac{P}{I}) = \alpha + \beta_{11}X_{11} + \beta_{12}X_{12} + \beta_{13}X_{13} + \beta_{14}X_{14} + \beta_{15}X_{15} + \beta_{21}X_{21} + \beta_{22}X_{22} + \beta_{23}X_{23}$$

X_{1j}=age group (j= 1~5)
X_{2k}=area

3.2.2 Part II: Performance of MMSE an AD8

3.2.2.1 The correlation between MMSE and AD8 and the correlation between tests and dementia

First, the Pearson correlations were used to assess associations between MMSE with AD8. The association between MMSE and dementia and the association between AD8 and dementia were also tested. Statistical tests were 2-tailed and results were regarded as significant at or below the 5% probability level.

3.2.2.2 Bayesian method for Sensitivity, Specificity of MSME and AD8

Third, Bayesian method was used to estimate the sensitivity and specificity of dementia without a gold standard for dementia diagnosis. A Bayesian approach, simultaneous inferences about the population prevalence and the sensitivity, specificity, and positive and negative predictive values of each diagnostic test are possible.

3.2.2.3 Logistic regression analysis

Fourth, Logistic regression analysis was used to explore whether using the two tests together resulted in any additional information in the prediction of dementia compared with the use of the tests separately. The following equation was derived from the logistic regression analysis:

Logit (case) =0.6392+0.4134AD8-0.174 MMSE

or Pr (case) =1/1+ $e^{-(0.6392+0.4134AD8-0.174\ MMSE)}$

where 'Logit (case)' is the logarithm of the odds of a subject being a case of dementia, which is equal to: log (probability of a case/probability of non-case). 'Pr (case)' is the probability of a case of dementia. AD8 and MMSE are the test score value.

3.2.2.4 Receiver operating characteristic curve

We used ROC (Receiver operating characteristic curve) analysis, curves were plotted of sensitivity versus 1 minus specificity for all possible cut-off scores of each test. The area under the curve (AUC) is an estimate of its discrimination .The AUC for each test was calculated using SAS 9.3.

ROC analysis and logistic regression can be regarded as complementary techniques, with some points of difference and some points in common. Logistic regression assesses whether there is a relationship between cases and one or more predictor variables and gives the optimal equation for predicting probability of cases. ROC analysis assesses the screening performance of a test by calculating the sensitivity and specificity of each cut point of the test against cases and graphically represents the tradeoffs of each cut-point. The use of logistic regression to optimally combine predictors and ROC analysis to represent the cut-point tradeoffs marries the

advantages of both techniques. The two techniques will usually yield similar findings. In logistic regression, if a predictor is significantly related to cases, then the AUC test of the performance of the screening instrument in ROC is also likely to be significant.

3.2.2.5 Bayesian estimation of disease prevalence and the parameters of diagnostic tests

It is common in population screening surveys or in the investigation of new diagnostic tests to have results from one or more tests, none of which can be considered a gold standard. For example, two methods often used in population-based surveys for estimating the prevalence of dementia are based on MMSE and AD8. However, it is known that results from MMSE examinations may underestimate the prevalence, while AD8 may results in overestimation .Using a Bayesian approach, simultaneous inferences about the population prevalence and the sensitivity, specificity, and positive and negative predictive values of each diagnostic test are possible.

A review of frequentist (non-Bayesian) approaches to inference from data in the presence of misclassification is given by Walter and Irwig. In general, one can observe P different populations, each subject in each population receiving D different diagnostic tests. Here the term "diagnostic test" is used generically to denote any method of disease detection. For example, different observers of the same test or two

applications of the same test on a subject over time are considered as different tests. It is of interest to estimate parameters belonging to each population, typically the prevalence of disease, as well as the parameters of each diagnostic test.

3.2.2.6 Bayesian theorem for clinical reasoning

Suppose that each individual in a large population can be classified as true positive or negative for dementia. For each class of individual, true positive and true negative, we can consider the probability that the test such as AD8 or MMSE given a positive or negative number, as in the table below.

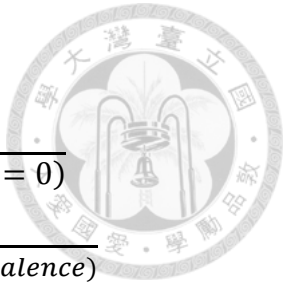
	Dementia		
	Yes (Y=1)	No (Y=0)	
TEST (+), X=1	M_1	a-M_1	a
TEST (-), X=0	M_2	b-M_2	b
	M_1+M_2	N-(M_1+M_2)	N

Let Y represent true disease status (Y=1: Disease Y=0: non-disease) specified by a binomial distribution. P(Y=1) stands for prevalence in population. Let X represent the result of test (X=1: positive; X=0: negative) also specified by a binomial distribution. The positive predictive value (PPV) is regarded as posterior probability. P(X=1) is defined as marginal distribution that is irrelevant to true disease status and can be decomposed by total law of probability.

$$\text{PPV} = \text{P}(\text{Y} = 1|\text{X} = 1) = \frac{P(X = 1, Y = 1)}{P(X = 1)}$$

$$= \frac{P(X = 1|Y = 1) \times P(Y = 1)}{P(X = 1|Y = 1) \times P(Y = 1) + P(X = 1|Y = 0)(Y = 0)}$$

$$= \frac{Sensitivity \times Prevalence}{Sensitivity \times Prevalence + (1 - Specificity) \times (1 - Prevalence)}$$



3.2.2.7 Bayesian estimation for early detection test in the absence of golden-standard diagnosis

One diagnosed test

The results of an early detection test for dementia are available on a random sample of subjects. No golden-standard test is available because it cannot practically be performed in community. The objective is to draw inferences about the prevalence (π), sensitivity (Se), and specificity (Sp), as well as PPV for the population. Based on the data in previous section, let a and b be the observed number of positive and negative test results, respectively, in the sample of N subjects. Let M_1 and M_2 be the information that is missing when there is no gold standard, that is, the number of true positive test results out of a and b, respectively. Thus M_1 is the number of true positives, and M_2 is the number of false negatives. Such missing information could be regards as 'latent data'.

The likelihood function of the observed and latent data shown in the table in the previous section is given by

$$L(a,b,M_1,M_2 \mid \pi, Se, Sp)=[\pi Se]^{M1}[\pi(1-Se)]^{M2}[(1-\pi)(1-Sp)]^{a-M1}[(1-\pi)Sp]^{b-M2}$$

$$=\pi^{M1+M2}(1-\pi)^{N-M1-M2}Se^{M1}(1-Se)^{M2}Sp^{b-M2}(1-Sp)^{a-M1} \quad (9)$$

The prior information in the form of a beta density, Beta (α, β), where α and β are parameters of interest will be assumed. This family of distribution was selected since its region of positive density, from 0 to 1, and because it is a flexible family, in that a wide variety of density shapes can be derived by selecting different choice of parameters from different studies. It also has the advantage of being the conjugate prior distribution for the binomial likelihood. Let (α.π, β.π), (Se.a, Se.b), and (Sp.a, Sp.b) represent the prior beta parameters for π, Se, and Sp. The poster distribution is the product of the likelihood and the prior distribution, it is given by

$$\pi^{M1+M2}(1-\pi)^{N-M1-M2}Se^{M1+Se.a}(1-Se)^{M2+Se.b}Sp^{M-Y2+Sp.a}(1-Sp)^{a-M1+Sp.b} \quad (10)$$

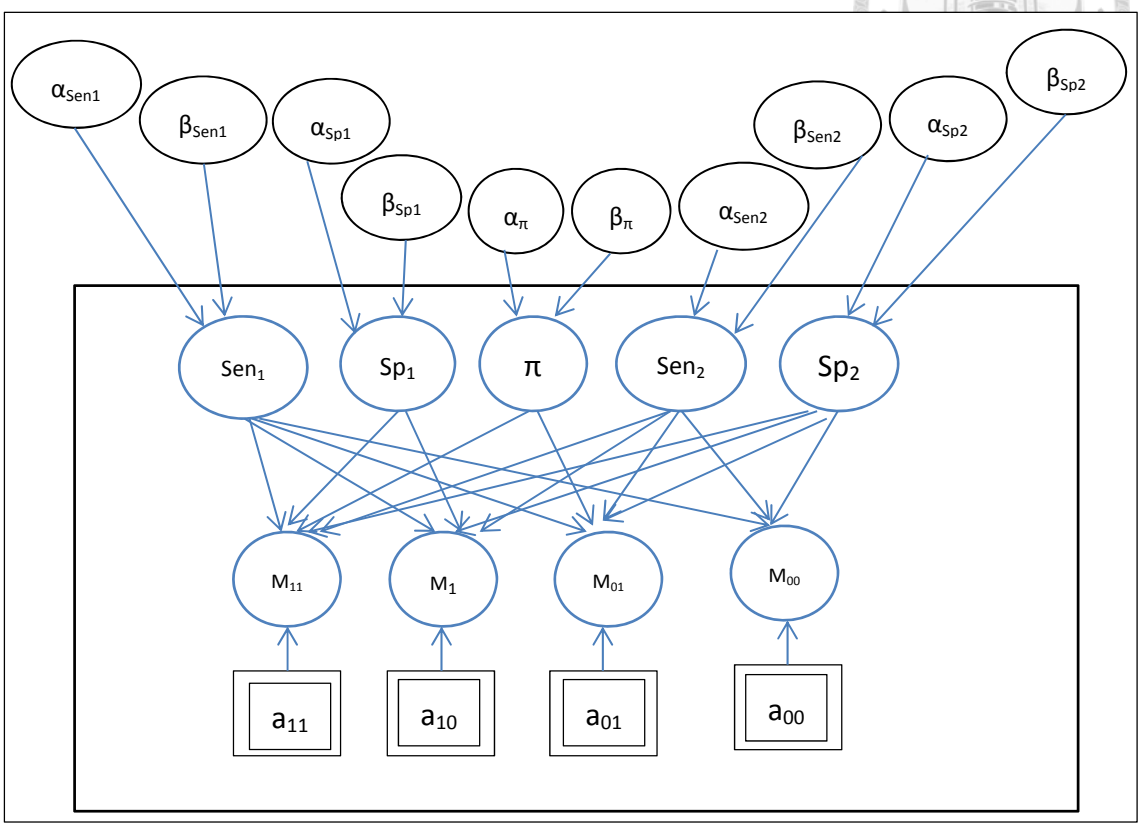
The latent data, M_1 and M_2, are not able to observe, impeding direct use of the above equation in calculating the marginal posterior densities of π, Se, and Sp. The inference is possible using a Gibbs sampler algorithm.

Two diagnosed test

Note M_{11}-M_{00} are four latent variables corresponding to the observed variable a11-a00 display in the 2x2 Table for the joint effect of two screening tools with AD8 and MMSE.

		AD8		
		+	–	
MMSE	+	a_{11}	a_{10}	$\mathbf{a_{11} + a_{10}}$
	–	a_{01}	a_{00}	$\mathbf{a_{01} + a_{00}}$
		$\mathbf{a_{11} + a_{01}}$	$\mathbf{a_{10} + a_{00}}$	**N**

The direct acyclic graphic (DAG) model for estimating the parameters of performance of two screening tools, AD8 and MMSE is diagrammed as follows. The Sen_1 and Sen_2 are indicated as the sensitivity of AD8 and the sensitivity of MMSE, respectively. The Sp_1 and Sp_2 represent the specificity of AD8 and the specificity of MMSE, respectively. π_i denoted as the prevalence of dementia. For capturing the sensitivity or specificity, for example, Parameters, α_{sen1} and β_{sen1} represents the beta parameters from prior or observed data for the sensitivity of AD8.



The likelihood functions for each combination of observed and true data for the two screening tools (AD8 and MMSE) are listed in the following table.

No. of screening	True Dementia	AD8	MMSE	Likelihood function
M_{11}	+	+	+	$\pi Sen_1 Sen_2$
M_{01}	+	+	–	$\pi Sen_1 (1\text{-}Sen_2)$
M_{10}	+	–	+	$\pi(1\text{-}Sen_1)\ Sen_2$
M_{00}	+	–	–	$\pi(1\text{-}Sen_1)\ (1\text{-}Sen_2)$
$a_{11} - M_{11}$	–	+	+	$(1\text{-}\pi)\ (1\text{-}Sp_1)\ (1\text{-}Sp_2)$
$a_{01} - M_{01}$	–	+	–	$(1\text{-}\pi)\ (1\text{-}Sp_1)\ Sp_2$
$a_{10} - M_{10}$	–	–	+	$(1\text{-}\pi)\ Sp_1(1\text{-}Sp_2)$
$a_{00} - M_{00}$	–	–	–	$(1\text{-}\pi)\ Sp_1\ Sp_2$

In order to estimate the parameters of π, Sen, and Sp, the full conditional distributions are required for modelling the four latent variables, M_{11}-M_{00}.

M_{11} is distributed as Binomial (a_{11}, $\frac{\pi Sen_1 Sen_2}{\pi Sen_1 Sen_2+(1-\pi)Sp_1 Sp_2}$)

M_{01} is distributed as Binomial (a_{01}, $\frac{\pi(1-Sen_1)Sen_2}{\pi(1-Sen_1)Sen_2+(1-\pi)Sp_1(1-Sp_2)}$)

M_{10} is distributed as Binomial (a_{10}, $\frac{\pi Sen_1(1-Sen_2)}{\pi Sen_1(1-Sen_2)+(1-\pi)(1-Sp_1)Sp_2}$)

M_{00} is distributed as Binomial (a_{00}, $\frac{\pi(1-Sen_1)(1-Sen_2)}{\pi(1-Sen_1)(1-Sen_2)+(1-\pi)Sp_1 Sp_2}$)

The Beta distributions were assigned to π, Sen_1, Sen_2, Sp_1, and Sp_2 as shown in DAG diagram.

Gibbs sampling will be used to sample from these full conditional distributions and the estimates of parameters on π, sensitivity, and specificity would be achieved after n cycles of iterations.

3.2.3 Part III: Cost-effectiveness analysis of community-based dementia screening

3.2.3.1 Decision tree with Markov decision model

Figures 3.2.1 shows the decision tree for five strategies including AD8, MMSE, parallel test, sequential test, and no screening. we defined ( ) as decision node that means we can select one of strategies and assigned (○) as chance node that indicates

events were determined by probability. The symbol of [+] indicates subsequent tree for five strategies. We used a Markov model to construct the nature course of dementia, comprising the states of normal, mild, moderate, severe and death, which modified from Neumann et al[10] (Figure 3.2.2).

