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隨機過程應用於預防巴金森氏症 Hoehn-Yahr 分類

疾病進展之實證評估

Evidence-based Evaluation of Preventing Progression of

Hoehn-Yahr-stage-based Parkinson's Disease with

Stochastic Process

溫瓊容

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中文摘要

研究背景　巴金森氏症是第二常見的退化性疾病，最終會導致身體功能下降以及減少壽命。及早治療可以延緩疾病的進展以及延長存活時間，故及早診斷及治療益發顯得重要。但根據巴金森氏症的異質性建構其疾病自然史並探討早期診斷巴金森氏症的效益的研究仍很少見。因此，本篇論文的研究目的主要有三：1.利用一個以社區為基礎的族群，比較主動偵測與被動偵測巴金森氏症的效益 2.建立以 Hoehn-Yahr 分類疾病階段(簡稱 H-Y stage)為基礎的巴金森氏症疾病自然史，並且將可能影響疾病自然史轉移速率的因子加入模式中 3.進行早期偵測巴金森氏症的成本效益分析。

材料與方法　本研究資料來源為 2001 年基隆社區巴金森氏症篩檢的資料。第一部分研究先比較兩種偵測巴金森氏症的方式(主動偵測與被動偵測)的累積偵測率及 H-Y stage 的分布。第二部分研究則利用非標準化的病例-世代設計於以 H-Y stage 為基礎的巴金森氏症疾病自然史。我們利用三階段及五階段的馬可夫模式去建構以 H-Y stage 為基礎的巴金森氏症疾病自然史。我們將可能影響疾病自然史的因子如基本資料、生活習慣以及飲食習慣也考慮於疾病自然史中。最後，我們利用所建構五階段的馬可夫模式，模擬 60 歲以上的研究世代，在追蹤 20 年後在不同篩檢策略下所得之巴金森氏症篩檢的成本效益及成本效用分析。疾病進展的參數得自第二部分得自實證資料所估計的自然病史，成本及效益均折現 3%，在模擬 1000 個樣本大小為 10000 人的世代族群所得在不同篩檢策略下的累積成本

效益/效用後，分別依每多增加一年及每多增加一生活品質校正年所需增加的成本、在不同的付費意願下的成本效益/效用接受曲線、及成本-效益/效用散佈圖進行比較。

結果 主動偵測和被動偵測分別偵測出 192 個以及 89 個巴金森氏症病人。主動偵測比被動偵測約可找出 1.8 倍多(95%CI: 1.4-2.3)的巴金森氏症病人，並且在主動偵測組中早期(H-Y stage I,II)的個案所佔的比例顯著多於被動偵測組 (80.4% vs. 61.5%, p=0.04)。

結果顯示疾病自然史在三階段的馬可夫模式中，一個 60 歲以上的人發生巴金森氏症的年發生率為千分之 8.2。從可偵測前期至臨床期的轉移率 0.5935 (95% CI: 0.4330-0.7541)，即其平均滯留期為 1.68 年。在五階段的馬可夫模式中，發生巴金森氏症的年發生率為千分之 7.8。從可偵測前期的早期到晚期(H-Y stage III+)的年轉移速率為 0.2498 (95% CI:0.1420-0.3576);從可偵測的早期到臨床早期的年轉移速率為 0.3982(95% CI: 0.2564-0.5399)。從可偵測晚期到臨床晚期的年轉移速率 2.1227(95% CI: 0.5109-3.7346)。考量不同的特性對五階段模式中各狀態間轉移速率的影響，結果顯示每增加 10 歲，發生巴金森氏症的相對危險性為 1.79 倍 (95% CI: 1.32-2.44) 且加速篩檢可偵測早期進展到可偵測晚期的速率，其相對危險性為 5.08 倍(95% CI: 1.94-13.29)。低尿酸濃度同樣為巴金森氏症的危險因子，其相對危險性為 1.54 倍 (95% CI: 1.04-

2.28)。教育程度較高者其自篩檢可偵測早期到晚期的速率亦較高 (RR=14.65,95% CI: 2.94-54.53)。

　　根據模擬的資料所得到不同篩檢間隔的結果來評估篩檢的效益中，每年篩檢可以降低71% (95%CI: 65-80%)進展至晚期巴金森氏症的百分比，若篩檢間隔分別為兩年、三年、四年或六年，則可以降低進展至晚期巴金森氏症的百分比分別為54% (95% CI: 45-62%)、43% (95%CI: 32-52%)、35% (95%CI: 23-45%)、以及25% (95% CI:12-36%)。

　　由決定性模式所得成本效益及成本效用分析的結果分別為每增加一人年需多花$1169到$1804；每增加一生活品質校正年需多花$1715到$2606。在每增加一人年之付費意願$20,000下，每年篩檢可得到最大的淨效益($280,687)，其次為每二年一次($280,511)及每三年一次($280,416)和無篩檢 ($280,113)，相同的趨勢亦反映在以生活品質校正年的淨效益結果。

　　機率性成本效益分析的結果顯示付費意願$20,000下，在參與率為100%及60%下具成本效益的機率為69-79%及64-74%；相對條件下具成本效用的機率分別為62.6%-70.2%和58.2%-62.6%。

結論　主動偵測比被動偵測的方式可偵測出幾乎兩倍的個案，並且可以減少49%的晚期巴金森氏的病人。結果顯示，一個60歲以上的人平均從篩檢可偵測期進展到臨床期的時間約為一年半。篩檢的間隔越密集，可以減少進展至H-Y stage晚期的比率越大。依H-Y疾病狀態去建構病人是屬於篩檢可偵測的早期進展到臨

床期或由篩檢可偵測的晚期進展到臨床期的疾病自然史模式，可提供巴金森氏症

早期偵測的探討空間。應用這些狀態轉移的參數，本論文說明了愈密集的篩檢間

隔可降低晚期巴金森氏症的比例愈大，具成本效益的機率也愈大。

關鍵字:巴金森氏症、早期篩檢、成本效益、Hoehn-Yahr 分類

Abstract

Background Parkinson's disease (PD) is the second most common degenerative disorder which will eventually cause functional decline and reduce lifespan. The development of therapies that slow disease progression and improve survival makes early detection and treatment of PD especially important. Besides, the characteristics of heterogeneity in natural history and the uncertainty in the decision analysis of early detection of PD prevention have not been fully investigated. The aims of this thesis consist of three parts: (1) the first was to to use a community-based cohort to compare the detection methods for active detecting PD. (2) the second was to elucidate the temporal natural history of Hoehn-Yahr-stage-based PD with a Markov process with and without the incorporation of covariates into different transitions corresponding to the natural history model and the third part was to evaluate the cost-effectiveness analysis.

Material and Method First part of data were derived from a community-based screening survey for PD in 2001. Cumulative detection rate and Hoehn-Yahr (H-Y) stage distribution of both the active and passive detection groups were estimated and compared.

In the second part, we use a non-standard case-cohort design for modelling the natural history of H- Y stage-base PD. We built a three-state and a five-state Markov

models for the H-Y stage-based natural history. Variables such as baseline characteristic, life style and dietary habit were collected and were incorporated into the model to assess the effect of each covariate on respective transitions.

In the final part, the Markov decision analysis was envisaged to estimate the cost-effectiveness and cost-utility of active screening for PD in the community setting for residents aged 60 years or older over a 20-year period. We used a five-state Markov model to simulate the progression of PD and the sequel afterwards. The cumulative cost under different strategies was also collected. Parameters of disease progression followed the empirical estimates of the temporal natural history in the second Part. The main outcome measure was cost per life-year gain and per quality-adjusted life-year (QALY) gained with a 3% annual discount rate. The scattered cost-effectiveness plane (CE plane) and acceptability curve was presented given a 1000 Monte Carlo simulated samples for running 10,000 trials.

Results One hundred and ninty-two IPD cases and 89 IPD were detected by the active and passive detection methods, respectively. The active method detected approximately 1.8-fold (95% confidence interval: 1.4-2.3) the IPD cases of the passive method. Early H-Y stage (stage I and II) IPD cases were statistically significantly higher in the active method than in the passive method (80.4% vs. 61.5%, p=0.04).

Base on a three-state homogeneous Markov model, annual incidence rate of being susceptible to PD for subjects aged 60 years or older was 8.2 per 1000 person-years. Annual transition rate from screening detectable (SD) phase to clinical detectable (CD) phase was 0.5935 (95% CI: 0.4330-0.7541), which yielded 1.68 years of mean sojourn time staying in the SD phase. In a five-state homogeneous Markov model, the estimate incidence of SD phase PD was similar to that estimated from the three-state model, 7.8 per 1000. The transition rate from H-Y I/II to H-Y III+ in the SD phase was 0.2498 (95% CI: 0.1420-0.3576). The transition rates from SD to CD for early stage (H-Y I/II) and late stage (H-Y III+) were 0.3982 (95% CI: 0.2564-0.5399) and 2.1227 (95% CI: 0.5109-3.7346), respectively. Considering the effects of patient specific covariate on the transitions in the five-state model, the results of multivariable analysis on multiple transition shows that advancing age led to an increased 10 years risk of developing PD (aRR=1.79, 95% CI: 1.32-2.44) and faster transition from HY I/II to HY III+ before surfacing to CD phase (RR=5.08, 95% CI: 1.94-13.29). Low level of uric acid also played the role of risk factor in the incidence of PD (RR=1.54, 95% CI: 1.04-2.28). High level of education strongly affected the transition from HY I/II to HY III+ before surfacing to CD phase (RR=14.65, 95% CI: 2.94-54.53).

In the simulated results for effectiveness of different screening interval, annual screening reduced 71% (95% CI: 64-77%) reduction of advanced stage (H-Y stage III+)

cases compared to no screen. When the inter-screening intervals were 2-yearly, 3-yearly,

4-year, or 6-yearly, reduction of advanced H-Y stage cases was 54% (95% CI: 45-62%),

43% (95% CI: 32-52%), 35% (95% CI: 23-45%), and 25% (95% CI: 12-36%),

respectively.
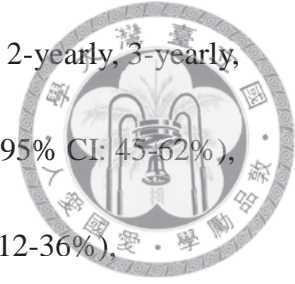
The results from deterministic Markov decision analysis of the cost-effectiveness

and cost-utility analysis shows that the incremental cost-effectiveness ratios (ICER) of

PD screening with different inter-screening intervals compared to no screen ranged from

$1169 to $1804 per life-year gained. The incremental cost-utility ratio ranged from

$1715 to $2606 per quality-adjusted life-year gained. The annual screen had the greatest

net monetary benefit (NMB) ($280,687) in terms of life-year gained, followed by

biennial ($280,511), triennial ($280,416) screen, and no screen ($280,113). The same
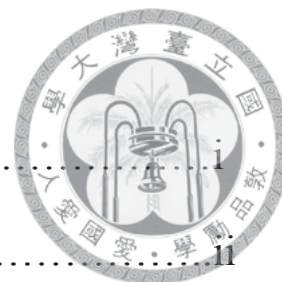
trend was observed for the NMB in terms of QALY gained.

The results of the probabilistic Markov decision models shows that the

probability of screening programs being cost-effective at $20,000 of willingness-to-pay

(WTP) was 69-79% and 64-74% given 100% and 60% of attendance rates, respectively.

The corresponding figures in the cost-utility analyses were 62.6%-70.2% and 58.2-

62.6% given 100% and 60% of attendance rates, respectively.

Conclusion The active method detected almost two times the PD cases as the passive

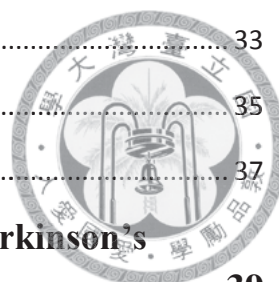method and also reduced 49 % (95% CI: 4%-73%) the IPD cases classed in H-Y stage III

or greater. Our results reveal that an individual aged 60 year or older who is susceptible to PD and entered the SD phase would progress to CD, on average around 1.5 years. The progression from the SD to the CD by H-Y stage had been quantified with detectable window for the identification of early H-Y stage before the transition to late H-Y stage which form the bases of the best-case estimates for the disease progression of PD in the absence of screening. With the application of these transition parameters, this thesis demonstrates that if the intensive screening for PD is offered, the large the reduction in late H-Y PD would be achieved and the probability of being cost-effective could be high.

Keywords: Parkinson's Disease, Early Screening, Cost-Effectiveness, Hoehn-Yahr Stage

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Chapter 1 Introduction

1.1 Impact of Parkinson's Disease

Parkinson's disease (PD) is the second most common degenerative disorder in the aging brain. It affects approximately 6.3 million people worldwide. As the disease progress, it will affect motor, autonomic, cognitive and emotional function and eventually reduce lifespan.[1, 2] The cardinal symptoms of PD such as tremor, rigidity, bradykinesia and postural instability involve motor control. Disability in PD derives predominantly from progressive motoric disturbance which may lead the patient become wheelchair-bound or bedridden. Such heath consequence results in a considerable burden of illness associated with PD. Although PD is still not curable, the advent of the levodopa raise the hope of improving both motor disability and survival in PD.[3] Before the introduction of Levodopa, previous epidemiological studies report that patients with PD had a shorter survival than the general population.[4] Hoehn and Yahr reported a mortality ratio 2.9 times higher in PD patients than that of the general population after adjustment for age, sex and race.[5]

1.2 Temporal Natural History Based on Hoehn and Yahr stage

The severity of PD is usually classified by Hoehn and Yahr stage (H-Y stage).[5] In the absence of treatment, the disease severity will progress to H-Y stage IV and V in 9.0 $\pm$ 7.2 and 14.0 $\pm$ 3.4 years.[5] Previous study reported that H-Y stage at baseline were greater in PD patients who had died during follow-up compared with that of survivors.[6] Besides, patients with H-Y stage greater than III reported the impaired quality of life and more non-motor symptoms.[7] This implies that H-Y stage plays an important role in the natural history of PD for assessing both disease progression and prognosis of H-Y stage.

In addition, those covariates associated with each transition rate between consecutive stages were also with high interest to use them into the natural history model to reduce the heterogeneity and also provide the information.

1.3 The Importance of Active Detective Method for Parkinson's Disease Classified by Hoehn and Yahr Stage

However, most studies detected PD cases by medical record review or service-based detection, which usually detected PD case with syndrome at the late stage rather than early stage.[8-14] Therefore, the incidence and prevalence of PD in door-to-door

survey were higher than those in record-based studies.[9] This discrepancy implies that

outreaching surveys can yield accurate PD prevalence and incidence rates. A study in

Taiwan showed that a community-based screening program identified more early stage

PD with H-Y stage I or II than that was performed in a clinical series.[15] Such active

method suggested the possibility of detecting PD at early stage, and accompanied with

the effectiveness of levodopa in delaying the progression of PD, the life expectancy and

the quality of life would be expected to be improved. While temporal natural history of

H-Y-stage-based PD was proposed by Hoehn and Yahr, early detection of PD was not

envisaged at that time. In the era of preventive medicine in the 21 century, it seems

feasible as a result of effective early treatment. Screening for PD has become feasible as

Liou et al has already done in such an active detection.[15] With the advent of screening

for PD, PD with H-Y stage can be further divided into the screening detectable (SD)

phase and clinical detectable (CD) phase. In my thesis, the temporal natural history of

PD with H-Y stage will be classified into the SD and the CD phase for estimating the

parameters of disease progression.