The simulation cohort of 10,000 subjects was divided into normal, mild, moderate, severe, and death groups. In these groups, regardless they were screened or not, they could be further divided into screened and non-screened detected cases due to not 100% sensitivity and specificity of screening tools. The three treatment nodes after screening were followed up by different levels of dementia outcomes: mild, moderate, and severe. For each disease state, the disease progression to different states changed with time. We therefore used a Markov node to represent the yearly dynamic change of disease status and assigned the corresponding cost and effectiveness according to different states of dementia.

The disease statuses were based on levels of severity of cognitive disability. The cycle length of each state was one year; the base case estimates of annual transition probability were derived from previous studies. According to the current survival studies of dementia[36-38], we simulated the Markov model for 10 years after the diagnosis of dementia. The relative risk for treatment in the early stage of dementia was applied from the mild to the moderate state in the Markov model.

3.2.3.2 Parameters assigned in Markov decision model

Our cost-utility analysis was performed based on Taiwanese scenario. The parameters assigned to the Markov cycle tree which were retrieved from literature review and empirical data in Taiwan. The base cases and their distribution of base cases for these parameters are listed in Table 3.2.1.

To fit in with Taiwanese scenario, prevalence rate, screening and some direct costs, and performance of screening tests referred to Taiwanese empirical data. The prevalence for mild, moderate, and severe dementia were 5.88%, 1.13,%, and 1.13%, respectively, based on the previous Taiwanese study[96]. The performance of screening tools was derived from local empirical study in Tainan. The screening and direct medical costs for dementia patients were measured on the basis of expert opinions.

The direct and indirect costs assigned in each dementia state which modified based on expert opinions. The direct costs included the medical expenses paid by National health insurance and out-of-pocket payments. The indirect costs mainly included caregiver time, which was calculated by opportunity cost of time and replacement cost. The cost parameters were specified by a triangular distribution, including the minimum, a mode and a maximum.

The healthy outcome measure was quality-adjusted life year (QALY). Given that

there has been no healthy utility survey done for Taiwanese dementia patients, we used the utility scores from Neumann's study, which measured QALY via the Health Utilities Index Mark II (HUI:2)[97]. Because the majority of dementia patients were cared at home in Taiwan, we used the scores of the community aspect of the utility in Neumann's study.

3.2.3.3 Probability cost-utility analysis

Based on Markov decision cycle, we applied a cost-utility analysis to calculate incremental cost-utility ratio to assess additional costs invoked in order to save an additional life year or a quality-adjusted life year (QALY) by screening. All effectiveness and costs were discounted at 3% annually. The Bayesian approach using Monte Carlo simulation was performed for probabilistic cost-utility analysis by simulating a 10,000 hypothetical cohort of elderly people in Taiwan. This cohort was randomized to different screening strategies to follow the Markov cycle as mentioned above. Figure 3.2.3 demonstrates the decision tree of parallel test as an example. This procedure was repeated 500 times to obtain unbiased base-estimate and 95% confidence interval for relevant estimates. Using the Monte Carlo Simulation method for the uncertainty of parameter, the simulated estimates of incremental cost and incremental utility, and ICUR were plotted and located in a four-quadrant

cost-effectiveness plane.

The $20,000 of willing to pay (WTP) referring to the average Gross Domestic Product in Taiwan was plotted to evaluate what is the percentage of the ICURs is below this threshold of WTP. The higher the percentage is, the more likely to be accepted by health decision-maker. We also plotted cost-utility acceptability curve. It represents the relative cost-utility as a function of the threshold ICUR, which uses ICURs to graph the changing percentage for which a comparable strategy is cost-utility relative to a baseline strategy. All these analyses were performed with TreeAge Pro 2012 software[98].

Chapter 4：Result

4.1 Prevalence and incidence of dementia in population-based cohort study

4.1.1 Age-specific and gender-specific prevalence, incidence rate

T Table 4.1.1 shows age-specific prevalence and incidence of dementia between 2000 and 2003 in population-based cohort in Taiwan. The overall prevalence rate of dementia for subjects aged 65 years and older was 2.9%, which was lower than 9.29 % estimated from a community-based survey. Age-specific prevalence rate increased with age, being double in every five-year age band until 80 years of age. The similar but larger prevalence trend was noted for the corresponding figures obtained from a community-based survey.

Following a normal fixed cohort from the year 2000 (excluding those who had dementia before 2000), 99,609 incident dementia cases were ascertained during the follow-up from 2000 to 2003. The incidence rate of total dementia was 1.83% in population-based cohort study. Incidence rate of dementia increased with age, doubling in every 5-year age bands similarly seen in the figures of groups. The incidence of dementia is approximately 21 times higher among persons older than 90 years compared with those between 65 and 69 years of age. The gender-specific

incidence was higher in females (19.4‰) than males (17.3‰). Women had an increased risk of dementia than men.

The P/I ratio enables us to assess the extent of awareness of being diagnosed as dementia. The age-specific P/I ratio of dementia are presented in table 1. Using the national figures from NHI (passive survey, clinical-diagnosed data), the overall dementia P/I ratio was 1.59 years in our study. The older the age of dementia, the P/I ratio is larger. In contrast, the P/I ratios based on a community-based screening survey (active survey, screening-diagnosed) were larger than those estimated form the NHI.

4.1.2 Poisson regression model

We also compare age- specific incidence rate of dementia in four main areas in Taiwan, we found there were difference in four areas of Taiwan. It seems that north Taiwan (urban) has higher incidence rate than central (rural) Taiwan. The finding suggests urban area of Taiwan has higher incidence rate of dementia than rural area of Taiwan. Table 4.1.2 shows the effects of age, gender, area on the risk of incidence rate of dementia by univariate and multivariate Poisson regression model. The result shows age, gender and area are risk factors of dementia.

4.1.3 Prevalence/incidence ratio

The prevalence /incidence (P/I) ratio enables us to assess whether the awareness of dementia treatment. The larger the ratio is, the better the treatment. The age-specific

P/I ratio were presented in table 4.1.1. The overall dementia P/I ratio was 1.59 years in our study.

Table 4.1.3 shows the adjusted P/I ratios of dementia. After adjusting area, the P/I ratio increased from 1.20 (1.15-1.24) for 70-74 age group to 3.27 (3.13-3.41) for 90+ age group in males. The P/I ratio was higher in northern area than other three areas in males. The East Taiwan had the lowest P/I ratio was also presented in Table 3. In females, the P/I ratio decreased from 1.69 (1.63-1.74) for 70-74 age group to 0.90 (0.86-0.94) for 90+ age group after adjusting area. The P/I ratio was higher in eastern area than other three areas in females.

The P/I ratio of screening-diagnosed (active survey) dementia was higher than clinical- diagnosed (passive survey) dementia. Table 4.1.4 shows the adjusted P/I ratios for passive survey and active survey. P/I ratios increased from 1.45 (1.43-1.47) for 65-79 age group to1.64 (1.61-1.66) for 80+ age group in passive survey. P/I ratios increased from 4.23 (2.68-6.69) for 65-79 age group to 4.77 (3.02-7.54) for 80+ age group in active survey.

The P/I ratio of dementia in our study were compared with other community studies in other countries.

4.1.4 Comparison other study on age-standardized incidence rate

The sex specific incidence rates of dementia were compared with Taiwan and other countries in table 4.1.5. These study show woman had high risk of dementia than man.

We also used world standard population for adjusting the incidence rate of dementia with age to compare our result with western countries. Table 4.1.6 shows the difference in age- standardized incidence rate of dementia in Taiwan, USA, and European. The adjusted standardized incidence rate of dementia was 17.5 per 10^3 person years in Taiwan, 14.6 per 10^3 person year in USA[99]: 13.1 per 10^3 person years in European[40]. Other community-based studies were also comparison in Table 4.1.7.The P/I ratio was higher in active screening study than passive survey in usual care of dementia.

4.2 Performance of MMSE and AD8 in community-based study

4.2.1 Baseline characteristics

There were a total 282 of participants (138 female and 144 male). The mean age of participants was 69.31 years (SD=10.27, range: 50 ~ 91 years). The distribution of education level was as follows: 29.79% illiteracy, 43.62% less than 6 years school

education, and 26.60% more than 6 years school education. Total of 279 informants responded to the interviews with AD8 screening questionnaire. Only two participants were unavailable for the MMSE test.

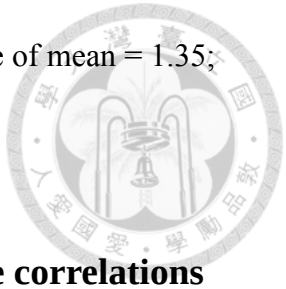
Of 282 study samples, there were 174 normal subjects , 84 with mild cognitive impairment, 18 with dementia who meet criteria with NIA-AA guideline in 2011： Criteria for all-cause dementia. Clinical diagnosis of dementia could not be made by physician for six participants.

Table 4.2.1 shows demographic characteristics and the average score of the AD8 and MMSE test of 282 samples in dementia screening program.

The prevalence of dementia by clinical diagnosis was 9.29% in our study. Table 4.2.2 shows the findings of AD8, MMSE and clinical diagnosis. The mean AD8 score was 0.56 (SD=1.09, range:0~8) and the mean MMSE was 23.93 (11 to 30 (Mean=23.93, SD=4.73, range 11-30). There were 64.7% persons who met criteria for all-causes dementia were AD8 abnormal (cutoff=2). There were 77.8% persons who met criteria for all-cause dementia were MMSE abnormal (cutoff =21).

Independent samples t-tests indicated that the dementia group (mean MMSE =19.05) was more impaired than the non-dementia (mean MMSE=25.2) group on MMSE (the difference of mean = 6.15; t = 5.28; df =189; $P < 0.001$) and AD8 (mean

dementia group AD8=1.71; non-dementia mean=0.36; the difference of mean = 1.35; t = -5.74; df=187; P < 0.001).



4.2.2 The correlation between MMSE and ADB and the correlations

Both AD8 and MMSE were highly associated with dementia as indicated in Table 4.2.3 The Pearson correlation coefficient between the two test was -0.37 (P<0.0001). Table 4.2.4 also shows the relationship between AD8 with MMSE.

4.2.3 Sensitivity and specificity of MMSE and AD8

The results for sensitivity, specificity, and positive and negative predictive values for the AD8, MMSE and the combined use (parallel or serial mode) in differentiating dementia from non-dementia are shown in Table 4.2.5. The sensitivity and specificity (validity) of the sole use of AD8 in dementia screening were 64.71% and 87.89%. The positive predictive value and the negative predictive value were 26.2% and 97.4%. The sensitivity and specificity (validity) of the sole use of MMSE in dementia with adjustment for education level were 41.18% and 84.50%. The corresponding positive predictive value and negative predictive value were 14.8% and 95.6%. Note that when the optimal cut-off score of 21 was used for the MMSE test (see below), the estimates of sensitivity and specificity were 77.78% and 73.58%, respectively. It is also very interesting to note that when the cutoff was raised to 26

used for the MMSE test in Western countries, the sensitivity was increased to 94.44 whereas the specificity was decreased to 28.26%.

The combination of AD8 with MMSE in the parallel mode (either of abnormal result of two tests) yielded 88.89% of sensitivity and 70.16% of specificity. The corresponding positive predictive value and negative predictive value were 17.2% and 98.9%. Note that the estimate of sensitivity was decreased to 72.2 and that of specificity was increased 75.2% when the criteria for positive result of screening in the parallel mode were modified as AD8 (+) and MMSE (+) or AD8 (-) and MMSE (+) and the estimate of sensitivity was further decreased to 61.1 and that of specificity was further increased 87.9% when the criteria for positive result of screening in the parallel mode were modified as AD8 (+) and MMSE (+) or AD8 (+) and MMSE (-).

The combination of AD8 with MMSE in the serial mode (the abnormal results of both tests) yielded 50.00% of sensitivity and 93.02% of specificity. These findings suggest that the combination of MMSE or AD8 in the parallel mode increased the sensitivity of dementia screening compared with the combination of MMSE with AD8 in the serial mode increased the specificity of dementia screening. The degree of enhancement in sensitivity and the compromise of the specificity was also dependent on what sort of the positive result of each test was included.

The results for sensitivity, specificity and positive and negative predictive

values for the AD8, MMSE and the combined use in detecting MCI plus dementia are shown in Table 4.2.6. The estimates of sensitivity and specificity of using AD8 test alone were 25.74% and 90.70%. The estimates of positive predictive value and negative predictive value were 61.9% and 67.5%. The estimates of sensitivity and specificity of using the MMSE test alone making allowance for education level were 24.75% and 87.36%. The estimates of positive predictive value and negative predictive value were 53.2% and 66.7%. Using the score 21 as the optimal cutoff yielded higher sensitivity (43.1%) but at the slight sacrifice of specificity (80.5%).

The estimates of sensitivity and specificity for the combined AD8 with MMSE with adjustment for education level in the parallel mode were 38.24% and 80.46%. Again, using the score 21 as the optimal cutoff yielded higher sensitivity (50.9%) but at the slight sacrifice of specificity (76.4%). It is expected that the corresponding figure of sensitivity was decreased and that of specificity was increased when the combined AD8 with MMSE with adjustment for education level or using the score 21 as the optimal cutoff in the serial mode was used.

Table 4.2.7 shows the similar findings on the validity of the accuracy in the detection of MCI. The all estimates of sensitivity for all the modes except the MMSE with 26 of cutoff were poor and the specificity was moderate.

Based on Table 4.2.5, the ability to rule in (sensitivity×PPV) and rule out

(specificity×NPV) dementia for AD8 alone was 0.17 and 0.86 for AD8 alone, 0.13 and 0.72 for MMSE with 21 as cutoff, 0.089 and 0.38 for MMSE with 26 cutoff, 0.061 and 0.81 for MMSE adjusted with education, 0.15 and 0.69 for the parallel mode, 0.17 and 0.87 for the serial mode.

These findings on the detection of both screening tools also suggest that combination of cognitive testing (MMSE) and informant questionnaire (AD8) in the parallel mode increased the sensitivity but decreased specificity in early detection of dementia whereas the combined both tests in serial mode acted in the opposite direction. The ability to rule in and rule out dementia also suggest AD8 alone and MMSE alone has still a low ability to rule in disease as the positive utility index was lower than 0.2 and the ability to rule out dementia was excellent as the negative utility index was between 0.81 and 0.92.

However, the application of both screening tools in the detection of MCI is very limited in the principle of rule-in accuracy.