1.4 Effectiveness of Early Detection and Treatment for Parkinson's Disease

Progression of disability on the H-Y stage has become slower with the introduction of levodopa treatment. The progression to severe PD would be rapid for those patients with delayed administration of levodopa therapy. [16, 17] The development of therapies that slow disease progression and improve survival makes early detection and treatment of PD especially important. The elucidation of temporal natural history of H-Y-stage-based PD also provide a pseudo-control group for evaluation for preventive strategy such as screening for early PD. It has been shown that screening for early PD can lead to 51% reduction for advanced stage of PD, and 25% mortality reduction.[18] Thus, early detection could relieve medical burden from PD not only for patients themselves, but for family members, and even the society.
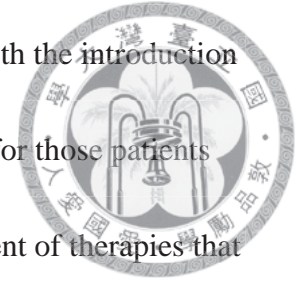
1.5 Cost-effectiveness Analysis of Early Detection for Parkinson' Disease

There are many economic evaluations for treatment of PD, but cost-effectiveness analysis for PD screening has been scarcely addressed. Most economic evaluation articles in PD were performed by deterministic approach although the uncertainly in natural history of PD and also in treatment of PD was well-known in this field. Since the advance in methodology of cost-effectiveness analysis has increasingly gained attention over the past decades, stochastic process in decision tree and using Bayesian

approach with probabilistic sensitivity analysis has also gained popularity to alleviate

concerns related to the dynamic changing of quality of life depending on disease status

and the uncertainty related to treatment and cost.

1.6   Motivation and Aims of the Study

There are few studies to depict the panorama of the natural history of PD based on

H-Y stage from various perspectives on epidemiological, clinical, and economic

aspects. Besides, the characteristics of heterogeneity in natural history and the

uncertainty in the decision analysis of early detection of PD prevention have not been

fully investigated.

The aim of this thesis includes four parts based on the principle of evidence-based

medicine.

Part I: To make use of a population and community-based cohort study to compare the two

detection methods for active detecting Parkinson's disease.

Part II: To elucidate the temporal natural history of Hoehn-Yahr-stage-based Parkinson's

disease with stochastic process in relation to early detection of PD based on empirical data

from Part I.

Part III: To identify H-Y stage-specific factors responsible for various transitions.

Part IV: Perform cost-effectiveness and cost-utility analysis for early detection of

Parkinson's disease through population-based screening.

Chapter 2 Literature Review

2.1 Burden of Parkinson's Disease

2.1.1 Clinical characteristics of Parkinson's Disease
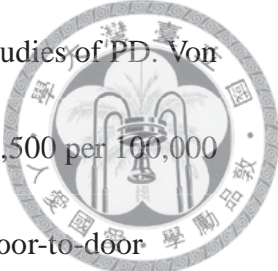
Idiopathic Parkinson's disease (IPD) is the second most common degenerative disorder in the aging brain, after Alzheimer's dementia. The cardinal signs of motor dysfunction of Parkinson's disease (PD) include resting tremor, bradykinesia, rigidity and postural reflex impairment. The pathological finding of the motor deficits in PD is degeneration of the dopaminergic neurons of the nigrostriatal pathway. Catecholaminergic and serotoninergic brain-stem neurons may also degenerate. These mechanisms may include protein misfolding, protein aggregation, mitochondrial dysfunction, oxidative stress and inflammation.[19-26]

2.1.2 Incidence

Overall, the incidence rates for PD in all groups ranged from 1.2 to 22 per 100,000 person-years. If restricted to older populations (age above 55 or 65 years), the incidence rates were increased between 410 and 529 per 100,000 person-years.[11, 27, 28] A systemic review of incidence studies of PD reported that the age-standardized incidence rates between 16 and 19 per 100,000 person-years.[29]

2.1.3 Prevalence

Unlike the few incidence studies, there are plenty of prevalence studies of PD. Von Campenhausen et al reported the prevalence rate range from 65.6 to 12,500 per 100,000 in European countries. Alves et al reported overall prevalence rate in door-to-door studies ranged from 167 to 5,703 per 100,000 worldwide.[30] Though previous two studies in China reported low prevalence rate of PD,[31, 32] Zhang et al directly examined 29,545 individuals reported a prevalence of 1,300 per 100,000 in individuals above 55 years.[14] The two door-to-door survey in Ilan and Kimen also reported the prevalence were 119 and 130 per 100,000 after calculate age-standardized prevalence proportions using the US population in 1970 as standard, [33, 34] which were similar to the prevalence in European countries.[10, 13, 35-37] Thus, the low prevalence in China may resulted from difference in methodology, rather than ethnic differences.

Although there are large variation in incidence and prevalence of PD, outreach surveys such as door-to door surveys usually reported higher incidence and prevalence compared to registry-based studies of ascertainment. To the best of our knowledge, no population-based data are available to compare different case-finding methods in PD detection.

2.2 Natural History of Parkinson's Disease with Hoehn-Yahr Stage

Margaret M. Hoehn and Melvin D.Yahr first introduce the H-Y stage based on the clinical disability of PD in 1967.[5] The comparable clinical disability of each stage are as follows:

Stage I- Unilateral involvement only, usually with minimal or no functional impairment.
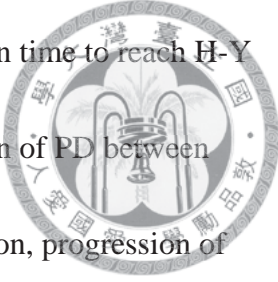
Stage II- Bilateral or midline involvement, without impairment of balance.

Stage III- First signs of impaired righting reflexes. This is evident as the patient turns or is demonstrated when he or she is pushed from standing equilibrium with the feet together and eyes closed.

Stage IV- Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

Stage V- Confinement to bed or wheelchair unless aided.

Hoehn and Yahr evaluate the total 183 patient of primary parkinsonism and provided the mean duration of each stage of illness was 3.0, 6.0, 7.0, 9.0, and 14.0 in stage I, II, III, IV and V, respectively. Progression of disability on the H-Y stage has become markedly slower with the advantage of levodopa treatment and studies from the post-levodopa era have found latencies to reach H-Y stage IV or V of up to 40 years.[38] Hely et al reported a

cohort of 146 PD patient with 10-year follow up data and found median time to reach H-Y

stage IV and V was around seven years.[39] Different rates of progression of PD between

studies might be due to differences in patient cohorts studied. In addition, progression of

motor impairment is likely non-linear in PD with severe declines in early stage versus late

stage of the disease, which was compatible with the exponential decline of neuronal cell

counts in the substantia nigra in the brain.[40] This is supported by the observations of faster

rates of progression of unified Parkinson's disease rating scale (UPDRS) in the first versus

the 10th year of disease.[41] Liou et al. reported the average duration in H-Y stage I, II and

III was estimated as 2.83, 6.62 and 1.41 years, respectively by proposing a five-state

Markov model.[15] These different rates of progression in PD between studies also

suggested heterogeneity in the natural history of PD.

To model the natural history of Parkinson's disease is often complicated by issues

of diagnostic accuracy, heterogeneity of different forms of the disease and the

confounding effects of age related comorbidities. The H-Y stage is used for evaluation

the progression of PD. The H-Y model assumes that PD is a progressive disease,

evolving from H-Y stage I to H-Y stage V. Since the introduction of L-dopa, detailed

information about how a patient's disease progressed form H-Y scale I to scale V for

untreated PD are unlikely to be quantifiable. The stochastic model was therefore

proposed. Stochastic models have been used in modelling the disease natural history of
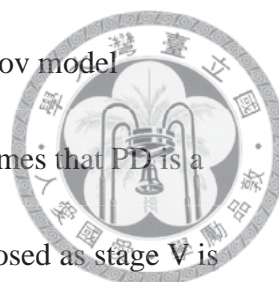
multi-state chronic diseases.[42, 43] Liou et al proposed a five-state Markov model

according to the disease severity by H-Y stage.[15] The H-Y model assumes that PD is a

progressive and irreversible disease. It means that an individual diagnosed as stage V is

supposed that he or she has transited from normal, through stage I, II, III and IV at entry

of study. (see the figure below)
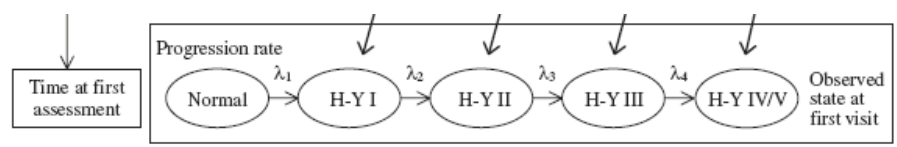
   However, the Markov model used to assume a homogeneous process that a

constant hazard rate with time for progression for state to state. This may be unrealistic

in medicine and biology.

2.3   Stochastic Models for Disease Natural History

2.3.1 Introduction of Markov Model

   A sequence of random variables $\{X_\alpha, \alpha = 0,1,\dots\}$ is called a Markov chain if, for every

collection of integers, $\alpha_0 < \alpha_1, < \cdots < \alpha_n < \beta$, the conditional distributions of

X_β satisfy the relation:

$$P_r\{X_\beta = i_\beta | X_{\alpha_0}, \dots, X_{\alpha_n}\} = P_r\{X_\beta = i_\beta | X_{\alpha_n}\}, \text{ for } i_\beta$$

The outcome in the future $(X_\beta = i_\beta)$ *is no longer dependent upon the past state*

$(X_{\alpha_0}, \dots X_{\alpha_{n-1}})$

For each X_α, the absolute probability is denoted by $P_r\{X_\alpha = i_\alpha\} = a_{i_\alpha}$

For every pair of random variables, X_α and X_β, the conditional probability is denoted by

$$P_r\{X_\beta = i_\beta | X_\alpha = i_\alpha\} = P_{i_\alpha.i_\beta}$$

The joint probabilities of $X_\alpha, X_\beta, X_\gamma$, for $\alpha < \beta < \gamma$, are given by

$$P_r\{X_\alpha = i_\alpha, X_\beta = i_\beta, X_\gamma = i_\gamma\} = a_{i_\alpha} P_{i_\alpha,i_\beta} P_{i_\beta,i_\gamma}, and \ P_r\{X_\alpha = i_\alpha, X_\beta = i_\beta\} = a_{i_\alpha} P_{i_\alpha,i_\beta}$$

Therefore, for any collection of integers $\alpha < \beta < \cdots < \delta < \varepsilon$, the joint probabilities are

$$P_r\{X_\alpha = i_\alpha, X_\beta = i_\beta, \dots, X_\delta = i_\delta, X_\varepsilon = i_\varepsilon\} = a_{i_\alpha} P_{i_\alpha,i_\beta} \dots P_{i_\delta,i_\epsilon}$$

A Markov chain with state space being the set of all the non-negative integers is

completely determined by the initial absolute probability distribution

$P_r\{X_0 = i_0\} = a_{i_0}$, $i_0 = 1,2, \dots$ and the transition probabilities

$$P_r\{X_{\alpha+1} = i_{\alpha+1} | X_\alpha = i_\alpha\} = P_{i_\alpha,i_{\alpha+1}} \ , \ i_\alpha, i_{\alpha+1} = 1,2, \dots \ \text{for} \ \alpha=0,1,\dots$$

The transition probabilities of a time homogeneous chain is denoted by

$$P_r\{X_{\alpha+1} = j | X_\alpha = i\} = P_{ij}$$

The transition probability P_{ij} for a three-state Markov model can be arranged in the form

of a matrix

$$P = \begin{pmatrix} P_{00} & P_{01} & P_{02} \\ P_{10} & P_{11} & P_{12} \\ P_{20} & P_{21} & P_{22} \end{pmatrix}$$

2.3.2 Three-state Homogeneous Markov Model for Disease Natural

History

Chen et al applied a three-state Markov model to estimate sojourn time in chronic

disease screening without data of interval cases.[43] They model the disease with a

continuous-time Markov process in which $X(t)$, the state of an individual at time t, is a

random variable with a state space $\Omega=\{0,1,2\}$, where 0 represents no disease, 1 represents

preclinical screen detective disease (PCDP) and 2 represents clinical phase (CP). The

clinical phase in this model is an absorbing state in Markov processes language because

the natural history cannot be estimated beyond diagnosis due to the effect of therapy. They

also assume this is a progressive model.

The transition rates in the three-state model can be expressed as an intensity matrix,

$$\begin{pmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & 0 & 0 \end{pmatrix} \tag{2-1}$$

λ_1 represents the transition rate from no disease to the PCDP, λ_2 represents the transition

rate from the PCDP to the clinical phase.

Given the transition intensity matrix above, transition probabilities for a three-state model

can be expressed as

$$\begin{pmatrix} P_{00}(t) & P_{01}(t) & P_{02}(t) \\ 0 & P_{11}(t) & P_{12}(t) \\ 0 & 0 & 1 \end{pmatrix} \tag{2-2}$$

$$P_{00}(t) = e^{-\lambda_1 t}$$

$$P_{01}(t) = \frac{\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{(\lambda_2 - \lambda_1)}$$

$$P_{02}(t) = 1 - \frac{\lambda_2 e^{-\lambda_1 t}}{\lambda_2 - \lambda_1} + \frac{\lambda_1 e^{-\lambda_2 t}}{\lambda_2 - \lambda_1} \qquad (2\text{-}3)$$

$$P_{11}(t) = e^{-\lambda_2 t}$$

$$P_{12}(t) = 1 - e^{-\lambda_2 t}$$

The likelihood function based on the prevalent screen in a cohort with N individuals is

$$L_1(.) = \prod_{m=1}^{N} \left(\frac{P_{01}(v_m)}{P_{00}(v_m) + P_{01}(v_m)} \right)^{x_m} \times \left(\frac{P_{00}(v_v)}{P_{00}(v_m) + P_{01}(v_m)} \right)^{1-x_m}$$

v_m represents age at fist screen for mth subject

$x_m = 1$ when the mth subject is detected as a positive case

$x_m = 0$ otherwise.

However, as the previous mention above, the Markov model used to assume a homogeneous process that a constant hazard rate with time for progression for state to state. This may be unrealistic in medicine and biology.

2.3.3 Three-state Model with Weibull Distribution

In order to deal with the non-constant hazard in the stochastic model, Chen et al propose a non-homogeneous three-state model for the disease natural history of oral cancer.[44] They model the time of transitions from normal to leukoplakia and leukoplakia to invasive carcinoma with two Weibull distributions. The transition probabilities for staying in a no disease state (state 0), transitions from normal to leukoplakia (state 1)
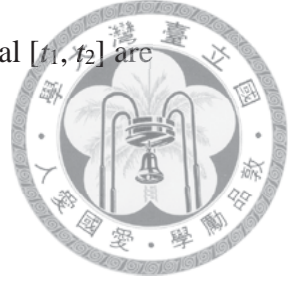
and from normal to invasive carcinoma (state 2) in a given time interval $[t_1, t_2]$ are

expression as follows:

$$P_{00}(t_1, t_2) = 1 - \int_{t_1}^{t_2} f_1(u)du$$

$$P_{01}(t_1, t_2) = \int_{t_1}^{t_2} f_1(u)\left(1 - \int_{u}^{t_2} f_2(v)dv\right) du \qquad (2\text{-}4)$$

$$P_{02}(t_1, t_2) = \int_{t_1}^{t_2} f_1(u) \int_{u}^{t_2} f_2(v)dvdu$$

$f_1(t)$ and $f_2(t)$ are the probability density function of Weibull distributions for time of

transition from states 0 to 1 and from state 1 to 2. The two Weibull distributions are

denoted as $W_1(\lambda_{10}, \gamma_1)$ and $W_2(\lambda_{20}, \gamma_2)$. λ_{10} and λ_{20} are scale parameters and γ_1 and

γ_2 are shape parameters for the two corresponding transitions. The transition rates as a

function of time are expressed as follows:

$$\lambda_i = \lambda_{i0}\gamma_i t^{\gamma_i - 1} \qquad \text{where i=1 or 2}$$

The probability of remaining in state i-1 in time t is

$$S_i(t) = \exp\left\{-\int_0^t \lambda_{i0}\gamma_i u^{\gamma_i - 1}\, du\right\} = \exp(-\lambda_{i0}t^{\gamma_i}) \qquad (2\text{-}5)$$

The corresponding probability density function is

$$f_i(t) = \lambda_{i0}\gamma_i u^{\gamma_i - 1}\exp(-\lambda_{i0}t^{\gamma_i})$$

The transition probabilities for staying in state 1 and state 2 were also denoted as

follows:

$$P_{11}(t_1, t_2) = 1 - \int_{t_1}^{t_2} f_2(u)du$$

$$P_{12}(t_1, t_2) = \int_{t_1}^{t_2} f_2(u)du \qquad (2\text{-}6)$$

The natural history from state 1 (leukoplakia) to state 2 (invasive carcinoma) is usually unobservable due to the interruption of medical treatment. We can only estimate parameters via equation (1), P_{00}, P_{01} and P_{02}.

2.3.4 Incorporation of patient specific covariates

The effect of patient specific covariates, say x, on the three-state stochastic model was assessed by the exponential regression model that treats scale parameter in the Weibull distribution as a function of patient-specific covariates. It is expressed as follows:

$$\lambda_{i0}^m = \lambda_{i00}\exp(\beta_{i0}\chi^m)$$

λ_{i00} : the scale parameter of Weibull distribution for state i

χ^m : a vector of covariates for subject m

β_{i0} : corresponding regression coefficient

2.3.5 Bayesian inversion for a non-standard case-cohort design

For an n-state disease natural history, n sets of random samples for each transition were selected in case-cohort study design in Chen et al. Let S denoted an indicator of whether a subject was sampled (S=1). For individual i, let $\pi_j^{t_i}$ be sampling fractions for state j at time t_i. $\pi_j^{t_i}$ was denoted as follows:

$$\pi_j^{t_i} = P(S = 1|0 \rightarrow j; t_i)$$

The sampling fractions for state j can be expressed as π_j if we assume that sampling

fractions are independent of the individual. Using Bayesian inversion, the probability of

transition of being state j at time t_i given a subject was sampled is

$P(0 \to j; t_i | S = 1)$

$$= \frac{P(S=1|0 \to j; t_i)P(0 \to j; t_i)}{\sum_{j=1}^{n} P(S = 1 | 0 \to j; t_i)P(0 \to j; t_i)} = \frac{\pi_j P(0 \to j; t_i)}{\sum_{j=1}^{n} \pi_j P(0 \to j; t_i)} = \frac{\pi_j P_{0j}(t_i)}{\sum_{j=1}^{n} \pi_j P_{0j}(t_i)} \qquad (2-7)$$

The transition probabilities $P_{0j}(t_i)$ are derived from equation (1).

Likelihood function, parameter estimation and model validation

The data on the first oral examination were used to estimate the parameters relate to the

disease natural history. This yields three possible observed transitions before the first

examination: staying in normal (state 0 → 0), normal to leukoplakia (state 0→ 1) and

normal to invasive carcinoma (state 0 → 2). According to the above equation,

$P(0 \to j; t_i | S = 1)$

$$= \frac{P(S=1|0 \to j; t_i)P(0 \to j; t_i)}{\sum_{j=1}^{n} P(S = 1 | 0 \to j; t_i)P(0 \to j; t_i)} = \frac{\pi_j P(0 \to j; t_i)}{\sum_{j=1}^{n} \pi_j P(0 \to j; t_i)} = \frac{\pi_j P_{0j}(t_i)}{\sum_{j=1}^{n} \pi_j P_{0j}(t_i)} \qquad (2-8)$$

The likelihood function for the normal-leukoplakia-invasive carcinoma cohort with

three covariates is

$$\prod_i \left(\frac{\pi_0 P_{00}(t_i)}{\sum_{j=0}^{2} \pi_j P_{0j}(t_i)} \right)^{n_{i0}} \left(\frac{\pi_1 \times P_{01}(t_i)}{\sum_{j=0}^{2} \pi_j P_{0j}(t_i)} \right)^{n_{i1}} \left(\frac{\pi_2 \times P_{02}(t_i)}{\sum_{j=0}^{2} \pi_j P_{0j}(t_i)} \right)^{n_{i2}} \qquad (2-9)$$

where n_{i0}, n_{i1}, and n_{i2} were counts of normal, leukoplakia and invasive carcinoma at

age i of the first examination.

2.3.6 Five-state non-homogeneous stochastic model
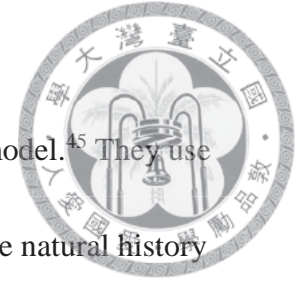
Chen et al further extended the three-state model to the k-state model.[45] They use normal-adenoma-carcinoma for colorectal cancer for the example. The natural history of the colorectal cancer is classified by adenoma size. The state space $\Omega=\{0,1,2,3,4\}$, where state 0 represent normal, state 1 represent diminutive adenoma, state 2 represent small adenoma, state 3 represent large adenoma, and state 4 represent invasive carcinoma. They apply the hazard rate from normal (state 0) to diminutive adenoma (state 1) change with time and denoted as $\lambda_1(t)$ with Weibull distribution. The Markov property was assumed for the remaining transition rate of λ_2 to λ_4 due to the complexity of algebra increases if each transition rate is modelled by the Weibull distribution. The natural history of the above process is divided into two parts: 1. Non-homogeneous Markov property for the hazard rate for normal to diminutive adenoma. 2. Homogeneous Markov property for the remaining transitions. The transition matrix is as follows:

$$
\begin{array}{c}
\begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \end{array}\\
\begin{array}{c} 0\\1\\2\\3\\4 \end{array}
\left(
\begin{array}{c|cccc}
-\lambda_1(t) & \lambda_1(t) & 0 & 0 & 0\\
0 & & & &\\
0 & & M & &\\
0 & & & &\\
0 & & & &
\end{array}
\right)
\end{array}
$$

The time of transition from states 0 to 1 is modeled by $\lambda_1(t)$ with Weibull distribution.

The remaining transition matrix M is as below:

$$M = \begin{matrix} & \begin{matrix} 1 & 2 & 3 & 4 \end{matrix} \\ \begin{matrix} 1 \\ 2 \\ 3 \\ 4 \end{matrix} & \begin{pmatrix} -\lambda_2 & \lambda_2 & 0 & 0 \\ 0 & -\lambda_3 & \lambda_3 & 0 \\ 0 & 0 & -\lambda_4 & \lambda_4 \\ 0 & 0 & 0 & 0 \end{pmatrix} \end{matrix}$$

As the non-homogeneous part that models the hazard rate of the onset of diminutive

adenoma with a Weibull distribution, the transition probabilities from state 0 (normal) to

state 1-4 can be derived as follows.

The probabilities for subjects staying as normal during [t_1, t_2] is

$$P_{00}(t_1, t_2) = 1 - \int_{t_1}^{t_2} f_1(u)du \qquad (2\text{-}10)$$

$f_1(t)$: the probability density functions of Weibull distribution for the transition from

state 0 to 1

The probabilities for an individual progressing from state 0 to state j during [t_1, t_2] is

$$P_{0j}(t_1, t_2) = \int_{t_1}^{t_2} f_1(u) \times P_{1j}^M(u, t_2)du \qquad (2\text{-}11)$$

j=1,2,3,4; $P_{1j}^M(.)$: transition probabilities derived from $P_{ij}^M(a, b)$

According to the equation as below,

$P(0 \rightarrow j; t_i | S = 1)$

$$= \frac{P(S=1|0\rightarrow j;t_i)P(0\rightarrow j;t_i)}{\sum_{j=1}^{n} P(S = 1|0 \rightarrow j; t_i)P(0\rightarrow j;t_i)} = \frac{\pi_j P(0\rightarrow j;t_i)}{\sum_{j=1}^{n}\pi_j P(0\rightarrow j;t_i)} = \frac{\pi_j P_{0j}(t_i)}{\sum_{j=1}^{n}\pi_j P_{0j}(t_i)} \qquad (2\text{-}12)$$

The likelihood function for adenoma-carcinoma is

$$\prod_i \left(\frac{\pi_0 P_{00}(t_i)}{\sum_{j=0}^{4}\pi_j P_{0j}(t_i)}\right)^{n_{i0}} \left(\frac{\pi_1 P_{01}(t_i)}{\sum_{j=0}^{4}\pi_j P_{0j}(t_i)}\right)^{n_{i1}} \left(\frac{\pi_2 P_{02}(t_i)}{\sum_{j=0}^{4}\pi_j P_{0j}(t_i)}\right)^{n_{i2}} \left(\frac{\pi_3 P_{03}(t_i)}{\sum_{j=0}^{4}\pi_j P_{0j}(t_i)}\right)^{n_{i3}} \left(\frac{\pi_4 P_{04}(t_i)}{\sum_{j=0}^{4}\pi_j P_{0j}(t_i)}\right)^{n_{i4}}$$

$$(2\text{-}13)$$

2.3.7 Semi-Markov Model
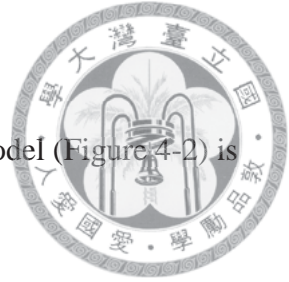
To consider death as an absorbing state, the five-state Markov model (Figure 4-2) is extended to the following model.
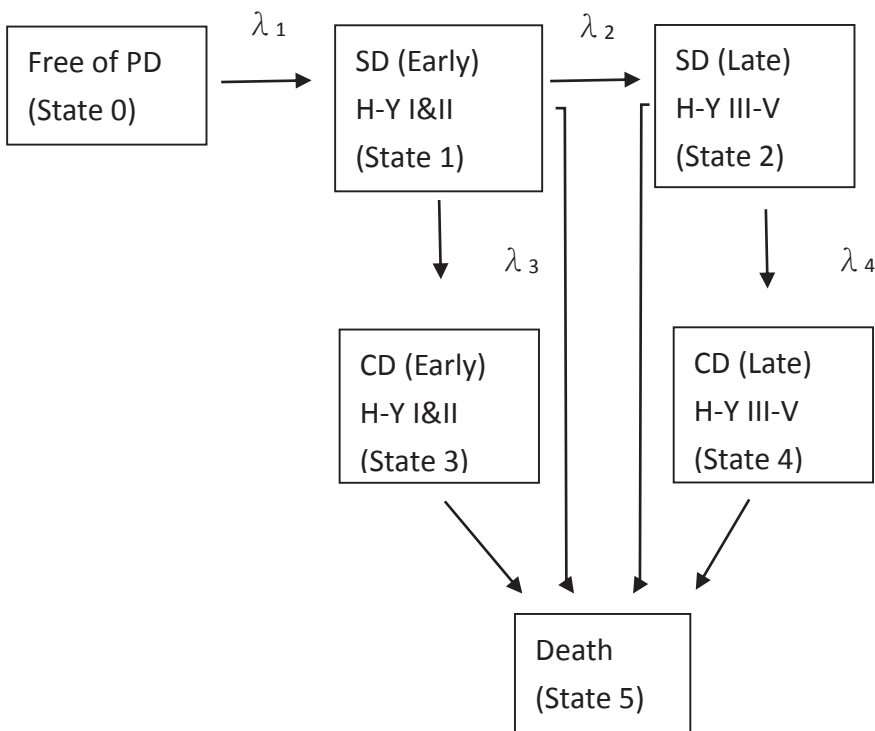
As the transition from the current sate to the next state, particularly absorbing state i.e. death, is highly dependent on how long they stay in the current stat, a six-state semi-Markov model will be proposed to model the temporal natural history of H-Y based PD. State space Ω, $\Omega=\{0,1,2,3,4,5\}$ is defined similarly as above. Let $X=\{X_0, X_1,\ldots, X_n\}$ denote n observed successive transitions for an individual during a period of time t, where X_0 is the initial state and X_n is the X final state after n transitions. We assume the total number of transition is finite and $X \in \Omega$. As a six-state semi-Markov process will be applied, in addition to X, which is said to form an embedded Markov chain, we still

require sojourn time distribution to depict the time spent in the current state before

transition to the next state. In parallel with X, $T = \{T_0, T_1, \ldots T_n\}$ is denoted to represent the

entry time into state X_n after n transitions. According to X and T, a semi-Markov process

can be formed by transition probabilities (P_{ij}) and distribution of sojourn time ($F_{ij}(t)$)

expressed by

$$P_{ij} = P(X_{n+1} = j | X_n = i) \tag{4-7}$$

P_{ij} is a homogeneous process

$$F_{ij}(t) = P(T_{n+1} - T_n \leq t | X_{n+1} = j, X_n = i)$$

For example, the transition from SD early H-Y stage (I&II) (j=1) to death (j=5) is

determined by the transition probability (P_{15}) and also the distribution for the time spent in

early SD H-Y stage $F_{15}(t)$.

$F_{ij}(t)$ is specified by a generalized Weibull distribution expressed by

$$F_{ij}(t) = 1 - \exp\left(-\left(\frac{t}{\sigma_{ij}}\right)^{\nu_{ij}}\right) \tag{4-8}$$

The parameters of σ and ν can change with time.

ν_{ij} and σ_{ij} are estimated using the maximum likelihood method.

Suppose we have N individual (m=1,…..N) and the subject m had n_m successive

transition. The observed sequence is denoted as $\{\chi_0^m, \ldots \chi_n^m\}$ and the corresponding entry

times into state X is denoted by $\{T_0^m, T_1^m, \ldots, T_{n_{m+1}}^m\}$.