4.2.4 Bayesian estimation of the validity of screening with MMSE and AD8

By using Bayesian estimation with the incorporation of information prior on prevalence and the validity of both screening tools in the absence of a golden standard

test (Table 4.2.8), the estimated prevalence was 4.8% (95% CI: 3.0%-7.3%) and 84.1% (95%CI: 76.9%-90.3%) of sensitivity and 77.1% (95%CI: 72.9%-81.0%) of specificity in early detection of dementia with the AD8 test (see Table 4.2.8). The corresponding figures were 6.1% (95% CI: 3.9%-8.9%) and 82.2% (95%CI: 80.7%-83.6%) of sensitivity and 86.1% (95%CI: 85.6%-86.5%) of specificity in early detection of dementia with MMSE test. In parallel testing, 97.2% (95%CI: 95.9%-98.3%) of sensitivity and 66.0% (95%CI: 62.5%-69.4%) of specificity were estimated in early detection of dementia given 4.9% (95%CI: 3.0%-7.2%) of prevalence. In serial testing, 69.4% (95%CI: 63.5%-74.3%) of sensitivity and 96.8% (95%CI: 96.2%-97.3%) of specificity were estimated.

The 5.0% (95% CI: 0.29%-13.6%) of prevalence and 80.7% (95%CI: 74.9%-85.9%) of sensitivity and 87.1% (95%CI: 82.4%-91.8%) of specificity were estimated in early detection of MCI with the AD8 test. The 2.7% (95% CI: 0.09%-12.3%) of prevalence and 62.6% (95%CI: 58.2%-66.96%) of sensitivity and 64.8% (95%CI: 62.5%-67.5%) of specificity were estimated in early detection of dementia with MMSE test. In parallel testing, 62.6% (95%CI: 58.2%-66.9%) of sensitivity and 64.8% (95%CI: 62.5%-67.2%) of specificity were estimated in early detection of dementia. In serial testing, 92.8% (95%CI: 90.4%-94.8%) of sensitivity and 55.8% (95%CI: 52.3%-59.2%) of specificity were estimated in early detection of

dementia.

4.2.5 Logistic regression analysis

A series of logistic regression models considering MMSE, AD8, education, and the interaction between MMSE and AD8 with -2 log likelihood and AIC values are listed in Table 4.2.9. It is apparent that MMSE, AD8, and education are three significant independent factors as the result of likelihood ratio test was statistically significant ($P < 0.05$). Table 4.2.9 also assesses the interaction of both MMSE and AD8 with adjustment for education level. There was a lacking of statistical significance of interaction between AD8 and MMSE in association with the risk for dementia (β=0.048 (SE=0.032), P=0.14). Table 4.2.10 shows the results of univariate analysis of each factor. The identified significant factors included AD8, MMSE, age, and education. Table 4.2.11 shows the additional influence of age and gender given three main variables have been considered, including MMSE, AD8, and education level. Note that age was a significant factor ($P=0 < 0.01$) in the univariate analysis whereas gender was not (P= 0.56). However, both were not statistically significant any more when three main variables have been considered.

4.2.6 ROC curve of MMSE and AD8

Figure 1 shows the results of the ROC analysis in differentiating dementia (n= 18) from non-dementia (all the other diagnoses including normal cases; n= 264) for the sample. The area under the ROC curve (AUC) of AD8 was 73.3% (60.7%-85.9%) and the AUC of MMSE: 77.4 %(67.6%-87.3%), the AUC of the parallel mode was 82.3% (75.1%-89.4%), and the AUC of the serial mode was 67.6% (53.4%-81.8%). These finding suggest good ability of the parallel mode to discriminate dementia from normal.

4.3 The cost-utility of community-based dementia screening

4.3.1 Simulated results of disease outcome

Table 4.3.1 shows the distribution of dementia by stage and death in the end of simulation under different screening circumstances for our simulated cohort, in which the prevalent dementia of mild, moderate, and severe stage of 5.88%, 11.3%, and 11.3%, respectively, was included at baseline. It can be seen that without screening program, the proportion of being mild, moderate, severe dementia and death was 8.75%, 4.14%, 13.10%, and 28.09%, respectively. Screening not only decreased the proportion of death, but also shifted dementia cases to earlier stages by down-staging

severe dementia to mild and moderate dementia. The dynamic curves by stage in a naïve cohort (dementia-free at baseline) in which the dementia patients did not take CEIs was shown in Figure 4.3.1(a). The dynamic curves of the same cohort taking CEIs were shown in Figure 4.3.1(b).

4.3.2 Base case results of the cost-utility analysis

Table 4.3.2 shows the results of cost-utility analysis of community-based dementia screening with different screening tools, including AD8, MMSE, and the parallel and serial modes of the two tools compared to no screening. The average quality-adjusted life-years (QALYs) accumulated for a specific person without screening taking place was 6.0847 years (95% CI: 6.0068, 6.1709) in a ten-year period. Screening with AD8 and MMSE brought in an extra of 0.0439 and 0.0429 QALYs, respectively. The parallel mode of AD8 and MMSE had the largest QALY gained (0.0439), whereas the serial test of the two tests had the smallest QALY gained (0.0363). As far as cost was concerned, the average cost for a person was $46285.9 (95% CI: $33488.6, $62241.8) if there was no screening program. The community-based dementia screening programs resulted in less cost, varying from $44450.0 for the parallel mode to $44960.2 for the serial mode. Collectively, the incremental cost-utility ratio (ICUR) suggested cost-saving for the community-based dementia screening programs.

Table 4.3.3 shows the results of cost-utility analysis of dementia screening if only direct cost on screening and medical expenditure were taken into account. The results show that a total of $3264.3 would be spent if no screening was taken place. The most expensive strategy was the parallel mode with an extra cost of $20.7, followed by MMSE ($19.7), serial mode ($18.1), and AD8 ($17.6). The ICURs for AD8, MMSE, parallel mode, and serial mode were $401.4, $457.7, $409.8, and $499.2 per QALY gained, respectively.

4.3.3 Probabilistic cost-utility analysis

Given 10,000 first order trials and 500 second order parameter samples in a Monte Carlo simulation, the scattered incremental cost-utility analysis for different screening strategies for community-based dementia screening compared with no screening was shown in Figure 4.3.2 (a)-(d). It was seen that roughly 80% simulations had their incremental cost-effectiveness results in the fourth quadrant (cost-saving) regardless which screening modality was chosen. Under the willingness-to-pay of $20,000, the probability of being cost-effective was 92.2%, 92.0%, 93.8%, and 88.6% for AD8, MMSE, parallel mode, and serial mode, respectively. Comparing parallel mode with single test, the proportions of being dominant for parallel test over AD8 and MMSE were 80% and 77.6%, respectively. The corresponding probabilities of

being cost-effective given WTP at $20,000 were 88.8% and 90%, respectively. The serial mode was inferior to the single mode. The proportions of being dominant for the serial mode over AD8 and MMSE were only 10% and 10.2%, respectively. The corresponding probabilities of being cost-effective given WTP at $20,000 were 11.4% and 12.8%, respectively.

When only direct cost was taken into account, roughly 40% simulation had superior results for AD8, MMSE, parallel and sequential tests of the two screening tools (Figure 4.3.3 (a)-(d)). The probability of being cost-effective was 97.6%, 97.2%, 99.0%, and 93.4% for AD8, MMSE, parallel mode, and sequential mode, respectively, given the willingness-to-pay as $20,000. The corresponding figures for parallel test were 95.4% over AD8 and 95.2% over MMSE. The counterparts for serial mode were 13.2% and 15.2% over AD8 and MMSE respectively.

The acceptability curve of cost-utility analysis is shown in Figure 4.3.4. The results showed that parallel mode was the best strategy among the four alternatives. The probability of being cost-effective for parallel test was 65% given zero WTP. This probability increased with increasing WTP, being 76% at WTP of $10,000, 82.8% at WTP of $20,000, and 85.8% at WTP of $30,000, 86.4% at WTP of $40,000, and 87.6% at WTP of $50,000.

When only direct cost was of concerned (Figure 4.3.5), no screening took the

lead at zero WTP with probability of being cost-effective as 53.4%. As WTP increased, the probability of being cost-effective for no screening decreased and the one for the parallel mode increased while the two strategies met (38%) at WTP of $850. After that, the probability of being cost-effective for the parallel mode increased dramatically and reaching a plateau of 90% at WTP of $15,000.

Chapter 5： Discussion

5.1 Summary of main findings and contributions

The major contributions of the current thesis include two aspects, clinical and public health implications for prevention of disability and death from dementia and the methodological development of statistical evaluation of epidemiology profiles and the community-based screening program for dementia.

The main findings and implications under the context of prevention of disability and death from dementia include three main points.

(1) Low awareness of dementia has been ascertained in routine health insurance health care system as the P/I ratio of community-based survey (active detection method) was greater than that of health insurance heath care system (passive detection method). This invokes the consideration of community-based screening for dementia in order to enhance awareness and also early detection and treatment of dementia in Taiwan.

(2) The main findings on the validity of the accuracy in the early diagnosis of AD8 and MMSE consist of the following points.

(A) AD had higher sensitivity but lower specificity in detection of dementia than MMSE when both tools were considered in population- and community-based screening.

(B) The optimal sensitivity and specificity could be achieved using the optimal cut-off based on empirical data.

(C) Compared with the use of AD8 or MMSE alone, the combination of AD8 with MMSE with the parallel mode enhanced the sensitivity whereas that with the serial mode enhanced the specificity.

(3) Community-based screening for dementia with AD8 and MMSE is more cost-effective and almost near cost-saving as the probability of being cost-effective according to acceptability curve of probabilistic analysis compared with no screening program. The most economic screening strategy is the parallel mode of combining AD8 with MMSE. .

The main contribution of the current thesis to the methodological development includes

(1) The development of a P/I-ratio-based regression model under the framework of generalized linear regression model to estimate the P/I ratio of active detection method in comparison with that of passive detection method after controlling for confounding factors.

(2) The application of Bayesian clinical reasoning model to model the validity of

combining multiple detection modalities i.e. AD8 and MMSE in the current application. The Bayesian model for multiple detection modalities in the absence of gold standard was applied to the estimation of posterior distributions of sensitivity and specificity by combing prior information on the use of AD8 and MMSE with the likelihood based on the current empirical data.

(3) The development Markov cycle decision tree model for economic evaluation of population-based screening program with AD8 in combination with MMSE.

5.2 Applications

5.2.1 Epidemiological assessment of dementia in Taiwan

5.2.1.1 Prevalence and incidence of dementia

The study, to our knowledge, is the first large scale population-based study to simultaneously estimate the prevalence and incidence of dementia in the same study. Their findings have significant implications for the etiology, patient behavior, infrastructure, and quality of health care for dementia. In the study, we have demonstrated age and gender-specific incidence and prevalence of dementia in Taiwan. As age is an independent risk factor for Alzheimer's diseases (AD), people in this age group of 85 or older are highest risk for AD. Our age-specific prevalence figure had the same trend with other studies as indicated in Jorm et al study showing

the exponential rise of dementia with age in a number of prevalence studies[100]. From the age of 65 years, the prevalence double every 5 years. However, our prevalence was considerably lower than other previous studies. The comparisons across studies should be taken with great caution as the majority of studies were based on an active community-based survey rather than based on population-based registry data. This can be supported by the fact that the prevalence of dementia form active community-based survey in our study was raised from 2.91% to 9.3%, which was close to two other surveys in Taiwan and other studies in Western countries as shown in Table 4.1.7. It is very interesting to note that the variation of incidence still exists but the disparity of incidence was smaller compared with that pf prevalence. This suggest the etiology of dementia was not fraught with heterogeneity across racial groups.

Women had an increased risk of dementia then men. The difference may be explained by the greater life expectancy and by a high survival rate of women with dementia compared with men diagnosed as dementia at the same age. We also compared our results with other countries. In this study, we found the adjusted incidence rate of dementia in Taiwan during 2000-2003 to be 1.83%, which is slightly lower than Sweden, USA and Japan, but higher than China.

5.2.1.2 Prevalence/incidence ratio

The P/I ratio reflected the awareness of dementia. The larger the ratio is, the better awareness of dementia. The crude P/I ratio in our NHI study (passive survey) and community study (active survey) were 1.59 and 5.08. The similar findings in adjusted P/I ratio were 1.45(1.43-1.47) and 4.23(2.68-6.69) for aged 65-79 years in our active and passive survey, respectively. The higher prevalence rate of dementia is attributed to active screening in community study. The possible cause may be related to the unawareness of family members on dementia and led to a delay treatment. Prospective longitudinal studies demonstrate serious deficiencies in the healthcare system's ability to recognize dementia and most dementia remains unrecognized in the primary care setting. Persons with mild dementia are more likely to go unrecognized by physicians and family (over 90%) than persons with moderate to severe dementia (over 70%). However, those with early disease were best treated with available medications [48, 49]. This postulate is supported by our findings through a population –insurance –registry-based study that underdiagnosed dementia in contrast to other studies based on a community active detection survey like our community-based survey. We also compared P/I ratio with other countries in Table 7. The P/I ratios were 2.4 in Denmark [101], 4.25 in Japan [102], 4.83 in Sweden[103], 6.25 in China[30], 6.4 in Italy[104], 5.47 in Spain[105], and 4.73 in USA[106]. Most of high P/I ratios

studies were based on active community-based screening survey and had a reflection of high awareness of early detection of dementia.

5.2.2 The validity of the accuracy of MMSE and AD8 in detecting dementia

Cut-off point of AD8 and MMSE

The optimal cut-off of 2 for Chinese version AD8 based on our community data was identical to that as estimated in the previous study. It may due to the fact that the Chinese version AD8 was not influenced by the different culture, age, education. But, the optimal cut-off of 21 for MMSE identified from the current study was lower than 23 or 26, both of which are two commonly chosen cut points in other studies. This implies that the cut point for MMSE may vary from area to area and it needs to be further validated by other community study.

AD8 alone

The estimates of sensitivity and specificity with AD8 alone were 64.71% and 87.89% in our community-based dementia screening. The area under the ROC curve (AUC) of AD8 was 73.3 (95%CI= (60.7-85.9)), which still suggests good ability of AD8 to discriminate dementia from normal as 95% CI did not cover 50%.

Comparing our community-based AD8 study with hospital-based AD8 study in Yang et.al study21, our community-based AD8 sensitivity (64.71%) was lower than

this previous hospital-based AD8 study (sensitivity=97.6%), but our specificity (87.89%) was superior to the hospital-based AD8 study (specificity=78.1%).

The sensitivity (64.71%) and the specificity (87.89) of our study were close to the sensitivity (68%) and the specificity (90%) of the K-AD8 study in Korea[55].

However, in America, the original version AD8 sensitivity (74%) conducted in America was higher than our study (sensitivity=64.71%) but their specificity (86%) was slightly is lower than our study (sensitivity=64.71%). Our data is similarly to the AD8 original study in America.

It is apparent that the disparity of validity in the accuracy of detecting dementia with AD8 between our study and the previous in Taiwan (Dr. Yang study) is mainly attributable to the different sources of study population as our study samples were based on community residents whereas those of the previous study were derived from clinical series.