The likelihood function

$$L(\sigma, \nu) = \prod_{m=1}^{N}\{\prod_{l=1}^{n_m}(P_{x_{l-1}^m x_l^m} f_{x_{l-1}^m x_l^m}(T_l^m - T_{l-1}^m) \times \sum_{J \neq x_{n_m}^m} P_{x_{n_m}^m j} S_{x_{n_m}^m j}(T_{n_{m+1}}^m -$$

$$T_{n_m}^m)^{\delta_{n_{m+1}}^m} \qquad (4\text{-}9)$$
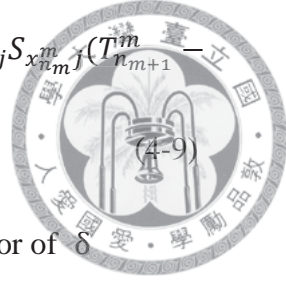
The latter part is related to right censoring with censoring indicator of δ

$\delta_{n_{m+1}}^m = 1$ if $X_{n_m}^m$ is not final state

$\delta_{n_{m+1}}^m = 0$ otherwise

2.4 Covariates associated with the progression of Parkinson's Disease

It is known that genetic susceptibility and environmental factors play a role in PD etiology and progression. Because 90% of PD are sporadic and the environmental factors involved with the majority of the cases of PD, it is important to understand the role of nutrition plays in both neuroprotection and neurodegeneration.

2.4.1 Risk Factors

Besides, there have been plenty of studies worked on the risk factors and protective factors of PD.[46] Some factors make major contribution to the onset of PD, such as age, sex, diary product intake, caffeine intake and smoking. Other factors may influence the rate of disease progression, such as age and caffeine intake. The different roles of risk or protective factors imply different preventive approaches. There has been a paucity of evidence that incorporate different factors into the natural history of PD.

Male Gender

In previous studies, the incidence of PD seems to be higher in men than in women. A significantly higher incidence rate of PD was found among men with relative risk (RR) being 1.5 times (95% confidence interval (CI) 1.24-1.95) greater than women in a meta-analysis of seven studies.[47] Another meta-analysis included 17 studies of PD also showed that a pooled male to female ratio of 1.46 (95% CI: 1.24-1.72) after adjusting for age.[48] This may suggested a protective effect of estrogen.

Age

Age per se is a risk factor of PD. Previous study reported that onset at an older age is associated with a faster progression rate and the development of cognitive failure.[49] Post et al followed 126 newly diagnosed PD patient for three years and also found that older age at onset predicts worse progression rate of disability and impaired quality of life.[50]

Body Mass Index (BMI)

The relationship between BMI and PD remained inconclusive. A recent meta-analysis studied the relationship between BMI and PD and found that PD patients had a significant lower BMI than controls (RR: 1.73, 95% CI: 1.11-2.35). It also revealed that H-Y stage III PD patients had a lower BMI than those with H-Y stage II (RR: 3.9, 95% CI: 0.1-7.7).[51] It might be due to the well-known risk factors of weight loss in PD patient included dyskinesia, dysphagia and hyposmia. In one longitudinal study, body weight and BMI

were not changed before the patient was diagnosed of PD, but BMI decreased

significantly after the diagnosis of PD, with a mean change in BMI of 2.13.[52] Besides,

another meta-analysis investigate the relationship between overweight/obesity and PD

found that 25≤BMI<30 may increase the risk of PD compared with BMI <25 in cohort

studies, while this risk was not found in case-control studies.[53] The causal relationships

between BMI and PD need further investigation.
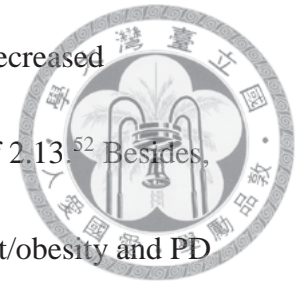
Dairy Products

In Health Professionals Follow-up Study and Nurses Health Study, there was a

positive association with dairy products and PD in men but not in women. The RRs were

1.8 (95% CI: 1.2-2.8, p for trend 0.004) and 1.1 (95% CI: 0.7-1.7, P value for trend 0.9)

for highest versus lowest quintile in men and women, respectively. No other food items

were related to PD risk in that study.[54] In Honolulu-Asia Aging study, Park et al reported

that intake of milk increased risk of PD, the RR was 2.3 (95% CI: 1.3-4.1, p for trend

0.007) for more than 16 oz of milk per day versus none.[55] A meta-analysis of all

prospective studies on dairy products showed a pooled RR of 1.6 (95% CI: 1.3-2.0) for

highest versus lowest quintile of milk or dairy products intake. The RR was 1.8 (95% CI:

1.4-2.4) in men and 1.3 (95% CI: 0.8-2.1) in women, respectively.[56] The mechanism of

diary product increased PD risk is unknown. The possible presence of dopaminergic

neurotoxins such as pesticides or polychlorinated biphenyls in dairy products may increase

the risk of PD.[54] Another explanation is that individuals who consume large amounts of

diary product may often have low serum uric acid levels.[57] Serum urate and uric acid have

been inversely correlated with the risk of PD.[58-60] Although the mechanism is unknown,

current evidence revealed a positive association between dairy products and PD, especially

in men.
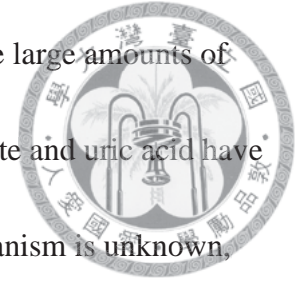
2.4.2 Protective Factors

Coffee

The relationship between coffee and PD has been studied broadly. In a meta-analysis

of eight case-control studies and five cohort studies,[61] the relative risks were 0.66 (95% CI

0.52-0.83) and 0.70 (95% CI: 0.56-0.88) for coffee drinkers versus non-coffee drinkers in

case-control studies and cohort studies respectively. The pooled RR was 0.69 (95% CI:

0.59-0.80) for coffee drinkers versus non-coffee drinkers and the RR was 0.75 (95% CI:

0.64-0.86) per three additional cups of coffee per day. The authors concluded that the

inverse association between coffee drinking and PD is strong because several confounders

such as age, gender, smoking and alcohol were all adjusted in most of the studies. Similar

finding also reported in the Health Professionals Follow-up Study (a cohort of men), there

is a strong inverse relationship of PD and coffee with RR 0.42 (95% CI: 0.23-0.78).[62]

However, in Nurses Health Study (a cohort of women), there was a U-shape relation with

lowest risk among women with moderate caffeine intake (1-3 cups of coffee per day).[62] In

contrast to the above findings, two prospective studies in Finland reported inverse

associations between coffee and PD of similar effect in men and women. The RR was 0.40

(95% CI: 0.23-0.71) for five cups of coffee per day or more versus none in five geographic

areas of Finland.[63] The RR was 0.26 (95% CI: 0.07-0.99) for 4-9 cups of coffee per day

versus none in Finnish Mobile Clinic study.[64] Caffeine acts as an adenosine receptor

antagonist suggests that it may has a neuroprotective effect.[65]

Smoking

A large number of studies have shown that cigarette smoking is inversely associated

with PD. A meta-analysis including 44 case-control and four cohort studies reported that a

pooled RR of 0.59 (95% CI: 0.54-0.63) for ever smokers versus non-smokers, 0.39 (95%

CI: 0.32-0.47) for current smokers versus non-smokers, and 0.80 (95% CI: 0.69-0.83) for

past smokers versus non-smokers.[61] Hernan et al found that the inverse association

between smoking and PD was stronger in cohort studies than in case-control studies.[61]

Another meta-analysis by including six prospective studies showed that a pooled of 0.51

(95% CI: 0.43-0.61) for ever smokers versus never smokers.[66] Though the extensive

inversely association between smoking and PD, it has been argued that the association

may be explained by numbers of bias. First, the information bias in the records of PD

diagnoses and smokers information. Second, there may be competing risks of selective

mortality from causes other than PD of smokers. Third, those who had PD may be less

prone to smoke or more prone to quit smoking. Although the causal relationship between

smoking and PD have been debated, a large number of prospective studies showed that

smoking decreases the risk of PD by around 50%. Experimental studies also showed that

nicotine and hydroquinone (the compounds of cigarette) did inhibit formation of α–

synuclein protein (protein that aggregates in Lewy bodies in PD).[67]

Alcohol

Unlike the strong protective effect in smoking and coffee drinking, the results from

the observational studies on alcohol consumption and PD risk are not consistent.[46] A

recent prospective cohort study (NIH-AARP Diet and Health Study) include 306,895

participants aged 50-71 years and 1,113 PD cases diagnosed between 2000 and 2006 and

found that the association differed by types of alcoholic beverages.[68] Compared with non-

beer drinkers, the odds ratios (ORs) for beer drinkers were 0.79 (95% CI: 0.68-0.92) for

less than one drink per day, 0.73 (95% CI: 0.50-1.07) for 1-1.99 drinks per day, and 0.86

(95% CI: 0.60-1.21) for more than 2 drinks per day, respectively. For liquor consumption,

there was a dose-dependent risk of PD, the ORs increased from 1.06 to 1.35 for < 1

drink/day to $\geq$ 2 drinks/day (p for trend < 0.03). A recent meta-analysis study reported

that a significant negative association was found between beer drinkers and PD risks (RR:

0.59, 95% CI 0.39-0.90), but not with wine and liquor (RR: 0.65, 95% CI: 0.47-0.90) for

male group. The negative association between beer consumption and risk of PD might be

due to the elevated uric acid effective in beer drinkers, because serum uric acid is inversely associated with PD risk and could delay the progression of PD.[69]
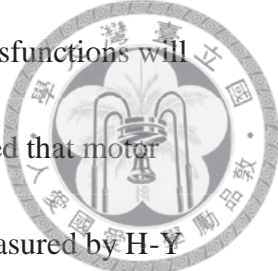
Uric acid

Higher serum uric acid level had been linked to low PD risk and also to slower clinical progression of PD.[70, 71] Two previous prospective cohort studies had assessed the relationship between uric acid concentration and PD. Higher serum uric acid was associated with lower PD risk (RR: 0.6, 95% CI 0.4-1.0 for median vs. below the median) in the Honolulu Asia Aging study of men.[72] The Rotterdam study also found lower PD risk with the increasing serum uric acid level (p for trend 0.04).[73] A prospective study based on health insurance data in British Columbia investigated the relationship between gout and risk of PD and found that subjects with gout and lower PD risk (RR:0.70, 95% CI 0.59-0.83).[74] Although there were few studies assessing the relationship between uric acid level and the PD risks, the prospective study design and their consistent results indicated a possible protective effect of uric acid. Besides, a hypothesis that uric acid played an antioxidant and radical scavenger of oxygen in aging was proposed in the 1980s.[75]

2.5 Quality of Life by Hoehn-Yahr Stage

Despite the medication or therapeutic intervention, the functional status of PD patients tend to progress gradually. Not only the motor disturbance but also non-motor

symptoms such as cognitive impairment, depression and autonomic dysfunctions will

affect the quality of life of PD patients. One previous study had reported that motor

deficit (measured by motor score of UPDRS) and disease severity (measured by H-Y

stage) explained only 18.9% of the variance of total Short Form 36 (SF-36), while non-

motor symptoms especially depression, sleep disorder and fatigue explained 61.7% of

the variance of SF-36 score.[76] This report seems to show that the quality of life is often

related to non-motor symptoms of PD. However, Hirayama et al studied the relationship

between quality of life and the PD disease severity and found that severity of PD

(measured by H-Y stage) is associated with quality of life measured by the World

Health Organization Quality of Life Instrument Short Form (WHOQOL-BREF). In that

study, the mean scores of four domains of WHOQOL-BREF including physical

capacity, psychological well-being, social relationships, and environment all decreased

significantly when the H-Y stage progressed.[77] A recent study also showed that the

health related quality of life (measured by PDQ-8 and PDQ-39) had significant

correlation with the H-Y stage (r_{PDQ-8}=0.376 and r_{PDQ-39}=0.442, both p<0.001).[78]

Leonaridi et al also prove that PD severity (measure by H-Y stage) is strongly

associated with reduced quality of life, increased disability and non-motor symptoms.[7]

These imply that H-Y stage may be a good model to assess the quality of life in PD

patient.

2.6 Cost-effectiveness Analysis in Parkinson's Disease
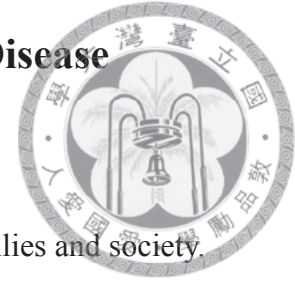
2.6.1 Cost Analysis of Parkinson's Disease

Parkinson's disease results in economic burden for patients, families and society.

Parkinson's disease patient often exhibit higher medical care utilization and costs. In

cost-of-illness studies, there are three types of costs including direct, indirect and

intangible costs. Direct costs often refer to direct treatment of the disease, while indirect

costs arise from consequences of the disease, such as loss of work or early retirement.

Intangible costs are those cannot be express by monetary values, such as pain,

depression or anxiety caused by a disease. Previous studies reported the annual cost of

PD patients vary widely. The annual direct cost ranged from $ 1,750 in Canada to

$17,560 in Germany.[79, 80] The variability in estimates also reflected differently in study

design, sample selection, case ascertainment as well as the different reimbursement.

Huse et al evaluate the burden of illness in Parkinson's disease and reported that total

annual direct costs were $23,101 (SD 27,529) per patient with PD versus $ 11,247 (SD

16,486) with controls. The direct cost calculated in that study include inpatient acute

care, inpatient non-acute (or long-term) care, emergency care, outpatient medical care,

and outpatient pharmacy.[81] In that study, the largest component for the total burden is

productivity loss (49.4%) and uncompensated care (18.8%). Most of the direct cost is

come from inpatient care and account for 20% of total cost. Johnson et al incorporated

the data including dementia rate, direct and indirect costs and health utility by H-Y stage

into a model to evaluate possible economic consequences of slowing progression of PD.

They reported that reducing PD progression rate could produce significant economic

benefit.[82]
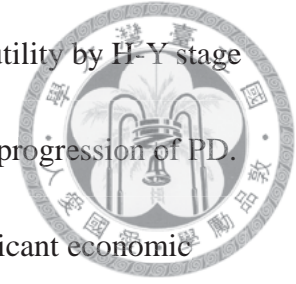
2.6.2 Cost Effectiveness Analysis of Parkinson's Disease

Cost-effectiveness analysis is a form of economic analysis that compares the relative costs

and outcomes (effects) of two or more courses of action. Most studies use surrogate

endpoints or focus on PD symptoms severity, complications, or impact on patient quality

of life. However, due to the wild spectrum of PD symptoms and its complications, it is

hard to assess the clinical effectiveness. Most of the cost-effectiveness study have used the

quality-adjusted life years (QALY) as a measurement of health related quality of life

(HRQoL). The QALY comprises two parts: 1. the time component that considers the gain

or loss of life time due to the choice of a certain treatment or intervention; 2. The HRQoL

is measure by its value on a scale from 0 (death) to 1 (perfect health).[83]

Lindgren et al evaluated the cost effectiveness of early treatment of PD with the

dopamine agonist cabergoline (with possible later addition of levodopa) compared with

standard levodopa therapy with respect to onset of motor complications. The study

reported that patients treated with cabergoline gained 0.31 years without motor

complications, at additional cost of 4,300 euros over a period of 5 year (13,900 euros per

year of motor complications avoided).[84] However, only direct costs were included in that study. Haycox et al developed a Markov model to compare rasagiline (MAO-B inhibitor) with the dopamine agonist pramipexole in early PD patients.[85] Compared with pramipexole, use of the rasagiline could prolong the time to levodopa initiation by 25% through a gain of 0.83 levodopa-free years (95% CI: 0.56-1.1). Besides, use of the rasagiline strategy was reported to generate a 5% gain in QALYs over 5 years compared with the pramipexole use. Dams et al review models of the cost effectiveness of treatments for PD.[86] Patients with early and advanced PD stages were evaluate, especially with motor complications. The outcome assessment include QALY, life expectancy, UPDRS score decreases…etc. There are two type of models including decision trees and Markov models. In that review, progression of disease measured by "off" times per day or H-Y stage were used as outcome to evaluate the costs and effectiveness of drug treatment or surgical intervention. However, most the cost-effectiveness study evaluated the treatment effect of the PD patient. There was little literature about the cost effectiveness of PD screening.
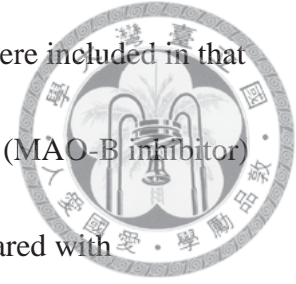
Chapter 3 Study Design and Data Source

3.1 Study Cohort

Study subjects enrolled in our study for the following analysis are originated from the participants involved in Keelung community-based integrated screening program (KCIS) from 2001 to 2004. The details of the KCIS program have been described in full elsewhere.[87] In brief, the KCIS program was not only a mass screening program for five neoplastic diseases and three non-neoplastic diseases but also included baseline survey on demographics, life style factors, reproductive history, menstrual status, dietary habits, personal disease. Sampling scheme for inviting participants was based on population registry in contemporaneous period as conducted for the KCIS program mentioned above. By dint of the KCIS program, several intervention programs and surveys have been considered since 2000. A 2001 one-stage neurological survey for idiopathic PD, by random setection of screening activity, provided a natural comparison similar to a randomized controlled trial. Of 20,951 residents aged 40 years or older participating in the KCIS program, 11,332 subjects were administered the active detection method and the remaining 9,621 subjects were subjected to the passive detection method. By the linkage of the screened subjects with health insurance claims records, we found 88 and 59 PD cases diagnosed before the year 2001 in the active and passive detection groups, respectively. The

active method included the 11,244 residents invited to attend the KCIS program in 2001.

The H-Y stage of the 58 PD cases diagnosed in 2001 was confirmed by the neurologists.

We reviewed the chart of all the 370 PD cases diagnosed by the linkage with health

insurance claims records from 2001 to 2004 and got 107 of them described H-Y stage

when PD diagnosed.
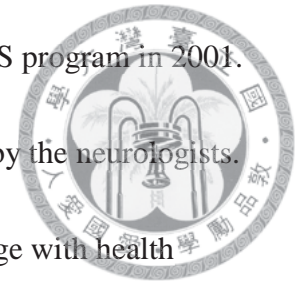
3.2 Study design

3.2.1 Cross-sectional survey

For the part I of this study "Using a population-based cohort study to compare the two

detection methods for detecting Parkinson's disease", we used a one-stage method in a

cross-sectional survey to detect PD. A total of 58 PD cases were detected.

PD ascertainment in active detection method

In this Keelung neurological survey, each of 11,244 participants was evaluated for

Parkinson's disease by neurologists from National Taiwan University Hospital using a

standardized diagnostic protocol including neurological examination, motor function

examination, and a thorough standardized history. The Unified Parkinson's Disease Rating

Scale (UPDRS)[88] was used to examine motor function.

The UPDRS is made up of five sections as follows:

- Part I: evaluation of mentation, behavior, and mood

- Part II: self-evaluation of the activities of daily life (ADLs) including speech, swallowing, handwriting, dressing, hygiene, falling, salivating, turning in bed, walking, and cutting food

- Part III: clinician-scored monitored motor evaluation

- Part IV: Hoehn and Yahr staging of severity of Parkinson's disease

- Part V: Schwab and England ADL scale

The four cardinal signs for parkinsonism are resting tremor, rigidity, bradykinesia, and impaired postural reflex. We defined those with parkinsonism as subjects in whom at least two of four cardinal signs were present. PD was diagnosed by ruling out parkinsonism caused by other reasons, such as vascular disease-related parkinsonism, drug-induced parkinsonism, multiple system atrophy, and parkinsonism secondary to brain insults. Except for subjects previously diagnosed with PD, every newly diagnosed PD case was evaluated again by another neurologist. The diagnoses were reviewed and discussed by a group of senior neurologists. The remaining 11,186 non-PD cases were followed by linkage of these screenees with health insurance claims record to track potential diagnosis of PD between 2001 and 2004.

PD ascertainment in passive detection method

For the passive method, 9,560 subjects filled out the screening questionnaires for Parkinson's disease. The validation of the questionnaires has been described elsewhere.[89,]

[90] The overall validity of this instrument was measured in a hospital sample of 30 patients with Parkinson's disease and the sensitivity was 100%. Specificity was investigated in 30 hospital visitors free of Parkinson's disease and other diseases and found to be 95%. Subjects who screened positive for Parkinson's disease were informed by a trained nurse to seek medical help. We examined screenee data for 2001 to 2004 to estimate the incidence rate by year by the linkage of these screenees with the National Health Insurance claims for PD, using the International Classification of Disease, Ninth Revision (ICD-9) code 332.0 for Parkinson's disease. We defined the PD cases if the code 332.0 appeared consecutively more than 3 times in the same individual. The KCIS project was approved by local health committee, which was run by the health authority in Keelung.
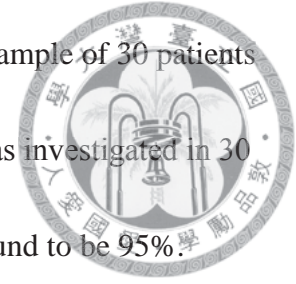
3.2.2 Natural History of Parkinson's Disease with Hoehn-Yahr Stage with Stochastic Process Based on Case-cohort Design

For the second part, since we did not have complete information on H-Y stage, we used a non-standard case-cohort design as mentioned in the chapter 2 of literature review for assessing the natural history of H-Y stage-based Parkinson's disease. Because the average age onset of PD is around 60 years old. We included participants age 60 and older for the following analysis.

Of 9,970 subjects age 60 and older involved in 2001, we excluded 141 PD cases diagnosed before the year 2001 by the linkage of the screened subjects with health insurance claims

records. Fifty-five new PD cases was detected by the screening program. The H-Y stage of

the 55 PD cases diagnosed in 2001 was confirmed by the neurologists. The remaining 9,774

non-PD cases were followed by linkage of these screenees with health insurance claims

record to track potential diagnosis of PD between 2001 and 2004. There were 208 PD cases

diagnosed by the linkage with health insurance claims records from 2001 to 2004. We

ascertained 62 of 208 PD cases to confirm their H-Y stage by chart review. The flow chart

of the participant age 60 and older was illustrated in figure 5-2-1.
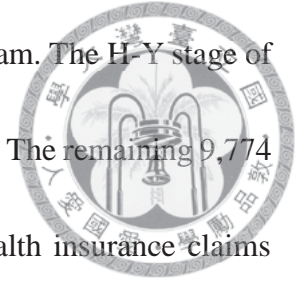
The sampling fraction of screening detective and clinical detective cases was 1 (55/55)

and 62/208, respectively. These two sampling fractions in each state would be applied to get

transitional probability in the following models by using Bayesian inversion.

3.2.3 Data Collection

Information of anthropometric measurement, blood pressure measurement,

biochemical markers, personal medical history, food intake questionnaire, and life style

factors were collected and described as follows.

Anthropometric measurement

Body height, waist and hip circumferences were measured by a trained staff to the

nearest 0.1 cm. Body weight (BW) was measured to the nearest 0.1 kg. Waist

circumference was measured at the midway point between the inferior margin of the last

rib and iliac crest in a horizontal plane. Hip circumference was measured as the maximal

circumference over the buttocks. Body mass index (BMI) was calculated as weight (kg)

divided by height squared (m2).

Blood pressure measurement

Blood pressure (BP) was measured with an automated sphygmomanometer twice

with five-minute headway. BP was then calculated according to an average of the two

measurements. High BP was defined as a systolic BP$\geqq$140mmHg and/or diastolic BP$\geqq$

90mmHg.

Biochemical markers

A venous blood sample was taken after 12 hours of fasting for measuring plasma

glucose, triglycerides, total cholesterol (TCHO), low-density lipoprotein (LDL)

cholesterol and high-density lipoprotein (HDL) cholesterol, serum uric acid(SUA),

glutamyl oxaloacetic trasaminase (GOT), glutamyl pyrubic transaminase (GPT), blood

urea nitrogen (BUN), creatinine…ect. Low uric acid level wad defined as SUA<5.5

mg/dl.

Questionnaire

Demographic data, personal medical history, family medical history, lifestyle factors,

and dietary intake habits were collected from a structured questionnaire administered by a

trained staff. Personal and family medical history included the chronic diseases, such as

hypertension, diabetes mellitus, gout, hyperlipidemia, cardiovascular disease (CAD),

cerebrovascular disease…etc, and cancers, such as breast cancer, cervical cancer, colon

cancer…ect. Lifestyle factors such as cigarette smoking, alcohol drinking and betel quid

chewing were classified as never, quit and current user. About the diet intake habits, the

food molds and standard dishes of each food were displayed to show the proportion of

each food that was consumed at one time. Every participant was asked about the diet

habits during past six months food categories include meat, vegetables, fruits, beans,

viscus, fish, seafood, milk and caffeine drinks. Frequency of every food category intake

was divided into five groups: more than two times per day, one time per day, 2-3 times per

week, 2-3 times per month, and never or seldom use. We defined frequencies less than 2-3

times per week as less intake of that food categories.

3.2.4 Homogeneous Markov model incorporated with covariates associated with the transition rates

We incorporated the covariate that would possible associated with the transition rates

with various stochastic processes (see below) according to the previous literature review.

Variables such as age, sex, smoking, coffee drinking and alcohol drinking (listed in table

5-2-5) were put into the model from normal to SD phase in three-state Markov model.

Variables include age and coffee drinking were incorporated to the model from SD phase

to CD phase.

3.2.5 Cost-effectiveness analysis for early detection of Parkinson's disease

We used a five-state Markov model to construct cost-effectiveness of screening based

on the simulated experiments on the randomized strategies. A controlled trial with

hypothetical cohort of general population aged 60 years and older were simulated for the

disease progression of PD with H-Y stage by different screening regimes (see Figure 3-1).

Each subject was followed up for 20 years or to death. The decision structure for the

control group was illustrated in Figure 3-2-1. The symbol in the end of each treatment

arm, Ⓜ, indicates a Markov chain for the stochastic process for advanced PD evolving

with time. We used 1 year as the length of each cycle in the Markov decision model. We

used both deterministic and probabilistic cost-effectiveness approach to perform CEA

analysis.

Chapter 4 Hoehn-Yahr stage-based natural history of

PD with Stochastic Process

4.1 Homogeneous Markov model

4.1.1 Model Specification

Three-state Markov Model without H-Y stage

We use a three-state homogenous Markov Model to describe the natural history of PD. The disease natural history was modelled with a continuous-time Markov process in which X(t), the state of an individual at time t, is a random variable with a state space $\Omega=\{0,1,2\}$, where 0 represents free of PD, 1 represents PD in the SD phase, and 2 represents PD in the CD phase
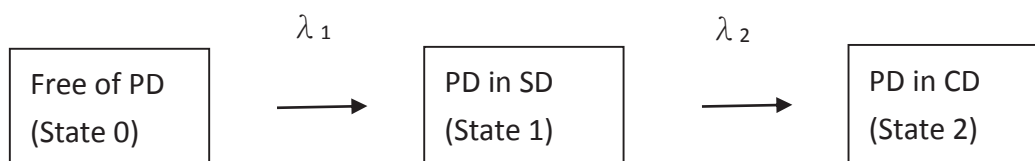
Figure 4-1 A three-state disease progression model.

We assigned the time of transition from state 0 to state 1 and state 1 to state 2 with two exponential distributions due to Markov property. The state 2 is defined as absorbing

state. The transition rates in the three-state model can be expressed as an intensity matrix,

$$
Q = \begin{array}{c} \\ 0 \\ 1 \\ 2 \end{array}
\begin{array}{ccc} 0 & 1 & 2 \\ \end{array}
\begin{pmatrix} -\lambda_1 & \lambda_1 & 0 \\ 0 & -\lambda_2 & \lambda_2 \\ 0 & 0 & 0 \end{pmatrix}
\tag{4-1}
$$

Based on the backward Kolmogorov equations, and following the convention for denoting stochastic processes, the transition probability matrix $\mathbf{P}(t)$, with elements $P_{ij}(t)$ denoting the transition probability from state i to state j, related to $\mathbf{Q_t}$ (Cox and Miller, 1965; Chiang, 1980) may be written as follows:

$$
\frac{d}{dt}\mathbf{P}(t) = \mathbf{Q_t}\mathbf{P}(t) \qquad t \geq 0
\tag{4-2}
$$

subject to $\mathbf{P}(0) = \mathbf{I}$

The matrix of transition probabilities denoted by $\mathbf{P}(t)$ for staying in free of PD, transitions from free of PD to state 1 and from free of PD to state 2 can be expressed as follows:

$$
\mathbf{P}(t) = \begin{pmatrix} P_{00}(t) & P_{01}(t) & P_{02}(t) \\ 0 & P_{11}(t) & P_{12}(t) \\ 0 & 0 & 1 \end{pmatrix}
\tag{4-3}
$$

Five-state Markov Model with H-Y stage

For the SD and CD phase being classified into early H-Y (I&II) and late H-Y (III-V), the above three-state Markov model can be extended to a five-state Markov mode, as

delineated in Figure 4-2 as follows:
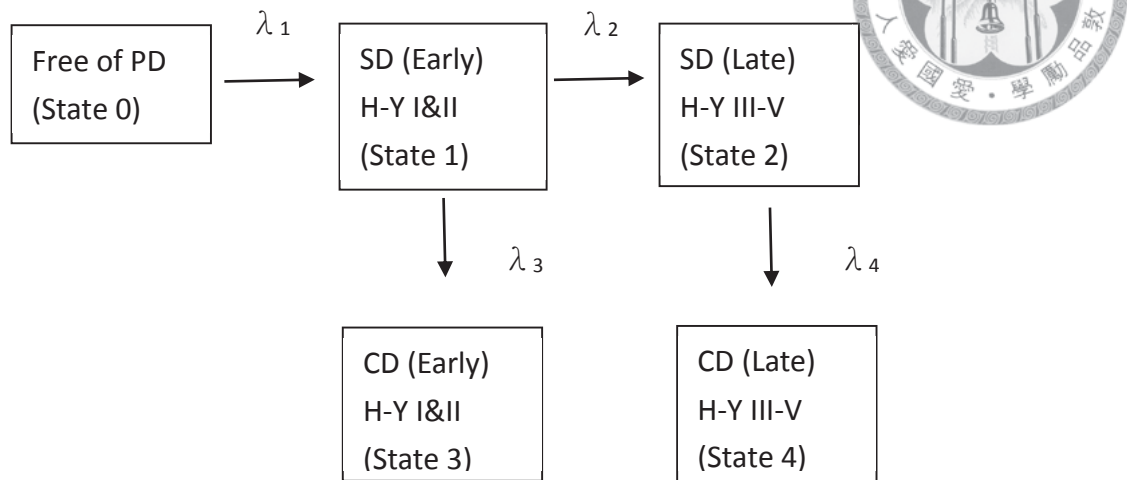
Figure 4-2 A five-state disease progression model.