As far as the use of the MMSE in identifying MCI is concerned, the sensitivity was poor regardless of which screening strategy was adopted. The ability to rule in dementia is therefore very poor and the ability to rule out dementia was a little higher but still moderate.

To sum up, the K-AD8 is a sensitive screening tool in detecting early dementia in community-based study as the ability to rule out and also rule in dementia was

higher with AD8 than the MMSE regardless of which method is based on to classify the subjects as abnormal result. The application of AD8 to detecting MCI is very limited given the current finding.

MMSE alone

The MMSE is the most widely used cognitive test. A cut-off of 23 versus 24 (23v24) was recommended by Folstein et al in persons with at least 8 years of education [14]. However, many other cut-offs have been tested by using the receiver operator curve (ROC) analysis of specific populations together with adjustments for age and education in Grigoletto et al. and Crum et al studies. Given the optimal cutoff, the sensitivity of and the specificity of the MMSE method in our community-based dementia screening was 77.78% and 73.58%, which was lower than the result of meta-analysis study also the result of another community-based study[107] with cut-off point 21/22 (the sensitivity =82.8% and specificity=86.9%).

The comparison of the validity of the accuracy in early diagnosis of dementia should be taken with great caution as the selection of cutoffs is highly dependent on whether you want to “rule in” or “rule out” dementia, which is determined by the characteristics of the underlying selected population. It should be noted that different cutoffs selected for different populations have been noted in a meta-analysis study. In memory clinical setting, the pooled estimates of sensitivity, specificity, positive

predictive value, and negative predictive value were 79.8%, 81.3%, 86.3%, and 73.0%, respectively. The corresponding figures were 71.1%, 95.6%, 94.2%, and 76.4% in mixed specialist hospital setting and 78.4%, 87.8%, 53.6%, and 95.7% in non-clinical community setting. It is obvious that in the non-specialist setting the MMSE was the best to rule out dementia (as a product of specificity and NPV was higher) but to moderately rule in dementia (as a product of sensitivity and PPV was not higher) whereas the opposite was seen in specialist setting.

The similar findings were noted in our community-based screening with AD8 and the MMSE. For the MMS, when the cutoff was raised from 21 to 26, the ability to rule out dementia was decreased from 0.72 (sen×PPV) to 0.38 although the ability to rule in dementia was still slightly higher with 21 of cutoff than 26 of cutoff.

Regarding the use of the MMSE in identifying MCI, limited evidence was found. The MMSE had very limited value in making a diagnosis of MCI against healthy controls and modest rule-out accuracy[108]. It had similarly limited ability to help identify cases of Alzheimer's disease against MCI. Our study has a similar finding with the MMSE applied to detecting MCI.

Combined use MMSE and AD8

Compared with other studies, the combination use of MMSE with AD8 (parallel test) had slightly lower accuracy(sensitivity=88.89%) than MMSE with IQCDOE

(sensitivity = 91%)[109] but higher specificity(specificity=71%) than MMSE with IQCODE (specificity =63%)[109] The combination use of MMSE with AD8 (parallel test) (sensitivity=88.89%) had higher accuracy by MMSE with OSCE (sensitivity=83.1%)[110].

The ability to rule in and rule out dementia was not elevated by using the parallel test as combing two screening tools may consider the optimal property between sensitivity and specificity rather than only heavy-side of “rule-in” and “rule-out” accuracy.

Our main finding suggests the combination of cognitive testing (MMSE) and informant questionnaire (AD8) increased the sensitivity with parallel mode and increased the specificity with the serial mode. If we put emphasis on “rule-in accuracy” the parallel test in dementia community screening to improve diagnosis accuracy would be suggested. If we put emphasis on “rule-out accuracy” the serial test in dementia community screening to improve diagnosis accuracy would be suggested. However, the optimal accuracy between “rule-in” and “rule-out” principle is uncertain and had better be determined by economic appraisal, which is the main objective of the third part.

ROC curve of AD8 and MMSE

For the logistic regression analysis, our results were comparable to those of Mackinnon and Mulligan[111]. The MMSE score alone was a strong and statistically significant predictor of dementia cases. The large the value for the change of AIC values, the greater the importance of a test (or combination) is attached to the prediction of clinical dementia cases in Table 4.2.9. Adding the AD8 results in a further statistically significant improvement in case prediction. This is further evidence that these two tests provide somewhat different and additive information in screening for dementia.

Prevalence of dementia in community-based study

The prevalence of dementia order than 65 years by clinical diagnosis was 9.29% in community-based study. The result was similar to the result of nationwide survey of Taiwan[96]. The prevalence of MCI was 30.4%.

The prevalence of dementia order than 65 years by clinical diagnosis was 9.29% in community-based study. The result was similar to the result of nationwide survey of Taiwan[96]. The prevalence of MCI was 30.4%.

5.2.3 Cost- effectiveness analysis of community-based dementia screening

Community- based dementia screening may be one method that can be used to achieve earlier detection and earlier initiation of therapy with consequent reduced time spent in more costly treatments and care for severe dementia. The cost of dementia care places a significant financial burden on both family and society in general. However, it is possible that more effective treatments may be developed in the future for dementia. Our results suggest that community based dementia screening can gain a substantial effectiveness due to earlier detection and treatment compared to routine medical care in the absence of screening.

Overall, our community based dementia screening program met the criteria described by Cadman et al. in 1984[80] for an effective community disease screening program[80] and demonstrated a benefit of 0.0065 QALYS for dementia screening related over a ten-year period in Markov model simulations compared to standard treatment with no community based screening.

The increased costs associated with dementia screening in first years may be attributed to greater rates of detection and treatment of mild dementia during those years compared to care without screening. Similarly, the cost savings that occurred

during years 8 through 10 were attributed to decreased costs for care of individuals in moderate and severe dementia states with community based dementia screening compared to no screening. We employed the GDP per capita of Taiwan in 2014 ($22518) as a threshold of cost per QALY gained in the base-case analysis.

We believe the majority of the effectiveness results from decreased need for care-giver support, by decreasing the duration spent in more severe disease stages which require large of caregiver support compared to less severe disease stages.

The potential benefit by community based dementia screening identified in our study are dependent on the detection of a sufficient number of previously undiagnosed cognitively impaired individuals. In our study we identified new and previously undiagnosed MCI and very early dementia.

This rate of detection of previously undiagnosed individuals is in good agreement with previously reported detection rates for community based screening programs which have ranged from 9%-14%[59, 112].

The effect of community based dementia screening on the early diagnosis of Alzheimer's disease has also been demonstrated by Barker et al. in 2005[90]. The study showed that subjects with Alzheimer's disease who were referred from a memory screening program presented with higher mean MMSE scores and shorter durations of illness than those referred by physicians or family members.

Community-based dementia screening can reduce healthcare costs associated with caring for demented individuals through earlier detection and treatment, resulting in proportionately reduced time in more costly advanced stages[27]. Saito et al. demonstrated 9.8% reduction in cost of dementia care over a ten-year period, primarily through increased duration in mild stages and reduced time in more costly moderate and severe stages[27].

In the base-case result, the expected incremental QALY per screened person over 65 years was 0.0009, which was much smaller than the result of a previous study in UK[113] (0.193). This can be explained by differences in patients' characteristics between the two studies. First, while the previous study evaluated cost-effectiveness for early assessments of high-risk individuals presenting with subjective memory complaints, the subjects in this study were individuals over 65 years who participated voluntarily in a program to evaluate their cognition. Second, our study included an empirical cohort of dementia patients to run the cost- effectiveness model. This cohort consisted of 71.67% in a normal state, 16.04% in a MCI state, 5.88% in a mild state, 1.13% in a moderate state, and 1.13% in a severe state according to the nationwide dementia screening program findings. Third, we assumed that all dementia patients who were diagnosed by the program started treatment with donepezil

Compared with NDEDP study in Korea, the cost per QALY gained ranged from

$24,150 to $35,661 depending on the age group. (over 65, over 70, over 75, over 80). The ICER over 65 group in NDEDP study is $35,661 which was different from our near cost-saving results. The reason accounting for the disparity between the two studies is that our cost-effectiveness of community-based organized screening targeted to all the subjects in the underlying community but the Korean study was based on opportunistic screening. It would be expected that if the screening rate was reduced to the level of opportunistic screening at 30% screening rate the results would be similar.

5.3 Methodological development

5.3.1 The P/I-ratio-based regression model

This is the first time to develop a P/I-ratio-based statistical regression model to estimate the adjusted P/I ratio for the reflection of awareness and the quality of care for dementia with adjustment for age, gender, and geographic variation. This method considers the effect of covariates affecting not only prevalence assuming binomial distribution but also incidence assuming Poisson distribution. The application this model is also very useful for estimating the degree of enhancement in detection of disease when the active method is compared with the passive method.

5.3.2 Meta-analysis with Bayesian estimation

In addition to our empirical study on community-based screening for dementia

with AD8 and MMSE, we successfully applied the Bayesian analysis for estimation of sensitivity and specificity of screening tests in the absence of gold standard diagnosis of dementia to complete a meta-analysis. This study has demonstrated that it is possible to achieve a significant improvement in the community dementia screening by combination a cognitive status (MMSE) with an informant (AD8).

The estimated AD8 sensitivity (84.1%) in our study was higher than K-AD8 study (sensitivity=68%) in Korea, but the estimated specificity (77.1%) was lower than K-AD8 study (specificity=90%) in Korea[55]. The estimated AD8 sensitivity (84.1%) in our study is higher than study (sensitivity=74%) in America, but the estimated specificity (77.1%) is lower than study (specificity=86%) in America[25].

The results for sensitivity, specificity and positive and negative predictive value in dementia screening suggest that the combination use of AD8 or MMSE (parallel test) had higher estimated sensitivity (97.2%) than either MMSE (82.2%) or AD8(84.1%) alone . Besides, the combination use of AD8 with MMSE (Serial tests) had higher estimated specificity (96.8 %) than AD8 (76.7%) or MMSE (86.1%) alone.

5.3.3 Probability cost-effectiveness analysis

We developed a stochastic rather than deterministic Markov cycle decision model for the comparison of various screening modalities compared with no screening but also multiple screening modalities versus single modality. This model is

very flexible in the modification of the relevant parameters for further analysis. Other merits of our model included the following points. First, we successfully used transition probabilities and efficacy derived from Taiwan and other countries published before. Doing so renders the results of cost-effectiveness analysis credible. Second, our analysis considers the impact of treatment on the caregivers of dementia patients. Third, the assignment of statistical distribution to each parameter makes the cost-effectiveness analysis to capture the first-order and second-order property of uncertainty of the parameters of interest.

5.4. Limitations

5.4.1 The P/I ratio study

The data used in this study is derived from NHI claims data. It could be argued that the ICD coding would be less accurate than that of a conventional neurologic survey. There are third justifications for using the NHI data set to estimate the prevalence and incidence of dementia. First, the neurologists are scattered in clinics across Taiwan as well as being based in medical centers or hospitals and our Health insurance system encourages people with dementia to have regular clinical visits to their neurologist. The disease is either managed directly by a neurologist or indirectly following referral by other physicians. Second, there are up to three ICD codes independently recorded for each individual claim (including comorbidity) were

collected, the accuracy of our method for identifying cases was enhanced. For example, for a patient with chronic dementia with DM and hypertension, the three ICD codes would be recorded as 331.0, 401, and 250 when the consultation was related to dementia and as 250, 401, and 290.40 when it was related to diabetes. To be identified as a patient with dementia, a patient had to make at least two claims where one of the three ICD codes was 290, 290.40, and 331.0. Third, the accuracy of claim codes is regularly checked by audit committees formed of experts and located in each of six regions of Taiwan. Typically, each committee selects a random sample of medical records to review to verify the accuracy of claim data.

5.4.2 Limitation of community-based dementia screening

The limitation of our study was that it was not based on a random sample from the whole population but limited to one rural township the application of our results to external population should be taken with great caution. In addition, our sample was based on Taiwanese people, it is unknown whether these results can be generalized to other racial groups. Furthermore, there are several potential barriers to the implementation of community based dementia screening including the use of physician screeners and the lack of voluntary participation of seniors.

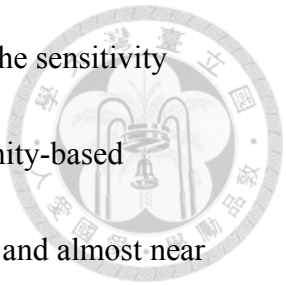
5.4.3 Limitation of cost-effectiveness analysis

The major limitation of our cost-effectiveness analysis is that there are lacking

empirical data derived from Taiwan to support the adequacy of the relevant parameters. These include cost, particularly indirect cost on health care giver, utility of the severity of dementia, survival by different stages of dementia, and the transition probabilities used in the Markov model simulations. Moreover, the proposed Markov cycle decision tree model has not yet validated by using the external data, which should be considered in the future.

5.5 Conclusion

As there is an increasing trend in rates of dementia when aging population has been increasing but awareness is low, considering an effective and efficient community based dementia screening programs is of paramount important. This has been upheld by the current findings on low awareness of dementia has been ascertained in routine health insurance health care system as the P/I ratio of community-based survey (active detection method) was greater than that of health insurance heath care system (passive detection method). The results regarding the validity of the accuracy in the early diagnosis of AD8 and MMSE shows AD8 had higher sensitivity but lower specificity in detection of dementia than MMSE when both tools were considered in population- and community-based screening. The optimal sensitivity and specificity of MMSE could be achieved using the optimal cut-off based on empirical data. Compared with the use of AD8 or MMSE alone, the



combination of AD8 with MMSE with the parallel mode enhanced the sensitivity whereas that with the serial mode enhanced the specificity. Community-based screening for dementia with AD8 and MMSE is more cost-effective and almost near cost-saving compared with no screening program. The most economic screening strategy is the parallel mode of combining AD8 with MMSE. There are two three novelty of the methodological development including (1) a P/I-ratio-based regression model under the framework of generalized linear regression model to estimate the P/I ratio of active detection method in comparison with that of passive detection method after controlling for confounding factors; (2) the application of Bayesian model for multiple detection modalities in the absence of gold standard for estimating posterior distributions of sensitivity and specificity by combing prior information on the use of AD8 and MMSE with the likelihood based on the current empirical data; and (3) the development Markov cycle decision tree model for economic evaluation of population-based screening program AD8 in combination with MMSE.