The intensity matrix is expressed as

$$
Q(t) = \text{state} \;
\begin{array}{c}
0 \\ 1 \\ 2 \\ 3 \\ 4
\end{array}
\begin{pmatrix}
-\lambda_1 & \lambda_1 & 0 & 0 & 0 \\
0 & -(\lambda_2 + \lambda_3) & \lambda_2 & \lambda_3 & 0 \\
0 & 0 & -\lambda_4 & 0 & \lambda_4 \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0
\end{pmatrix}
\tag{4-4}
$$

PD is classified by H-Y stage. The state space $\Omega = \{0,1,2,3,4\}$, where state 0 represents free

of PD, state 1 represents SD in early H-Y stage (I&II) PD, state 2 represents SD in late H-

Y stage (III-V) PD, state 3 represents CD in early H-Y stage (I&II) PD, and state 4

represents CD in late H-Y stage (III-V) PD.

Again, the intensity of transition probabilities matrix **P**(t) are derived in a similar manner.

4.1.2 Likelihood

The detailed likelihood functions for estimating the natural history parameters are decomposed by round of screens and detection modes.

Three-State Markov model

(1) Active group at prevalent Screen

Suppose subjects invited to active screen (prevalent screen) at age m, the probabilities of being PD-free (P_{s1_0}) and screen-detected PD (P_{s1_1}) are written as follows.

P_{s1_0} (Probability of being PD-free at first screen)

$$= \frac{\text{Probability of PD-free at age of entry } m}{(\text{Probability of PD-free at age of entry } m \ + \text{Probability of SD PD at age of entry } m)}$$

$$= \frac{P_{00}(m)}{P_{00}(m) + P_{01}(m)}$$

(4-5)

P_{s1_1} (Probability of being SD PD at first screen)

$$= \frac{\text{Probability of SD at age of entry } m}{(\text{Probability of PD-free at age of entry } m \ + \text{Probability of SD PD at age of entry } m)}$$

$$= \frac{P_{01}(m)}{P_{00}(m) + P_{01}(m)}$$

(4-6)

(2) Active group in the follow-up period

There were two possibilities in the follow-up period after the prevalent screen for those considered as PD-free at prevalent screen. The first was clinically-detected (CD) cases due to symptoms and signs, and the second was censored subjects until the end of follow-up. The probability of CD cases (P_{f_2}) and censored cases (P_{f_c}) are expressed as follows.

P_{f_2}(Probability density of surfacing to clinical-detected state at time t)
= (Probability of transition from PD-free to SD state in t and instantaneously progress to CD at t)
$= P_{01}(t) \times \lambda_2$ (4-7)

P_{f_c}(Probability of not being clinical-detected during follow up period in time t)
= (Probability of staying in PD-free or probability of entering to SD state in t)
$= P_{00}(t) + P_{01}(t)$ (4-8)

Note that, in the above formulae, t is the time interval between the prevalent and the end of follow-up, or time between the diagnosis of CD patients and first screen for the CD patients.

(3) Passive Group

The probabilities of developing clinically detected Parkinson's disease (P_{P_2}) and not being diagnosed as Parkinson's disease (P_{P_c}) for those not invited to the community-based active screen are expressed as follows. In the following formula, m represents the

age at the time when subjects were invited to community-based screen which did not

contain the examination for Parkinson's disease (initial time of study), and t_2 represents

the time period from the initial time of study to the diagnosis of clinically-detected

Parkinson's disease or to the end of the follow-up.

P_{p_2}(Probability of developing CD in the passive group

$=$

$\frac{[(\textit{Probability of free of PD at age of first invitation } m \times \textit{probability of surfacing to CD state at time } t_2)}{+ (\textit{probability of being SD state at age of first invitation } m \times \textit{probability of surfacing to CD state at time } t_2)}}{\textit{Prabability of free of PD +probability of SD state at age of entry } m}$

$= \dfrac{[P_{00}(m) \times P_{01}(t_2) \times \lambda_2 + P_{01}(m) \times P_{11}(t_2) \times \lambda_2]}{[P_{00}(m) + P_{01}(m)]}$ (4-9)

P_{p_c}(Probability of not developing CD in the passive group)

$=$

$\frac{[(\textit{Probability of PD−free at age of first invitation } m \times \textit{probability of staying in PD−free or entering into SD state in time } t_2) + (\textit{probability of SD state at age of first invitation } m \times \textit{probability of staying in SD state in time } t_2)]}{\textit{Probability of free of PD+probability of SD state at age of entry } m}$

$= \dfrac{[P_{00}(m) \times (P_{00}(t_2) + P_{01}(t_2)) + P_{01}(m) \times P_{11}(t_2)]}{[P_{00}(m) + P_{01}(m)]}$ (4-10)

Random subset of samples for the three-state Markov model

For some special study design such as a case-cohort study, only a fraction of cohort

was sampled for study. The likelihood function for estimation is based on the conditional

probability for subjects in different detection modes and rounds given the sample was

selected (S=1).

(1) Active group at prevalent Screen

Applying the Bayesian conversion, the conditional probability of being PD-free ($P^*_{s1\_0}$) and screen-detected PD ($P^*_{s1\_1}$) are written as follows.

$P^*_{s1\_0}$(Conditional probability of PD-free at first screen given the selected sample)

$$= \Pr\left(P_{s1\_0} \mid S = 1\right)$$

$$= \frac{\Pr\left(S = 1 \mid P_{s1\_0}\right) \times P_{s1\_0}}{\sum\limits_{i \in 0,1} \Pr\left(S = 1 \mid P_{s1\_i}\right) \times P_{s1\_i}}$$

$$= \frac{\pi_{s1\_0} \times P_{s1\_0}}{\sum\limits_{i \in 0,1} \pi_{s1\_i} \times P_{s1\_i}}$$

$$(4\text{-}11)$$

$P^*_{s1\_1}$(Conditional probability of SD PD at first screen given the selected sample)

$$= \Pr\left(P_{s1\_1} \mid S = 1\right)$$

$$= \frac{\pi_{s1\_1} \times P_{s1\_1}}{\sum\limits_{i \in 0,1} \pi_{s1\_i} \times P_{s1\_i}}$$

$$(4\text{-}12)$$

where π_{s1_0} and π_{s1_1} are random sample fractions for PD-free and SD PD at the prevalent screens.

(2) Active group in the follow-up period

The probabilities of sampled CD cases ($P^*_{f\_2}$) and censored cases ($P^*_{f\_c}$) are derived in a similar way and expressed as follows.

$P_{f1\_2}^{*}$(Conditional probability of being clinically-detected in the follow-up period given the selected sample)

$= \Pr\left(P_{f1\_2'} \mid S = 1\right)$

$= \dfrac{\pi_{f\_2'} \times P_{f\_2'}}{\displaystyle\sum_{i \in 2',c} \pi_{f\_i} \times P_{f\_i}}$

(4-13)

$P_{f1\_c}^{*}$(Conditional probability of not being clinically-detected in the follow-up period given the selected sample)

$= \Pr\left(P_{f1\_c} \mid S = 1\right)$

$= \dfrac{\pi_{f\_c} \times P_{f\_c}}{\displaystyle\sum_{i \in 2',c} \pi_{f\_i} \times P_{f\_i}}$

(4-14)

Note that in the above formulae, it was cumulative probability of developing clinically-detected Parkinson's disease in the follow-up period $\left(P_{f\_2'} = P_{02}(t)\right)$ used instead of probability density $\left(P_{f\_2} = P_{01}(t) \times \lambda_2\right)$ shown in equation (4-7) due to the derivation for conditional probability in the Bayesian approach.

(3) Passive Group

The conditional probabilities for selected samples of developing clinically detected Parkinson's disease ($P_{P\_2}^{*}$) and not being diagnosed as Parkinson's disease ($P_{P\_c}^{*}$) for those not invited to the community-based active screen are expressed as follows.

$P_{P\_2}^{*}$(Conditional probability of developing CD in the passive group given the selected sample)

$= \Pr\left(P_{P\_2'} \mid S = 1\right)$

$= \dfrac{\pi_{P\_2'} \times P_{P\_2'}}{\displaystyle\sum_{i \in 2',c} \pi_{P\_i} \times P_{P\_i}}$

(4-15)

$P^*_{P\_c}$(Probability of not developing CD in the passive group)

$$= \Pr\left(P_{P\_c} \mid S = 1\right)$$

$$= \frac{\pi_{P\_c} \times P_{P\_c}}{\sum\limits_{i \in 2',c} \pi_{P\_i} \times P_{P\_i}}$$

<div align="right">(4-16)</div>

Similarly, it was cumulative probability of developing clinically-detected Parkinson's disease in the passive group $\left(P_{f\_2'}\right)$ used instead of probability density $\left(P_{f\_2}\right)$ shown in equation (4-9).

Five-State Markov model

(1) Active group at prevalent Screen

The probabilities of being PD-free (P_{s1_0}), SD H-Y I/II (P_{s1_1}), and SD H-Y III+ (P_{s1_2}) are written as follows.

$$P_{s1\_0} \text{ (Probability of being PD-free at first screen)} = \frac{P_{00}(m)}{P_{00}(m) + P_{01}(m) + P_{02}(m)} \tag{4-17}$$

$$P_{s1\_1} \text{ (Probability of SD H-Y 1/2 at first screen)} = \frac{P_{01}(m)}{P_{00}(m) + P_{01}(m) + P_{02}(m)} \tag{4-18}$$

$$P_{s1\_2} \text{ (Probability of SD H-Y 3+ at first screen)} = \frac{P_{02}(m)}{P_{00}(m) + P_{01}(m) + P_{02}(m)} \tag{4-19}$$

(2) Active group in the follow-up period

The probability of CD H-Y I/II (P_{f_3}), CD H-Y III+ (P_{f_4}) and censored cases (P_{f_c}) are expressed as follows.

P_{f_3}(Probability density of entering into CD H-Y 1/2 at time t) $= P_{01}(t) \times \lambda_3$ (4-20)

P_{f_3}(Probability density of entering into CD H-Y 3+ at time t) $= P_{02}(t) \times \lambda_4$ (4-21)

P_{f_c}(Probability of not being clinically-detected during follow-up period in time t)
$= P_{00}(t) + P_{01}(t) + P_{02}(t)$ (4-22)
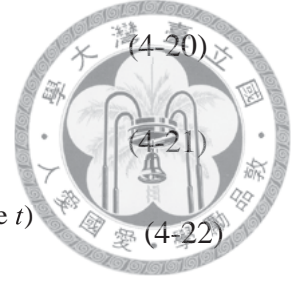
(3) Passive Group

The probabilities of developing clinically detected Parkinson's disease H-Y I/II (P_{P_3}), H-Y III+ (P_{P_4}) and not being diagnosed as Parkinson's disease (P_{P_c}) in the passive group are expressed as follows.

P_{P_3}(Probability of developing CD H-Y 1/2 in the passive group at t_2)

$$= \frac{\left[P_{00}(m) \times P_{01}(t_2) \times \lambda_3 + P_{01}(m) \times P_{11}(t_2) \times \lambda_3 \right]}{\left[P_{00}(m) + P_{01}(m) + P_{02}(m) \right]}$$ (4-23)

P_{P_4}(Probability of developing CD H-Y 3+ in the passive group at t_2)

$$= \frac{\left[P_{00}(m) \times P_{02}(t_2) \times \lambda_4 + P_{01}(m) \times P_{12}(t_2) \times \lambda_4 + P_{02}(m) \times P_{22}(t_2) \times \lambda_4 \right]}{\left[P_{00}(m) + P_{01}(m) + P_{02}(m) \right]}$$ (4-24)

P_{P_c}(Probability of not developing CD in the passive group in time t_2)

$$= \frac{\left[P_{00}(m) \times \left(P_{00}(t_2) + P_{01}(t_2) + P_{02}(t_2) \right) + P_{01}(m) \times \left(P_{11}(t_2) + P_{12}(t_2) \right) + P_{02}(m) \times P_{22}(t_2) \right]}{\left[P_{00}(m) + P_{01}(m) + P_{02}(m) \right]}$$

(4-25)

Random subset of samples for the five-state Markov model

(1) Active group at prevalent Screen

Applying the Bayesian conversion, the conditional probability of being PD-free ($P^*_{s1\_0}$), SD H-Y I/II ($P^*_{s1\_1}$), and SD H-Y III ($P^*_{s1\_2}$) are written as follows.

$P^*_{s1\_0}$(Conditional probability of PD-free at first screen given the selected sample)

$$= \frac{\pi_{s1\_0} \times P_{s1\_0}}{\sum\limits_{i \in 0,1,2} \pi_{s1\_i} \times P_{s1\_i}} \qquad (4-26)$$

$P^*_{s1\_1}$(Conditional probability of SD H-Y 1/2 at first screen given the selected sample)

$$= \frac{\pi_{s1\_1} \times P_{s1\_1}}{\sum\limits_{i \in 0,1,2} \pi_{s1\_i} \times P_{s1\_i}} \qquad (4-27)$$

$P^*_{s1\_1}$(Conditional probability of SD H-Y 3+ at first screen given the selected sample)

$$= \frac{\pi_{s1\_2} \times P_{s1\_2}}{\sum\limits_{i \in 0,1,2} \pi_{s1\_i} \times P_{s1\_i}} \qquad (4-28)$$

where π_{s1_0}, π_{s1_1} and π_{s1_2} are random sample fractions for PD-free, SD H-Y I/II, and SD H-Y III+ at the prevalent screens.

(2) Active group in the follow-up period

The probabilities of sampled CD H-Y I/II ($P^*_{f\_3}$), CD H-Y III+ ($P^*_{f\_4}$) and censored cases ($P^*_{f\_c}$) are derived in a similar vein and expressed as follows.

$P^*_{f1\_3}$(Conditional probability of being CD H-Y 1/2 in time t given the selected sample)

$$= \frac{\pi_{f\_3} \times P_{f\_3}}{\sum\limits_{i \in 3',4',c} \pi_{f\_i} \times P_{f\_i}} \qquad (4-29)$$

$P^*_{f1\_4}$(Conditional probability of being CD H-Y 3+ in time t given the selected sample)

$$= \frac{\pi_{f\_4'} \times P_{f\_4'}}{\sum\limits_{i \in 3',4',c} \pi_{f\_i} \times P_{f\_i}} \qquad (4-30)$$

$P^*_{f1\_c}$(Conditional probability of not being clinically-detected in the follow-up period given the selected sample)

$$= \Pr\left(P_{f1\_c} \mid S = 1\right)$$

$$= \frac{\pi_{f\_c} \times P_{f\_c}}{\sum\limits_{i \in 3',4',c} \pi_{f\_i} \times P_{f\_i}}$$

Similarly, it was cumulative probability of developing CD H-Y I/II $\left(P_{f\_3'} = P_{03}(t)\right)$ and

H-Y III+ $\left(P_{f\_4'} = P_{04}(t)\right)$ Parkinson's disease in the follow-up period used instead of

probability density $\left(P_{f\_3} = P_{02}(t) \times \lambda_3, \text{ and } P_{f\_4} = P_{03}(t) \times \lambda_4\right)$ shown in equation (4-7).

(3) Passive Group

The conditional probabilities for selected samples of developing CD H-Y I/II

($P^*_{P\_3}$), H-Y III+ ($P^*_{P\_4}$) Parkinson's disease and not being diagnosed as Parkinson's

disease ($P^*_{P\_c}$) in the passive group are expressed as follows.

$P^*_{P\_3}$(Conditional probability of developing CD H-Y 1/2 in the passive group given the selected sample)

$$= \frac{\pi_{P\_3'} \times P_{P\_3'}}{\sum\limits_{i \in 3',4',c} \pi_{P\_i} \times P_{P\_i}}$$

$P^*_{P\_4}$(Conditional probability of developing CD H-Y 3+ in the passive group given the selected sample)

$$= \frac{\pi_{P\_4'} \times P_{P\_4'}}{\sum\limits_{i \in 3',4',c} \pi_{P\_i} \times P_{P\_i}}$$

$P^*_{P\_c}$(Probability of not developing clinically-detected PD in the passive group)

$$= \frac{\pi_{P\_c} \times P_{P\_c}}{\sum\limits_{i \in 3',4',c} \pi_{P\_i} \times P_{P\_i}}$$

Similarly, it was cumulative probability of developing CD H-Y I/II $\left(P_{P\_3'} = P_{03}(t)\right)$ and

H-Y III+ $\left(P_{P\_4'} = P_{04}(t)\right)$ Parkinson's disease in the follow-up period used instead of

probability density $\left(P_{P\_3} = P_{02}(t) \times \lambda_3, \text{ and } P_{P\_4} = P_{03}(t) \times \lambda_4\right)$ shown in equation (4-7).

4.1.3 Estimation of parameter

The total likelihood and log-likelihood functions can be obtained using the

probability functions derived in the previous section. The maximum likelihood estimates

(MLEs) are the solutions of the simultaneous equations

$$\frac{\partial \ell(\cdot)}{\partial \theta} = 0, \tag{4-35}$$

where $\ell(\cdot)$ is the log-likelihood function and θ is the vector of parameters. The

variance–covariance matrix is derived from the inverse of the negative Hessian matrix,

evaluated at the MLE. The asymptotic confidence intervals for each estimate were also

calculated.

4.2 Incorporation of patient specific covariates

The effect of patient specific covariates, say *x*, on the three-state, and five-state

model was assessed by the exponential regression model. It is expressed as follows:

$$\lambda_i^m = \lambda_{i0} \exp(\beta_i \chi^m) \tag{4-36}$$

where λ_{i0} denote the baseline transition rate for transition rate *i* (*i*=1, 2 in the three-state

Markov model and *i*=1, 2, 3, 4 in the five-state Markov model), χ^m is a vector of

covariates for subject m, and β_i is a vector for the corresponding regression coefficients.

In the five-state Markov model, we estimated the effects of covariates on all four transition rates, $\lambda_1 - \lambda_4$. To assess whether the net force of progression from free of PD to CD with H-Y I/II was different from the net force of progression from free of PD to CD with H-Y III+, the Wald test was conducted with the following hypothesis

$$H_0: \beta_1 + \beta_2 + \beta_4 = \beta_1 + \beta_3$$

$$H_1: \beta_1 + \beta_2 + \beta_4 \neq \beta_1 + \beta_3$$

The Wald χ^2 statistics was computed as

$$\chi^2 = \frac{\hat{\beta}_2 + \hat{\beta}_4 - \hat{\beta}_3}{Var(\hat{\beta}_2 + \hat{\beta}_4 - \hat{\beta}_3)} \tag{4-37}$$

where $Var(\hat{\beta}_2 + \hat{\beta}_4 - \hat{\beta}_3)$ was derived from the inverse of negative Hessian matrix, evaluated at MLE. The term of $\hat{\beta}_2 + \hat{\beta}_4 - \hat{\beta}_3$ was called net force coefficient.

4.3 Simulation for the effect of screening policy

To elucidate the benefit from early detection of screening in terms of severe cases (H-Y stage III or more severe) reduction, we conducted a computer simulation to apply to a hypothetical cohort with the same sample size (n=9829) as we used in the current study. The simulation was for a 12-year period with 1-, 2-, 3-, 4-, and 6-yearly screening interval

and another scenario assuming no screen taking place (Figure 3-1).
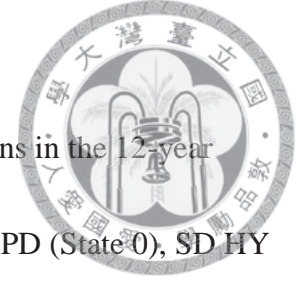
Taking 2-yearly screening as an example, there would be 7 screens in the 12-year

period. Let N denote the cohort size. The predicted number of free of PD (State 0), SD HY

I & II (State 1), and SD HY III-V (State 2) at prevalent screen were

$$n_{1,0} = N \times \frac{P_{00}(Age)}{P_{00}(Age)+P_{01}(Age)+P_{02}(Age)} \tag{4-38}$$

$$n_{1,1} = N \times \frac{P_{01}(Age)}{P_{00}(Age)+P_{01}(Age)+P_{02}(Age)}$$

$$n_{1,2} = N \times \frac{P_{02}(Age)}{P_{00}(Age)+P_{01}(Age)+P_{02}(Age)}$$

, respectively, where Age (60 in the current study) denotes age at prevalent screen. The

conditional probability of excluding State 3 (CD, HY I&II) and State 4 (CD, HY III-V)

was for left-truncating cases who had surfaced to the CD phase and not been recruited

for screening at age 60 years old.

The predicted number of those in State 0, State 1, and State 2 at second screen were

$$n_{2,0} = n_{1,0} \times P_{00}(2) \tag{4-39}$$

$$n_{2,1} = n_{1,0} \times P_{01}(2)$$

$$n_{2,2} = n_{1,0} \times P_{02}(2)$$

Those surfacing into the CD phase in either H-Y I&II (State 3) and H-Y III-V (State

4) between the first and the second screen were calculated as

$$n_{2,3} = n_{1,0} \times P_{03}(2) \tag{4-40}$$

$$n_{2,4} = n_{1,0} \times P_{04}(2)$$
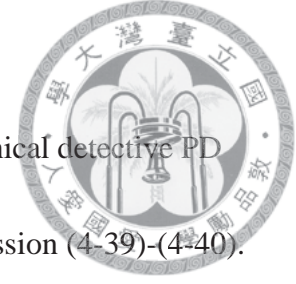
Similarly, the predicted numbers of screening detective and clinical detective PD

after the third screen can be derived in the same way following expression (4-39)-(4-40).

If there was no screening taking place, the predicted numbers of free of PD (state 0),

PD in SD H-Y I&II (State 1), SD H-Y III-V (State 2), CD H-Y I&II (State 3), and CD H-

Y III-V (State 4) in 12-year were

$$n_{c,0} = N \times \frac{P_{00}(Age) \times P_{00}(12)}{P_{00}(Age) + P_{01}(Age) + P_{02}(Age)} \qquad (4\text{-}41)$$

$$n_{c,1} = N \times \frac{P_{00}(Age) \times P_{01}(12) + P_{11}(Age) \times P_{11}(12)}{P_{00}(Age) + P_{01}(Age) + P_{02}(Age)}$$

$$n_{c,2} = N \times \frac{P_{00}(Age) \times P_{02}(12) + P_{01}(Age) \times P_{12}(12) + P_{02}(Age) \times P_{22}(12)}{P_{00}(Age) + P_{01}(Age) + P_{02}(Age)}$$

$$n_{c,3} = N \times \frac{P_{00}(Age) \times P_{03}(12) + P_{01}(Age) \times P_{13}(12)}{P_{00}(Age) + P_{01}(Age) + P_{02}(Age)}$$

$$n_{c,4} = N \times \frac{P_{00}(Age) \times P_{04}(12) + P_{01}(Age) \times P_{14}(12) + P_{02}(Age) \times P_{24}(12)}{P_{00}(Age) + P_{01}(Age) + P_{02}(Age)}$$

4.4 Cost-effectiveness Analysis

Intervention Strategies

The intervention strategies, as opposed to no screening (control), that were compared

in a cost-effectiveness analysis were active screening for PD of different inter-screening

intervals for elderly aged 60 years or older (Figure 3-2-1). Under no screening, patients

were diagnosed as PD when the clinical symptoms and signs appeared and the stage of the

disease was confirmed. For screening strategies, community subjects received active

screening for PD without clinical symptoms and signs were aware.

Markov Decision Tree and Assignment of Parameters

In this thesis, a Markov cycle tree was constructed by conjoining the five-state

stochastic process pertaining to the temporal natural history of PD. The decision tree starts

from the four decision nodes of no intervention, screening in 1-year, 2-year, and 3-year

intervals. The basic idea for constructing the Markov decision tree was to construct the

tree structure for the baseline group (no screening) as it represents the subjects following

the temporal natural history of PD and also the Markov process for the sequale of PD. As

depicted in Figure 3-2-2, the detailed tree structure for the temporal natural history of PD

takes other causes of death into account. Each node represents the chance of moving from

the current state to the possible outcomes in the next cycle following the Markov

assumption. For example, the screen-detected early (SD HY I/II) at the current time may

be in SD late (HYIII+) or still in the SD early (HY I/II) in the next cycle if the patient did

not die from other causes of death. Based on the Markov assumption, annual transition

probabilities for each chance node were computed by the application of instantaneous

rates estimated in the previous section. The annual transition probabilities for each

transition are listed in Table 4-6-1.

Figure 3-2-3 also gives a delineation of the Markov cycle tree for the evolution of

the sequela of PD starting from PD-free until death from PD or from other causes of death

(OCD). Note that the terminal status (denoted by the triangle) of each tree represents the

state at the end of each cycle and would return the corresponding state to the beginning of

the Markov node (denoted by the circle (M)), following the Markov assumption except

PD death and OCD defined as the absorbing states that no longer moves. The entire cohort

was simulated by using the Markov cycle tree in this way to give a series of outcomes

during the simulation period. The parameters related to the Markov cycle tree on the

progression to the sequela of PD and also the utility for each state are shown in the

decision tree.
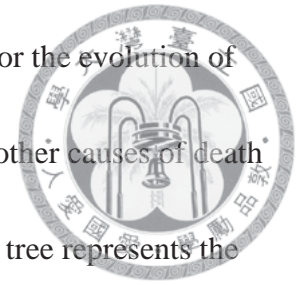
The tree structures for the five screening groups were similar to the baseline group.

The only difference between the screening group and the baseline group was the

possibility of entering into the treated states if the patients received the screening program

and treated for them the treatment efficacy would be given according to literatures. Listed

in Table 4-6-1, these base-case estimates were assigned to the decision tree structure. For

the parameters relating to the temporal natural history of PD, we specified their

distribution according to empirical estimates as well as their standard errors from the

empirical cohort.

Assignment of cost parameters

In addition to the cost involved in each specific test, since the Markov cycle tree can keep track of each disease state in each cycle, it is very straightforward to assign the corresponding cost parameter to each disease. The details in Table 4-6-1 are the base-case estimates of cost, which were further converted to $US with year 2008 values. Cost required for estimation included screen cost, outpatient cost, inpatient cost and home care cost. The outpatient cost was derived from the national health insurance data. We estimated the annual hospitalization cost according to the parameters from Shimbo et al.[91] The admission rates from different H-Y stage were derived from the parameters from Hassan et al.[92]

Outcome Measures

The outcome related to effectiveness is life year gained and quality-adjusted-life-year (QALY) gained in each screening strategy. We assigned effectiveness parameter as 0 if the individual was dead and assign the parameter as 1 if the individual was alive for a one-year cycle. Note that the utility values are those quoted from a previous study,[91] as described in Table 4-6-1.

All analyses were carried out from a societal perspective. Both effectiveness and costs were discounted at 3% annually.

Probability Cost-effectiveness Analyses

A series of incremental cost-effectiveness ratios (ICERs) were simulated with probabilistic sensitivity analysis, employing Monte Carlo simulation based on the specific assigned distributions of parameters mentioned above. In this thesis, the Markov Chain Monte Carlo (MCMC) technique was used to get the posterior distribution after integrating the second-order uncertainty from parameters and also integrated out the first-order uncertainty through micro-simulation. A total of 1000 times sampling based on a hypothetical cohort of 10,000 people was simulated. For those parameters with knowledge from previous studies and current empirical data, we applied Bayesian conjugated prior method to get the posterior distribution.

1. Prevalence of PD by each state

The number of counts(r) in each state follows a multinominal distribution and the corresponding probability(πi) of being each state follows its conjugated prior, Dirichlet distribution.

$$r \sim multi(n\,;\pi_1, \pi_2, \pi_3, \pi_4)$$

$$p(r) \propto \pi_1{}^{r_1} \pi_2{}^{r_2} ... \pi_k{}^{r_k}$$

$$r_j = 0,1,2...n\,;\ \sum_{j=1}^{k} r_j = n$$

$$\pi \sim Dirichlet\,(\alpha_1, \alpha_2, ..., \alpha_k)$$

$$p(\pi) \propto \pi_1{}^{\alpha_1 - 1} \pi_2{}^{\alpha_2 - 1} ... \pi_k{}^{\alpha_k - 1}$$

$$\alpha_1, ..., \alpha_k > 0; \quad \sum_{j=1}^{k} \pi_j = 1$$

$$p(\pi) \propto \pi_1^{\alpha_1 + r_1 - 1} \pi_2^{\alpha_2 + r_2 - 1} ... \pi_k^{\alpha_k + r_k - 1}$$

Posterior distribution: Dirichlet $(\alpha_1 + \gamma_1, \alpha_2 + \gamma_2, ..., \alpha_k + \gamma_k)$
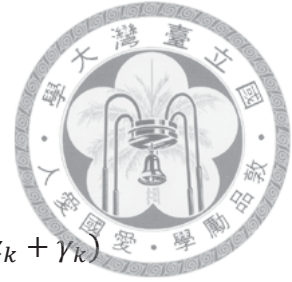
2. Transition rate for the disease natural history of PD

According to the five-state Markov model, we assumed that all participants were in any stage of the nature history of PD and the disease progression is irreversible. It was defined as free of PD (state 0), SD early (H-YI/II) phase (state 1), SD late (H-Y III+) phase (state2), CD early phase (state 3), CD late phase (state 4). There are four parameters $(\lambda_1 - \lambda_4)$ representing each transitional rate. We used Gamma distribution to assign the transition rate between each state in the natural history of PD.

3. Attendance rate

The attendance rate of screening was assumed to be 80%. The sensitivity analysis was done by using 60% and 100% attendance rate.

4. Cost distribution

The screen cost was derived from expert's opinion, which we applied triangular distribution for the screen cost. The lognormal distribution was applied to other cost items.