Table 3.2.1 Distribution assigned for parameters in probabilistic cost-utility analysis

Parameters	Base case estimate	Distribution
Prevalence[90]		
Mild dementia	5.88%	
Moderate dementia	1.13%	
Severe dementia	1.13%	
Screening Interval	Every 5 year	
AD8		
Sensitivity	84.1%	Beta(14.3, 2.7)
Specificity	77.1	Beta(128.0, 38.0)
MMSE		
Sensitivity	82.2%	Beta(14.8, 3.2)
Specificity	86.1%	Beta(142.9, 23.1)
Parallel Test		
Sensitivity	97.2%	Beta(18.5, 0.5)
Specificity	66.4%	Beta(110.2, 55.8)
Sequential Test		
Sensitivity	69.1%	Beta(13.8, 6.2)
Specificity	96.8%	Beta(160.7, 5.3)

Parameters	Base case estimate	Distribution
Transition probability[2]		
(Nature history)		
Normal to mild[114]	0.047	
Mild to moderate	0.25387	
Mild to severe	0.0774	
Mild to death	0.021	
Moderate to mild	0.09773	
Moderate to severe	0.44886	
Moderate to death	0.053	
Severe to death	0.153	
Transition probability[2, 115]		
(Post treatment)		
Normal to mild[2, 114]	0.047	
Mild to moderate	0.22054	
Mild to severe	0.0774	
Mild to death	0.021	
Moderate to mild	0.09773	
Moderate to severe	0.2467	

Parameters	Base case estimate	Distribution
Moderate to death	0.053	
Severe to death	0.153	
Costs[116]		
Medical cost of mild*	1,418	Triangular (706, 1418, 2836)
Care cost of mild*	11,644	Triangular (5822, 11644, 23288)
Medical cost of moderate*	1,765	Triangular (883, 1765, 3530)
Care cost of moderate*	23,626	Triangular (11813, 23626, 47252)
Medical cost of severe*	2,113	Triangular (1056, 2113, 4226)
Care cost of severe*	37,262	Triangular (18613, 37262, 74524)
Screening Cost		
AD8	11.87	
MMSE	10.68	
Parallel	12.42	
Sequential	10.97	
QALY[97]		
Mild	0.68	Beta (26.98, 12.69)
Moderate	0.54	Beta (24.45, 20.83)

Parameters	Base case estimate	Distribution
Severe	0.37	Beta (8.84, 15.06)

*All cost were in USD

Table 4.1.1: Age and gender specific prevalence and incidence rate of dementia

Gender	Age	Prevalent Case	Total Population	Prevalence %	Incident case	Person years	Incidence %	P/I[#] ratio
Male	65-69	2620	333391	0.79	5757	983219	0.59	1.34
	70-74	4247	326658	1.3	10349	948879	1.09	1.19
	75-79	6000	205981	2.91	13622	575801	2.37	1.23
	80-84	6564	94920	6.92	11009	248459	4.43	1.56
	85-89	5041	38710	13.02	6279	93985	6.68	1.95
	90+	3445	11363	30.32	2278	23246	9.8	3.09
Subtotal		27917	1011023	2.76	49774	2873587	1.73	1.6
Female	65-69	2850	325651	0.88	5803	960760	0.6	1.47
	70-74	5203	255964	2.03	8976	742221	1.21	1.68
	75-79	7198	172188	4.18	11695	481181	2.43	1.72
	80-84	6481	93801	6.91	11098	245000	4.53	1.53
	85-89	4101	45555	9	7730	109449	7.06	1.27
	90+	2132	17126	12.45	4563	33389	13.67	0.91
Subtotal		27965	910285	3.07	49865	2571999	1.94	1.58
All	65-69	5470	659042	0.83	11560	1943978	0.59	1.41
	70-74	9450	582622	1.62	19325	1691100	1.14	1.42
	75-79	13198	378169	3.49	25317	1056982	2.4	1.45
	80-84	13045	188721	6.91	22107	493459	4.48	1.54
	85-89	9142	84265	10.85	14009	203434	6.89	1.57
	90+	5577	28489	19.58	7291	56635	12.87	1.52
Total		55882	1921308	2.91	99609	5445586	1.83	1.59
Active Survey Data								
	65-79	11	135	8.15*	56202	4692060	1.2	6.79
	80-90+	6	51	11.76*	43407	753528	5.76	2.04
	total	17	183	9.29*	99609	5445586	1.83	6.59

[#]P/I ratio= prevalence/incidence ratio

*Prevalence was estimated from other active survey study

Table 4.1.2 Effects of Age, gender, geographic on the risk of incidence rate of dementia by Poisson regression model

Variable	Univariate		Multivariate	
	RR (95%CI)	P-value	RR (95%CI)	P-value
Age		<.0001		<.0001
65-69	1.00		1.00	
70-74	1.02 (0.99-1.04)		1.01(0.99-1.04)	
75-79	1.03 (1.01-1.06)		1.03(1.01-1.05)	
80-84	1.05 (1.03-1.08)		1.05(1.03-1.07)	
85-89	1.09 (1.06-1.12)		1.09(1.06-1.12)	
90+	1.14(1.11-1.18)		1.14(1.11-1.18)	
Gender	1.01 (1.00-1.02)	0.2003	1.01(1.00-1.03)	0.0450
Area		0.0057		0.0146
Central	1.00		1.00	
North	1.02(1.00-1.04)		1.01(1.00-1.04)	
South	1.00(0.98-1.01)		0.99(0.98-1.02)	
East	1.03(0.99-1.07)		1.02(0.97-1.06)	

Table 4.1.3 Adjusted P/I ratios of dementia measured by passive survey

Variables	Regression Coefficient (2.5%-97.5%)	Adjusted P/I ratios (2.5%-97.5%)
Male		
Intercept	0.197(0.145-0.248)	
Age		
65-69	baseline	1.35(1.29-1.41)
70-74	-0.12(-0.176-0.063)	1.20(1.15-1.24)
75-79	-0.091(-0.145-0.037)	1.23(1.19-1.27)
80-84	0.141(0.087-0.195)	1.55(1.51-1.60)
85-89	0.36(0.304-0.417)	1.93(1.86-2.00)
90+	0.886(0.823-0.949)	3.27(3.13-3.41)
Area		
Central	baseline	1.20(1.17-1.24)
North	0.186(0.15-0.222)	1.45(1.41-1.49)
South	0.096(0.056-0.136)	1.32(1.29-1.37)
East	-0.322(-0.417-0.228)	0.87(0.80-0.96)
Female		
Intercept	0.251(0.2-0.302)	
Age		
65-69	baseline	1.47(1.41-1.54)
70-74	0.137(0.082-0.191)	1.69(1.63-1.74)
75-79	0.152(0.1-0.205)	1.71(1.66-1.76)
80-84	0.032(-0.021-0.085)	1.52(1.47-1.57)
85-89	-0.148(-0.204-0.091)	1.27(1.22-1.32)
90+	-0.492(-0.557-0.428)	0.90(0.86-0.94)
Area		
Central	baseline	1.37(1.32-1.41)
North	0.211(0.175-0.247)	1.69(1.64-1.73)
South	0.025(-0.015-0.066)	1.40(1.60-1.44)
East	0.889(0.807-0.97)	3.32(3.07-3.59)

Table 4.1.4 Adjusted P/I ratios of dementia in comparison between passive and active survey

Variables	Regression Coefficient (2.5%-97.5%)	Adjusted P/I ratios (2.5%-97.5%)
Intercept	0.252(0.220-0.283)	
Age 65-79 vs. Age 80+	0.120(0.100-0.140)	
Active Survey vs. Passive Survey	1.071(0.614-1.53)	
Passive Survey		
Age 65-79		1.45(1.43-1.47)
Age 80+		1.64(1.61-1.66)
Active Survey		
Age 65-79		4.23(2.68-6.69)
Age 80+		4.77(3.02-7.54)

Table 4.1.5 The incidence rate (per 1000 person years) of dementia by gender

Area	Age Range	Male	Female	All
Taiwan	**65+**	17.3	19.4	18.3
Japan [102]	**65+**	19.3	20.9	20.0
European [40]	**65+**	14.4	21.3	18.4
Sweden [103]	**75+**	22.9	45.7	40.0
Spain [105]	**65+**	10.8	14.3	12.8
Italy [104]	**65-84**	12.9	13.8	13.3
USA [106]	**65+**	19.2	21.0	20.3

Table 4.1.6 The Age-standardized incidence rate of dementia (per 1000 person years) in European, Sweden, Spain, Italy, USA, and Taiwan

Country	Age Range	Incidence rate	Age-standardized incidence rate
Taiwan	**65+**	18.3	17.5
European [40]	**65+**	18.4	13.1
Sweden [103]	**75+**	40.0	33.8
Spain [105]	**65+**	12.8	10.2
Italy [104]	**65-84**	13.3	11.5
USA [106]	**65+**	20.3	14.6

Table 4.1.7 Prevalence, incidence, and ratio of dementia in Taiwan and other community-based studies

Countries	Age Range	Study type	Area	Prevalence %	Incidence %	P/I Ratio
Taiwan (NHI)	65+	cohort	Rural/urban	2.91	1.83	1.59
Taiwan (Active survey)	65+	screening	Rural	9.29	1.83	5.08
Taiwan(Chen)[117]	65+	screening	Rural/urban	10.55	1.83	5.77
Taiwan(Sun)[96]	65+	screening	Rural/urban	8.14	1.83	4.45
Denmark [101]	65-84	cohort	Urban	7.10	2.95	2.40
Japan[102]	65+	cohort	subrural	8.50	2.00	4.25
China[30]	65+	screening	Urban	6.19	0.99	6.25
Sweden[103]	75+	cohort	Urban	19.3	4.00	4.83
Italy[104]	65-84	cohort	Rural/urban	8.00	1.25	6.40
Spain[105]	65+	cohort	Rural/urban	5.79	1.06	5.47
USA[106]	65+	cohort	Urban	9.60	2.03	4.73

Table 4.2.1 Demographic characteristics and average scores in AD8 and MMSE tests of 282 samples in dementia screening program

Characteristic	Numbers	Percentage(%)	AD8	MMSE
50-59	60	21.28	0.17±0.59	27.91±2.20
60-69	82	28.72	0.28±0.64	25.39±3.84
70-79	90	31.91	0.78±1.24	21.89±4.15
80+	52	18.09	1.10±1.50	20.51±4.88
Gender				
Male	144	51.06	0.59±1.23	22.59±5.06
Female	138	48.94	0.54±1.06	25.23±3.99
Education level				
Illiteracy	84	29.79	0.83±1.31	19.77±3.90
< 6 years	123	43.62	0.56±1.09	24.02±3.90
>6 years	75	26.60	0.22±0.65	28.43±1.66

Table 4.2.2 The findings of AD8, MMSE and clinical diagnosis

Characteristic	Numbers	%	Clinical diagnosis		
			Normal N=174	MCI N =84	Dementia N=18
AD8					
Normal(<2)	235	84.2	156 (90.7%)	69(82.1%)	6(35.3%)
Abnormal(≥2)	44	15.7	16(9.3%)	15(17.9%)	11(64.7%)
MMSE*					
Normal	231	82.5	152(87.4%)	66(78.6%	10(58.8%)
Abnormal	49	17.5	22(12.6%)	18(21.4%))	7(41.2%)
AD8 or MMSE*					
Normal	203	73.1	140(80.5%)	58(69.1%)	5(27.8%)
Abnormal	73	26.9	34(19.5%)	26(30.9%)	13(72.2%)
AD8 and MMSE*					
Normal	260	94.2	170(97.7%)	77(91.7%)	13(72.2%)
Abnormal	16	5.8	4(2.3%)	7(8.3%)	5(27.8%)
MMSE**					
Normal(>21)	198	71.7	140(80.5%)	54(64.3%)	4(22.2%)
Abnormal(≤21)	78	28.3	34(19.5%)	30(35.7%)	14(77.8%)
AD8 or MMSE**					
Normal	183	66.3	133(76.4%)	48(57.1%)	2(11.1%)
Abnormal	93	33.7	41(23.6%)	36(42.9%)	16(88.9%)
AD8 and MMSE**					
Normal	249	90.2	165(95.8%)	75(89.3%)	9(50.0%)
Abnormal	27	10.7	9(5.2%)	9(10.9%)	9(50.0%)

*with education adjustment

** With optimal cut-off score of 21

Table 4.2.3 The relationship between tests and dementia

Tests	**Pearson Correlation Coefficients**	**P-value∗**
AD8	0.27	P<0.0001
MMSE	-0.26	P=0.0004

∗P value by Pearson Correlation Coefficients

Table 4.2.4 The relationship between AD8 and MMSE

Tests	**Pearson Correlation Coefficients**	**P-value∗**
AD8 with MMSE	-0.37	P<0.0001

∗P value by Pearson Correlation Coefficients

Table 4.2.5 Performance of individual tests and the combination of tests for early detection of dementia

Tests	Sensitivity(%)	Specificity(%)	Positive predictive value(%)	Negative predictive value (%)
AD8*	64.71 (40.41-83.22)	87.89 (83.00-91.51)	26.2	97.4
MMSE (cut off=21)	77.78 (53.53-91.41)	73.58 (67.99-78.51)	16.9	97.98
MMSE(cut off=26)	94.44 (69.36-99.22)	38.26 (32.59-44.51)	9.44	99.0
MMSE** (adjust)	41.18 (21.04-64.7)	84.50 (79.39-88.51)	14.8	95.6
Parallel testing 1¥ (AD8 or MMSE#)	88.89 (64.78-97.21)	70.16 (64.30-75.51)	17.2	98.9
Parallel testing 2¥ (AD8 or MMSE#)	61.11 (37.86-80.21)	87.98 (83.42-91.5)	26.19	97.00
Parallel testing 3¥ (AD8 or MMSE#)	72.22 (48.10-87.94)	75.19 (69.56-80.51)	16.88	97.49
Serial testing (AD8 and MMSE#)	50.00 (28.42-71.58)	93.02 (89.20-95.51)	33.3	93.0

* With cut-off score of 2 ** With education adjustment # with optimal cut-off score of 21

¥

Parallel 1 positive: AD8 (+) MMSE(+) and AD8(+) MMSE(-)and AD8 (-) MMSE(+)

Parallel 2 positive: AD8 (+) MMSE (+) and AD8 (+) MMSE (-)

Parallel 3 positive: AD8 (+) MMSE (+) and AD8 (-) MMSE (+)

Table 4.2.6 Performance of individual tests and the combination of tests for early detection of memory impairment (MCI plus Dementia)

Tests	**Sensitivity(%)**	**Specificity(%)**	**Positive predictive value (%)**	**Negative predictive value (%)**
AD8*	25.74	90.70	61.9	67.5
MMSE**	24.75	87.36	53.2	66.7
AD8 or MMSE**	38.24	80.46	53.4	68.9
AD8 and MMSE**	11.8	97.70	75.0	65.4
MMSE#	43.14	80.46	56.4	70.7
AD8 or MMSE#	50.98	76.44	55.9	72.7
AD8 and MMSE#	17.7	94.8	66.7	66.3

* with cut-off score of 2

** with education adjustment

with optimal cut-off score of 21

Table 4.2.7 Performance of individual tests and the combination of tests for early detection of mild impairment impairment (MCI)

Tests	**Sensitivity(%)**	**Specificity(%)**	**Positive predictive value(%)**	**Negative predictive value (%)**
AD8*	17.86	90.80	48.39	69.60
	(11.06-27.54)	(85.51-94.29)		
MMSE (cut off=21)	35.71	80.46	46.88	72.16
	(26.22-46.46)	(73.90-85.69)		
MMSE(cut off=26)	79.76	48.28	42.68	83.17
	(69.82-87.03)	(40.95-55.69)		
MMSE** (adjust)	21.43	87.36	45	69.72
	(13.94-31.47)	(81.55-91.53)		
Parallel testing 1¥ (AD8 or MMSE#)	42.86	76.44	46.75	73.48
	(32.75-53.61)	(69.57-82.16)		
Parallel testing 2¥ (AD8 or MMSE#)	17.86	90.80	48.39	69.60
	(11.06-27.54)	(85.51-94.29)		
Parallel testing 3¥ (AD8 or MMSE#)	35.71	80.46	46.88	72.16
	(26.22-46.46)	(73.90-85.69)		
Serial testing (AD8 and MMSE#)	10.71	94.83	50	68.75
	(05.67-19.32)	(90.36-97.29)		

* With cut-off score of 2 ** With education adjustment # with optimal cut-off score of 21

¥

Parallel 1 positive: AD8 (+) MMSE (+) and AD8 (+) MMSE (-) and AD8 (-) MMSE (+)

Parallel 2 positive: AD8 (+) MMSE (+) and AD8 (+) MMSE (-)

Parallel 3 positive: AD8 (+) MMSE (+) and AD8 (-) MMSE (+)

Table 4.2.8 Bayesian analysis in prevalence estimation and screening test evaluation in the absence of a gold-standard test

Outcome Tests	**Prior Prevalcne**	**Prior Probability**	**Estimated Prevalence (95%CI)**	**Estimated Sensitivity (95%CI)**	**Esitmated Specificity (95%CI)**
Dementia					
AD8	Beta(18, 264)	Sen~Beta(105,19)[20]	4.8%	84.1%	77.1%
		Spe~Beta(114,66) [20]	(3.0%-7.3%)	(76.9%-90.0%)	(72.9 %-81.0%)
MMSE	Beta(18, 264)	Sen~Beta(2205,479)[23]	6.1%	82.2%	86.1%
		Spe~Beta(20100,3235) [23]	(3.9%-8.9%)	(80.7%-83.6%)	(85.7%-86.6%)
Parallel testing	Beta(18, 264)	Sen~Beta(105,19) [20]		97.2%	66.4%
		Spe~Beta(114,66) [20]	4.9%	(95.8%-98.2%)	(62.8%-69.7%)
Serial testing	Beta(18, 264)	Sen~Beta(2205,479) [23]	(3.0%-7.2%)	69.1%	96.8%
		Spe~Beta(20100,3235) [23]		(63.0%-74.0%)	(96.2%-97.4%)
Memory Impairment					
AD8	Non-informatic prior	Sen~Beta(155,37) [23]	5.0%	80.7%	87.1%
		Spe~Beta(96,16) [23]	(2.8%-13.6%)	(74.9%-85.9%)	(82.4%-91.8%)
MMSE		Sen~Beta(298,177) [23]	2.6%	62.6%	64.8%
		Spe~Beta(875,505) [23]	(0.09%-12.3%)	(58.2%-66.9%)	(62.5%-67.2%)
Parallel testing		Sen~Beta(155,37) [23]		92.8%	55.8%
		Spe~Beta(96,16) [23]	2.4%	(90.4%-94.8%)	(52.3%-59.2%)
Serial testing		Sen~Beta(2205,479) [23]	(0.09%-9.1%)	50.5%	95.1%
		Spe~Beta(20100,3235)[23]		(45.6%-55.3%)	(93.5%-96.6%)

Table 4.2.9 Logistic regression of clinical diagnosis dementia status against MMSE and AD8 for sample (n=282)

Variable	-2logL	AIC	P
None	133.88	133.88	
MMSE	110.35	114.35	<0.0001
AD8	114.95	118.95	<0.0001
Education	125.76	129.76	0.0044
MMSE+AD8	105.38	111.38	0.0258
MMSE + education	110.24	116.24	0.7401
AD8+Education	110.84	116.84	0.0426
MMSE+AD8+education	105.14	113.14	0.8869
MMSE+AD8+MMSE*AD8+Education	103.04	113.04	0.1473

Table 4.2.10 Effects of MMSE, AD8, Age, gender and education, on the risk of dementia by Logistic regression model (Univariate analysis)

Variable	Regression coefficient	Standard Error	OR	95%CI	Wald Chi-Square	P-Value
AD8	0.6067	0.1618	1.834	1.336- 2.519	14.0518	0.0002
MMSE	-0.2187	0.0553	0.804	0.721-0.896	15.6480	<.0001
Education	-1.4138	0.5027	0.243	0.091-0.651	7.9099	0.0049
Gender	-0.2838	0.490	0.75	0.288-1.967	0.3353	0.5626
Age	0.1104	0.0328	1.117	1.047-1.191	11.3194	0.0008

Table 4.2.11 Effects of MMSE, AD8, and other risk factor on dementia by Logistic regression model (Multivariate analysis, model 1-3)

Variable	Regression coefficient	Standard Error	OR	95%CI	P-Value
Model 1					
Intercept	0.639	1.29			0.62
AD8	0.413	0.18	1.51	1.05-2.17	0.025
MMSE	0.174	0.06	0.84	0.75-0.94	0.003
Model 2					
Intercept	0.459	1.34			0.733
AD8	0.421	0.18	1.52	1.06- 2.19	0.023
MMSE	-0.158	0.07	0.85	0.75-0.97	0.019
Education	-0.299	0.62	0.74	0.22-2.48	0.628
Model 3					
Intercept	1.816	1.62			0.262
AD8	-0.514	0.66	1.43	0.98-0.67	0.433
MMSE	-0.226	0.08	0.89	0.77-1.03	0.007
Education	-0.295	0.61	0.86	0.25-2.89	0.137
Age	0.06	0.04	1.06	0.98-1.15	0.153
Gender	0.094	0.6	1.1	0.34-3.59	0.876

Table 4.3.1 The distribution of simulated cohort of dementia by stage and death in the end of simulation (year 10)

Screening strategy	Status at year 10					RR	
	Normal	Mild	Moderate	Severe	Death	Severe	Death
No Screen	0.4591	0.0875	0.0414	0.1310	0.2809	1.0000	1.0000
AD8	0.4591	0.0978	0.0618	0.1133	0.2680	0.8646	0.9540
MMSE	0.4591	0.0976	0.0614	0.1136	0.2683	0.8674	0.9549
Parallel test	0.4591	0.0993	0.0647	0.1108	0.2661	0.8457	0.9472
Serial test	0.4591	0.0960	0.0584	0.1162	0.2702	0.8871	0.9618

Table 4.3.2 Cost-utility analysis for different screening strategies compared with no screening over 10-year span, considering both direct and indirect cost

Strategy	Cost ($US)	Incremental Costs	QALY	Incremental QALYs	ICUR[c]
No Screen	46285.9 (33488.6, 62241.8)	(Reference)	6.0847 (6.0068, 6.1709)	(Reference)	(Reference)
AD8	44683.5 (32014.7, 58746.3)	-1602.4	6.1286 (6.0480, 6.2104)	0.0439	-36505.7
MMSE	44719.9 (32353.5 ,58886.6)	-1566.1	6.1276 (6.0502, 6.2103)	0.0429	-36466.4
Parallel test	44450.0 (31836.3, 58397.6)	-1836.0	6.1351 (6.0575, 6.2179)	0.0505	-36377.1
Serial test	44960.2 (32231.3, 59492.7)	-1325.7	6.1209 (6.0391, 6.2068)	0.0363	-36543.1

a ICUR: incremental cost-utility ratio

Table 4.3.3 Cost-utility analysis for different screening strategies compared with no screening over 10-year span, considering direct cost only

Strategy	Cost ($US)	Incremental Costs	QALY	Incremental QALYs	ICUR[a]
No Screen	3264.3	(Reference)	6.0847	(Reference)	
	(2300.1, 4368.4)		(6.0068, 6.1709)		
AD8	3281.9	17.6	6.1286	0.0439	401.4
	(2335.5, 4346.9)		(6.0480, 6.2104)		
MMSE	3283.9	19.7	6.1276	0.0429	457.7
	(2343.2, 4347.6)		(6.0502, 6.2103)		
Parallel test	3284.9	20.7	6.1351	0.0505	409.8
	(2334.4, 4340.2)		(6.0575, 6.2179)		
Serial	3282.4	18.1	6.1209	0.0363	499.2
	(2335.7, 4346.6)		(6.0391, 6.2068)		

ICUR[a]: incremental cost-utility ratio

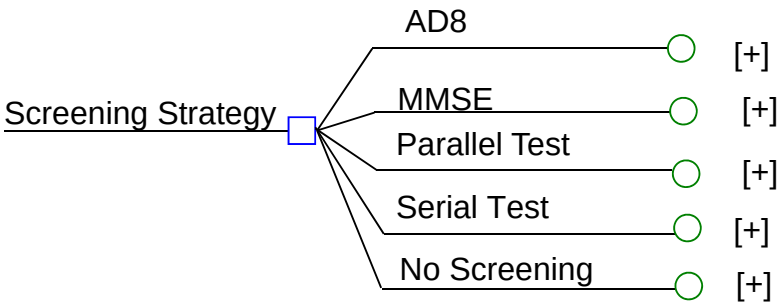


Figure 3.2.1 Strategies for community-based dementia screening

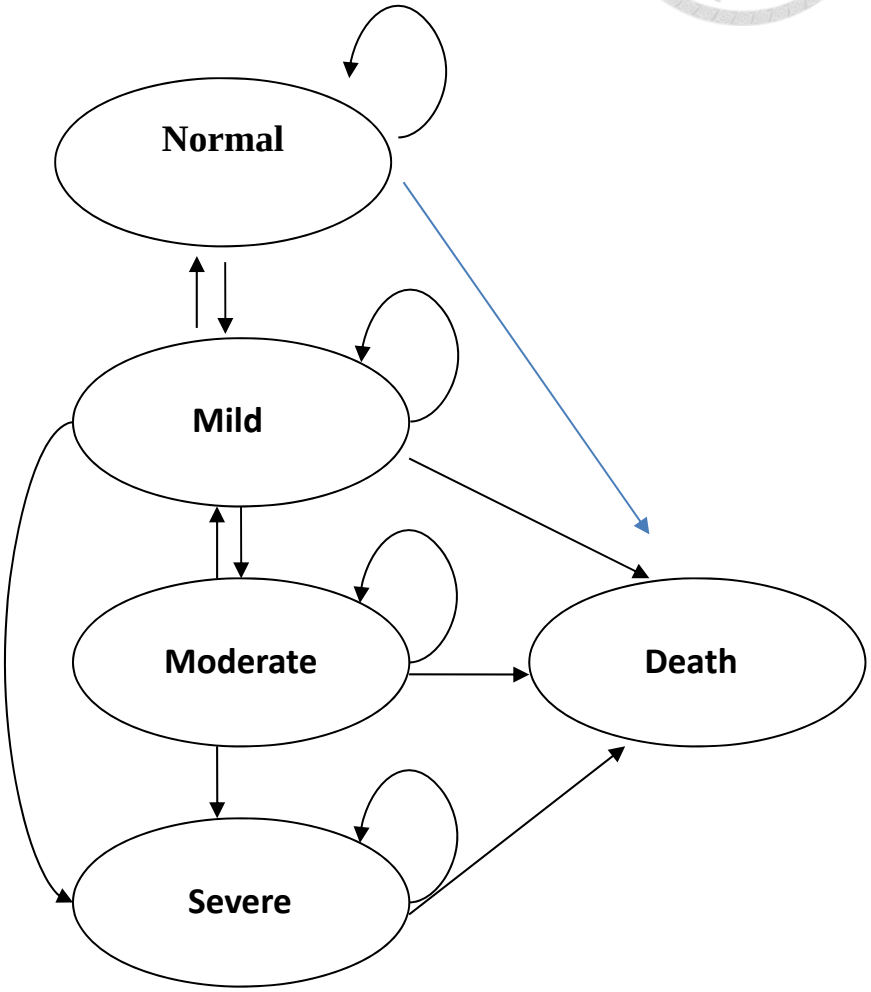


Figure 3.2.2 Five-state model for dementia progression for cost-effectiveness analysis

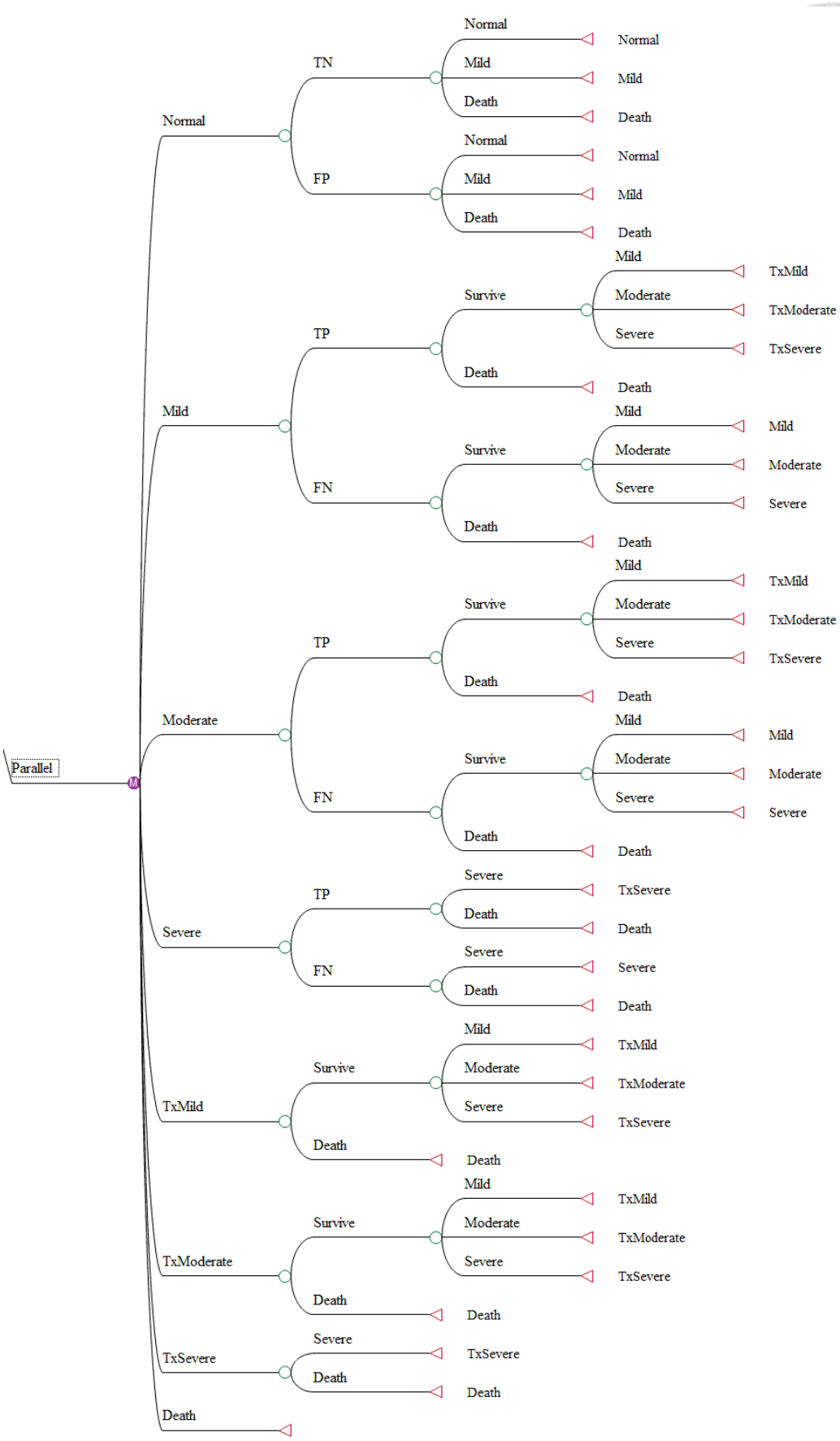
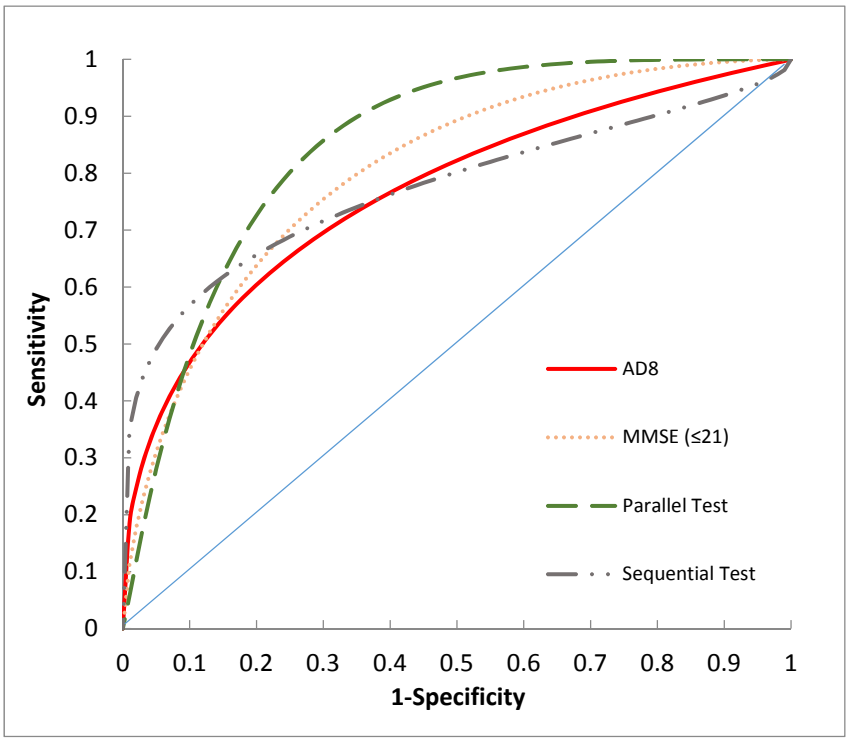


Figure 3.2.3 Markov decision tree with dementia screening program using Parallel Test



AUC of AD8: 73.3 (60.7-85.9)
AUC of MMSE (≤21): 77.4 (67.6-87.3)
AUC of Parallel Test: 82.3 (75.1-89.4)
AUC of Sequential Test: 67.6 (53.4-81.8)

Figure 4.2.1 ROC curve of AD8, MMSE and parallel test

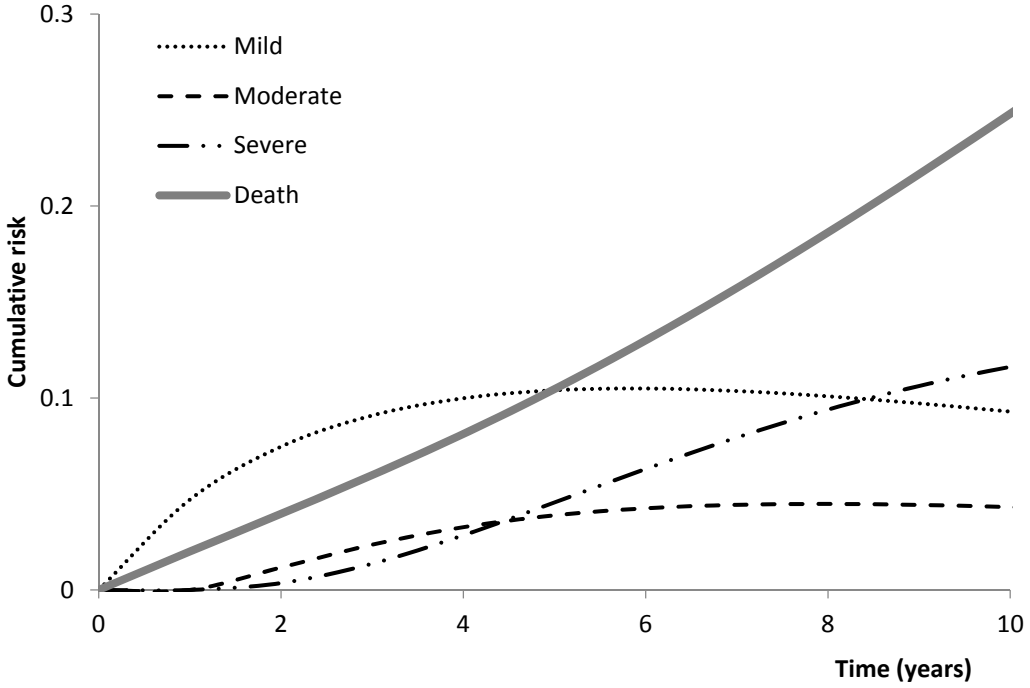
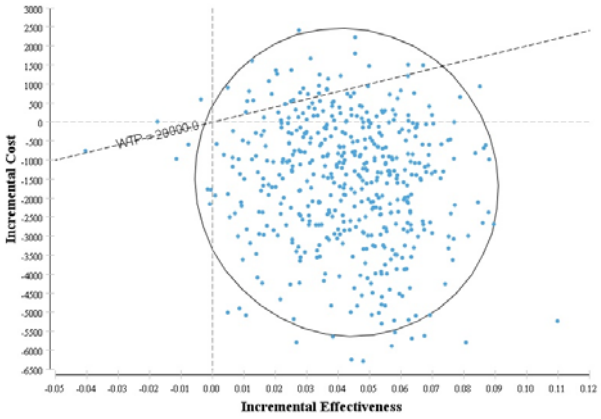


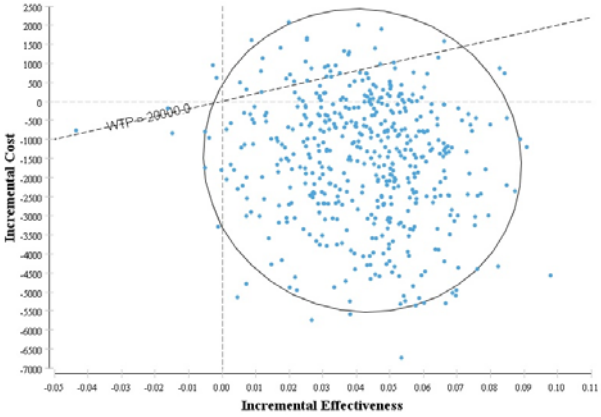
Figure 4.3.1 Distribution of disease status of dementia by stage and death by time in a naïve cohort

(a) AD8 vs no screening



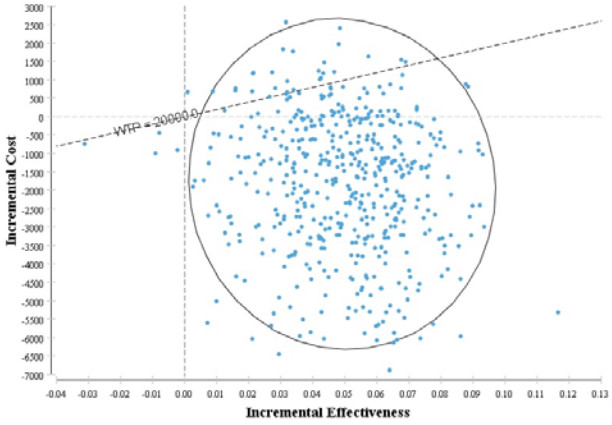
* AD8 was 92.2% being cost-effective over no screening

(b) MMSE vs no screening



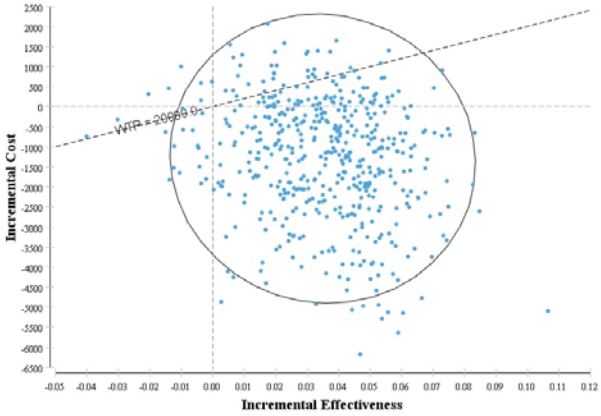
* MMSE was 92% being cost-effective over no screening

(c) Parallel test vs no screening



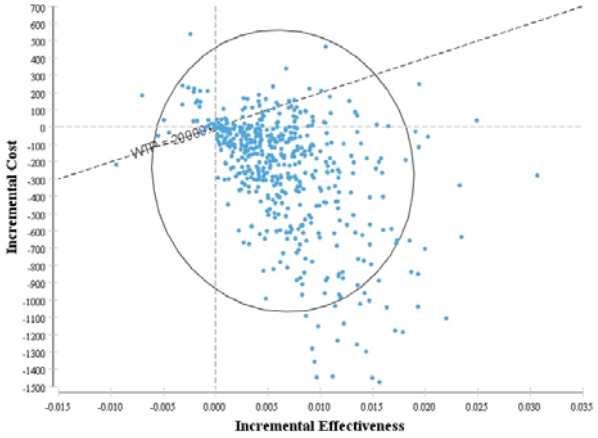
* Parallel test was 93.8% being cost-effective over no screening

(d) Serial test vs no screening



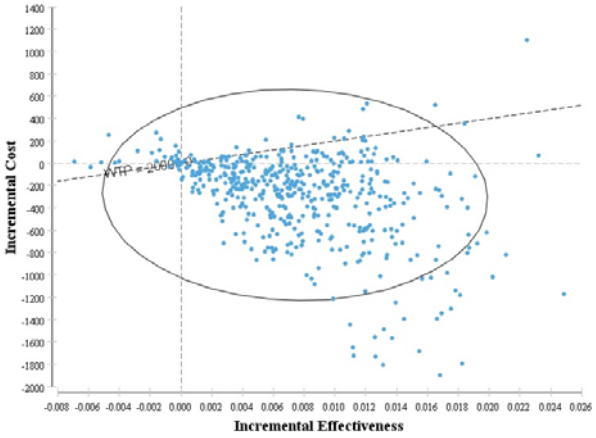
* Sequential test was 88.6% being cost-effective over no screening

(e) Parallel test vs AD8



* Parallel test was 88.8% being cost-effective over AD8

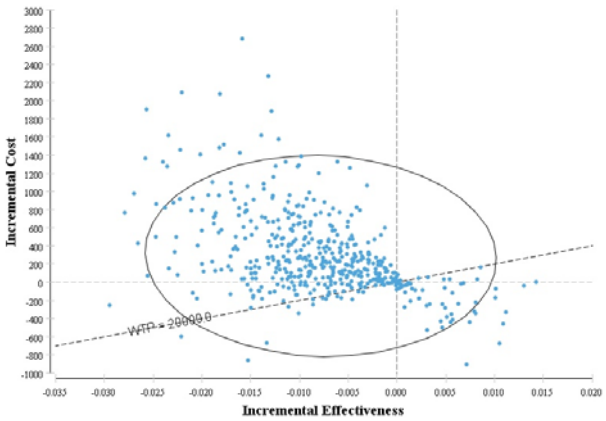
(f) Parallel test vs MMSE



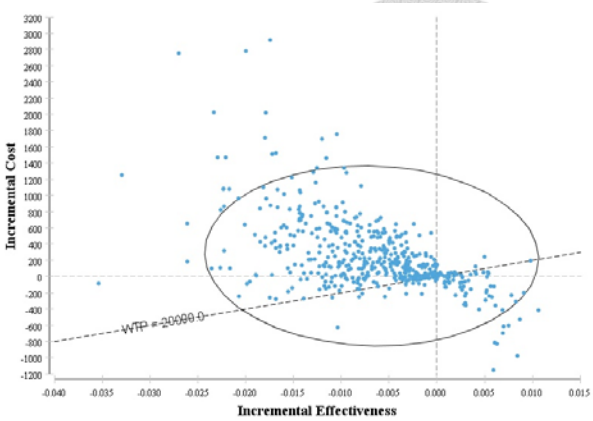
* Parallel test was 90.0% being cost-effective over MMSE

(g) Serial test vs AD8

(h) Serial test vs MMSE



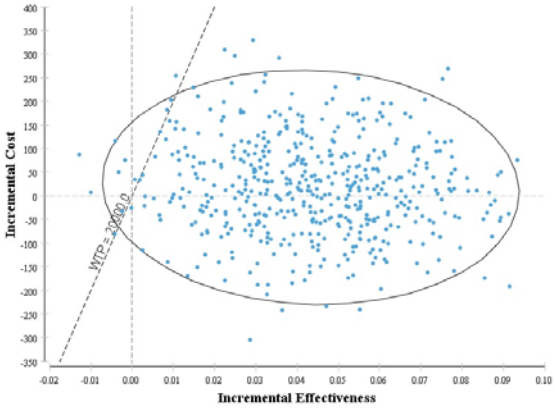
* Serial test was 11.4% being cost-effective over AD8



* Serial test was 12.8% being cost-effective over MMSE

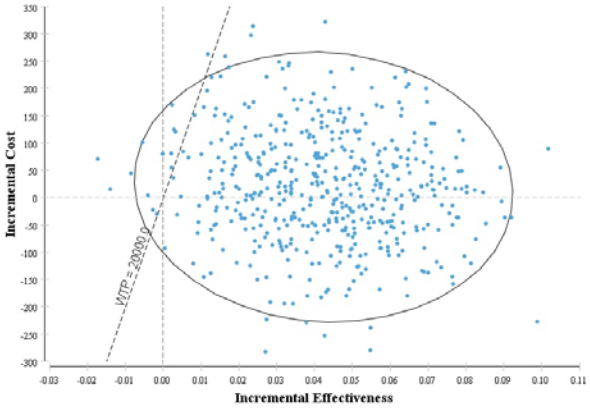
Figure 4.3.2 Scattered incremental cost-effectiveness analysis for different screening strategies for dementia compared with no screening over 10-year span, considering both direct and indirect cost

(a) AD8 vs no screening



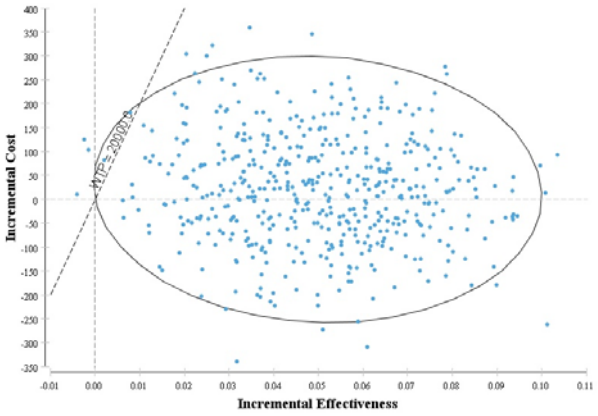
* AD8 was 97.6% being cost-effective over no screening

(b) MMSE vs no screening



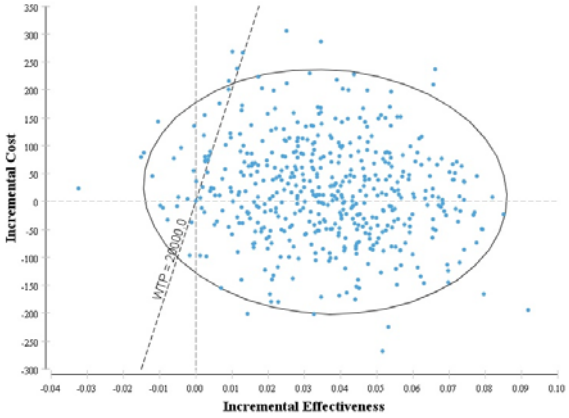
* MMSE was 97.2% being cost-effective over no screening

(c) Parallel test vs no screening



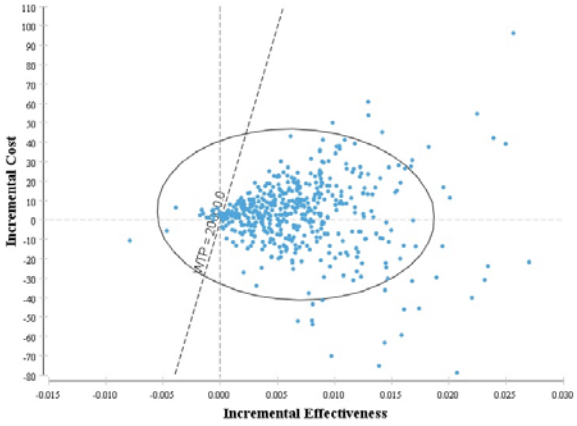
* Parallel test was 99.0% being cost-effective over no screening

(d) Serial test vs no screening



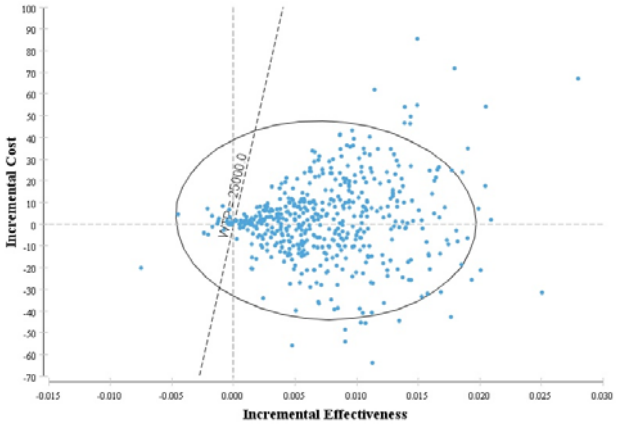
* Sequential test was 93.4% being cost-effective over no screening

(e) Parallel test vs AD8



* Parallel test was 95.4% being cost-effective over AD8

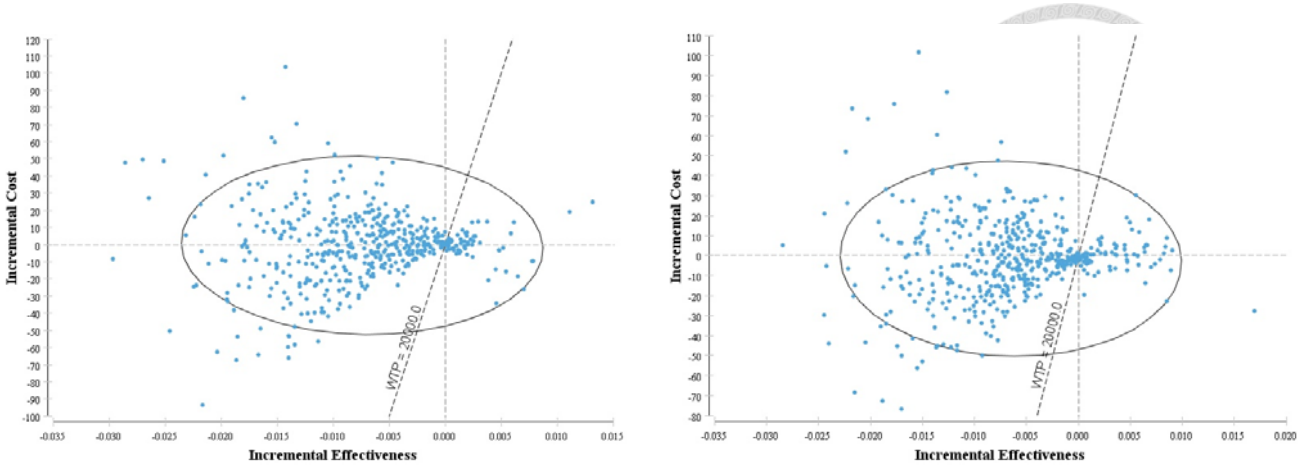
(f) Parallel test vs MMSE



* Parallel test was 95.2% being cost-effective over MMSE

(g) Serial test vs AD8

(h) Serial test vs MMSE



* Serial test was 13.2% being cost-effective over AD8

* Serial test was 15.2% being cost-effective over MMSE

Figure 4.3.3 Scattered incremental cost-effectiveness analysis for different screening strategies for dementia compared with no screening over 10-year span, considering only direct cost

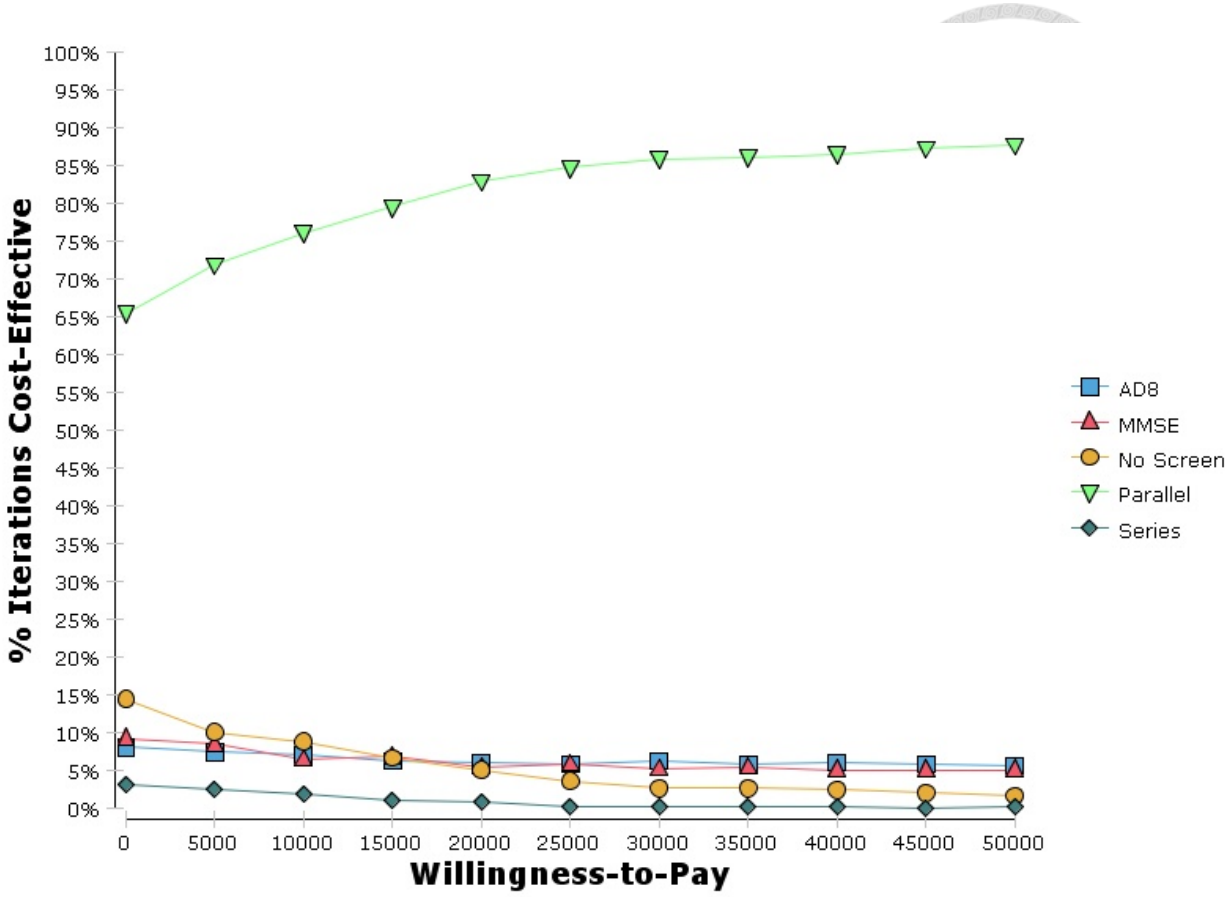


Figure 4.3.4 Acceptability curve for cost-effectiveness analysis dementia screening over 10-year span, considering both direct and indirect cost

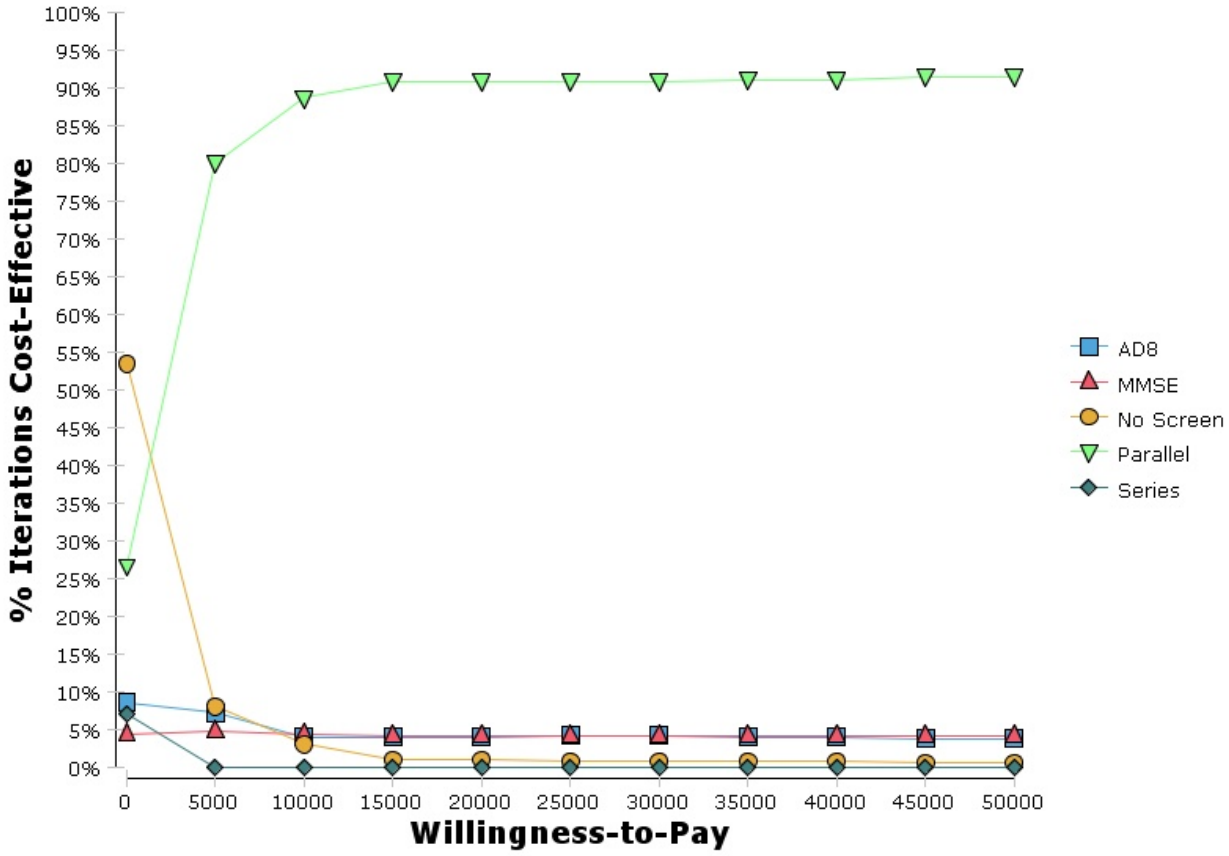


Figure 4.3.5 Acceptability curve for cost-effectiveness analysis dementia screening over 10-year span, considering only direct cost

References

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