Chapter 5 Results

5.1 Part I: Compare the two detection methods for detecting

Parkinson's disease

The flow chart of the part I study is presented in Figure 5-1-1. We randomly assigned the 20,951 participants into one of two detection groups. By linkage of the screenee with the health insurance claims record, we found 88 and 59 IPD cases diagnosed before year 2001 in the active and passive detection groups, respectively. Fifty-eight IPD cases were detected from 11,244 participants who received active detective. Among the rest of the 11,186 participants in active detective method group, 134 cases were diagnosed with IPD in the following 4 years. In all, 34, 42, 27, and 31 cases were diagnosed in 2001, 2002, 2003, and 2004, respectively. The detection rate for each year was $561.8/10^5$, $377.9/10^5$, $243.2/10^5$, and $278.3/10^5$, respectively (refer to Table 5-1-1). Among 9,560 participants who received the passive method, 103 IPD cases were detected in the following 4 years: 16, 29, 17, and 27 cases diagnosed in 2001, 2002, 2003, and 2004, respectively. The detection rate for each year was $390.8/10^5$, $305.0/10^5$, $178.9/10^5$, and $283.0/10^5$, respectively (refer to Table 5-1-2).

Table 5-1-3 shows the baseline characteristic data for the two groups. The baseline

characteristics for the two groups did not differ obviously except for certain parameters (weight and systolic blood pressure) which may have been due to the large sample size.

Table 5-1-4 shows the distribution of H-Y stage of the IPD cases detected by the two methods. Of the remaining 233 PD cases diagnosed by the linkage with health insurance claims records, 65 of the 233 PD cases were ascertained their H-Y stage by char review. Of 65 cases, 39 were in the active detection group, and 26 in the passive group. We analyzed the detection of the two methods of PD in the early stage (H-Y stage I or stage II) versus the late stage (H-Y stage III or greater). In the active detection group, 80.4% of PD cases were detected in the early stage (H-Y stage I and II). In the passive detection group, only 61.5% PD cases were diagnosed in the early stage. The risk ratio of being at H-Y stage III or greater for the active versus the passive detection method was 0.51 (95% CI: 0.27-0.96). The results show that the active detection method could reduce 49% (95% CI: 4%-73%) of PD cases from H-Y stage I to III. For the 58 PD cases diagnosed in 2001, up to 93·1% of PD cases were detected in the early stage. The risk ratio in 2001of being H-Y stage III or greater for the active versus the passive detection method was 0.18 (95% CI: 0.06-0.52).

The cumulative detection rate for the two groups was calculated and the result shown in Figure 5-1-2. The active method was able to detect approximately 1.8-fold (95% CI: 1.42-2.34) the PD cases of the passive method (p<0.0001), as shown in the crude estimate

in Table 5-1-5.

Table 5-1-5 shows the multi-variable adjusted relative risk (RR) for the two methods to detect PD. Variables that differed significantly between the two groups in Table 5-1-3 were adjusted. After adjustment for age (RR: 1.2, 95% CI: 1.16-1.20), weight (RR: 1.0, 95% CI: 0.98-1.02), waist circumference (RR: 1.0, 95% CI: 0.99-1.03), systolic blood pressure (RR: 1.0, 95% CI: 0.98-1.00), and diastolic blood pressure (RR: 1.0, 95% CI: 1.00-1.02), the active method was able to detect 1.95 fold (95% CI: 1.51-2.52) the IPD cases of the passive method.

5.2 Part II: To Elucidate the temporal natural history of Hoehn-Yahr- stage-based Parkinson's disease with stochastic process

5.2.1 Three-state Markov model

The flow chart for the study population, subjects aged 60 years and older, used for the elucidation of the temporal disease natural history of Hoehn-Yahr-stage-based Parkinson's disease was diagrammed in Figure 5-2-1. In this analysis, there were a total of enrolled 9,970 elderly subjects, 5,327 in the active group and 4,623 in the passive group. There were 75 PD cases (screen-detected, SD) ascertained in the prevalent screen, and another 103 PD cases diagnosed due to clinical symptoms before the end of

2004. In the passive group, 85 clinically-detected (CD) Parkinson's diseases patients

were ascertained in the follow up period. The proportion of late stage Parkinson's

disease (H-Y III+) were 11% (7/64), 38% (11/29) and 33% (8/24) in the SD, CD in

active group and CD in passive group, respectively. Note that the information of

missing H-Y stage was 15% and 72% for SD and CD cases, respectively.
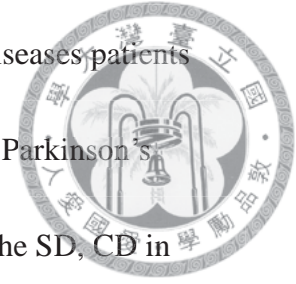
The estimated results of the temporal natural history for PD using a three-state

Markov model are shown in Table 5-2-2. The estimated annual incidence rate of screen-

detected PD for elderly subjects was 7.6 per 1000 person-years. Annual transition rate

from SD to CD was 0.6776 (95% CI: 0.5303-0.8429), which yielded 1.48 (95% CI;

1.21-1.89) years of sojourn time staying in the SD.

Figure 5-2-2 shows the cumulative risk of being PD in the SD and CD,

respectively. The cross-over of the two curves was at 2.8 years or so, half of which was

close to the mean sojourn time estimated above, which suggest an inter-screening

interval shall not be beyond 2.8 years. The absolute 20-year cumulative risks for PD

were 1% and 13.2% of those staying in the SD and those finally surfacing to the CD.

Figure 5-2-3 shows the risk of transition from the SD to the CD. The median

progression time from the SD to CD was 1.0 years. Once an old individual enters into

the SD, it is almost certain that he/she would surface to the CD without any treatment

during five-year follow-up. It is apparent that the progression from the SD to the CD was rather fast.

In this thesis, we estimated the temporal disease natural history of three-state Markov model based on PD-free subjects and PD cases whose H-Y stage information was available. Following the likelihood derived for the random subset of samples for the three-state Markov model mentioned in Section 4.2, the estimated results are shown in Table 5-2-3. The estimated incidence rate of screen-detected PD (8.2, 95% CI: 6.4-10.0 per 1000) was albeit slightly higher than that based on complete data (7.6 per 1000 in Table 5-2-2), and the transition rate from SD to CD (0.5935, 95% CI: 0.4330-0.7541) were slightly smaller than that with complete data (0.6776 in Table 5-2-2), respectively. Therefore, the estimated MST (1.68 years) was slightly longer than that estimated from the complete data (1.48 years, Table 5-2-2).

Figure 5-2-4 shows cumulative risk of being SD and CD Parkinson's disease based on the estimated results in Table 5-2-3. The cross-over of the two curves was also around 2.8 years. Figure 5-2-5 reveals the risk of transition from the SD to the CD. The median progression time from the SD to CD was around 1.2 year, which was slightly longer than its counterpart based on the complete data.

5.2.2 Five-state Markov model
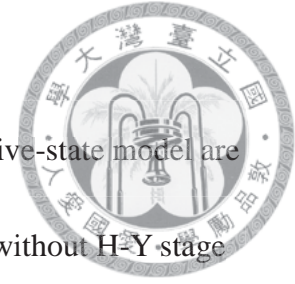
As far as H-Y stage is concerned, the estimated results for the five-state model are

shown in Table 5-2-4. In this approach, we treated those PD patients without H-Y stage

as unselected cases, and followed the likelihood derived in section 4-1 for the random

subset of samples for five-state Markov model. The estimate for incidence of SD was

similar to that estimated from the three state model, 7.8 per 1000. The transition rate

from H-Y I/II to H-Y III+ in the screen-detected stage (λ_2) was 0.2498 (95% CI:

0.1420-0.3576). The transition rates from SD to CD for early stage (H-Y I/II) (λ_3) and

late stage (H-Y III+) (λ_4) were 0.3982 (95% CI: 0.2564-0.5399) and 2.1227 (95% CI:

0.5109-3.7346), respectively.

Figure 5-2-6 shows the predicted 20-year risk of being advanced H-Y stage (III+)

for a 60-year-old subject was 5.2%. The corresponding risk for early H-Y was 9.3 %.

Divided by the SD and the CD, it can be observed that the majority of PD was

eventually surfaced to early H-Y PD cases, accounting for 8.2%, only 5.0% manifested

as the state of the CD for late H-Y PD cases during 20-years of follow-up. (Figure 5-2-

7)

Figure 5-2-7 shows the evolution of early H-Y stage and late H-Y stage. The

cross-over between SD early H-Y stage and CD early H-Y was around 4-year of follow

up. The cross-over between SD late H-Y and CD late H-Y was at very beginning of

follow-up.

5.2.3 Incorporation of patient specific covariates for the five-state Markov model

Table 5-2-5 shows the distribution of characteristics of subjects by Parkinson's disease. PD cases were more frequent in male (3.1%) than in female (2.3%) (p=0.0095). The proportion increased with age, from 1.2% for subjects aged 60-69, to 12% for those aged 90 years or older (p<0.0001). Subjects with lower BMI, smoking, low level of uric acid, less meat intake less fruit intake, and less coffee intake had higher proportion of PD cases than their complementary groups. The proportion seems even in different education level, drinking, and different level of vegetable intake, but not statistically significant except the marginal significance for low level of uric acid (p=0.0518) and lower BMI (p=0.0785).

Univariate analysis on single transition rate

Tables 5-2-6 ~ Tables 5-2-9 shows the results of univariate analysis on the four transition rates in separate models. For the transition from free of PD to SD H-Y I/II in the univariate analyses (Table 5-2-6), male, elderly age, low BMI (<22 kg/m^2), low uric acid (<5.5mg/dl), smoking, less meat intake, was statistically significant risk factors.

Alcohol drinking and less fruit intake also had higher risk for developing PD but only marginally statistically significant. Male had 58% higher risk (relative risk (RR) =1.58, 95% CI: 1.10-2.28). The incremental 10-year band age increased the risk of PD incidence by 88% (RR=1.88, 95% CI: 1.47-2.14). Elderly people with low BMI (<22 kg/m^2) had almost double risk for PD (95% CI: 1.4-3). Low uric acid (<5.5 mg/dl), ever smoking, and less meat intake had 50% excess risk of developing PD.
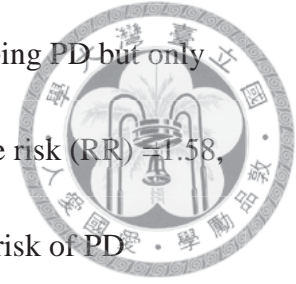
Considering the effect of covariates on transition from SD H-Y I/II to SD H-Y III+ only in the univariate analyses, only higher education level was statistically significant risk factor with the order of RR equal to 6.09 (95% CI: 2.28-16.26). Subjects with less intake of coffee (RR=0.33, 95% CI: 0.12-0.90) and low uric acid (RR=0.38, 95% CI: 0.17-0.89) were less likely to progress to late H-Y stage but remaining in screen-detected phase. The effect of age by 10-year was marginally statistically significant (RR=2.25, 95% CI: 0.97-5.21). (Table 5-2-7).

Table 5-2-8 shows the univariate analyses on the transition from SD H-Y I/II to CD H-Y I/II only. The results show the inverse relationship between the transition rate for entering into CD but remaining in early stage were noted for the covariates of male (RR=0.45, 95% CI: 0.24-0.87), per 10-year increased age (RR=0.36, 95% CI: 0.21-0.62), slimmer (RR=0.42, 95% CI: 0.20-0.87), and ever smoking (RR=0.49, 95% CI: 0.24-0.99).

For the transition from SD to CD for patients in the late stage (H-Y III+), there were lacking of significant risk factors identified, probably due to sparse cases for the late stage of PD in the study population for this thesis (Table 5-2-9).

Age, gender, and BMI-adjusted analysis on single transition rate

From the univariate analysis on single transition rate in previous section, a particular interest was placed on the similar analyses but adjusting for age, gender, and BMI. The estimates results for the four transition rates in the separated models are shown in Table 5-2-10 ~ 5-2-13. Table 5-2-10 shows that after adjusting for age, gender and BMI, low uric acid was positively associated with the incidence of SD Parkinson's disease (adjusted RR (aRR)=1.70, 95% CI: 1.16-2.49). Less intake of meat was marginally significant (aRR=1.38, 95% CI: 0.96-1.99), but ever smoking became insignificant (aRR=1.23, 95% CI: 0.80-1.90).

For the transition from SD H-Y I/II to SD H-Y III+, higher education level was still statistically significant after adjusting for age, gender, and BMI (aRR=10.15, 95% CI: 2.94-35.02). Subjects with low uric acid were still less likely to progress to late stage but remaining in SD early phase (aRR=0.34, 95% CI: 0.13-0.87) (Table 5-2-11).

After adjustment for age, gender, and BMI, ever smoking was no longer inversely related to the transition from SD to CD in early stage (H-Y I/II) (aRR=0.80, 95% CI:

0.35-1.85) (Table 5-2-12). For the transition from SD to CD for patients in the late stage (H-Y III+), there were still lacking of significant risk factors identified after adjusting for age, gender, and BMI (Table 5-2-13).

Univariate analysis on multiple transition rates

Table 5-2-14 shows the estimated results of univariate analyses on the four transition rates simultaneously. Advancing age by 10 years had higher risk of developing Parkinson's disease (RR=1.84) and the transition from early to late stage in SD early phase (RR=2.69). Elderly subjects with BMI less than 22 (RR=1.76), low level of uric acid (RR=1.61), alcohol drinking (RR=1.62), and less intake of fruit (RR=1.68) had higher risk of developing PD, but lacking of statistically significant effects on three other transition rates. Subjects with higher education level had higher risk of transition from early to late stage in SD phase (RR=5.71), but not on other transitions. This analysis also enabled one to assess the net force coefficient (NFC) on transition to CD H-Y III+ was larger than to CD H-Y I/II. The results show elderly age by 10-year (NFC=1.06), high level of education (NFC=0.80), less intake of fruit (NFC=0.38), and less vegetable intake (NFC=0.58) are worthy of being investigated for further analyses.

Multivariable analysis on multiple transition rates
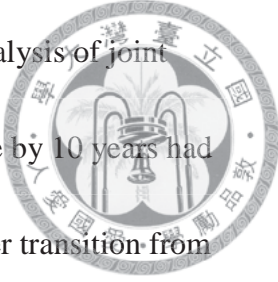
Table 5-2-15 shows the estimated results of the multivariable analysis of joint effects on the four transition rates. The results show that advancing age by 10 years had higher risk of developing PD (aRR=1.79, 95% CI: 1.32-2.44) and faster transition from HY I/II to HY III+ before surfacing to CD phase (RR=5.08, 95% CI: 1.94-13.29). Low level of uric acid also played the role of risk factor in the incidence of PD (RR=1.54, 95% CI: 1.04-2.28). High level of education strongly affected the transition from HY I/II to HY III+ before surfacing to CD phase (RR=14.65, 95% CI: 2.94-54.53). Table 5-2-16 also had the full model but further added the effects of less fruit and vegetable intake as suggested by the results of NFC. The results of this model were close to their counterparts in Table 5-2-15.

5.3 Part III: Cost-effectiveness of Population-based Screening for PD

5.3.1 Simulation for the effect of screening policy

Table 5-3-1 showed the simulated results based on estimated transition rates in Table 5-2-4 to a hypothetical cohort of 9829 elderly people in 12-year period. The results showed that without screening, there would be 35% Parkinson diseases were H-Y stage III or more severe at diagnosis. However, annual screen would bring down the figure to

10.2%, referring to 71% (95% CI: 64-77%) severe stage cases reduction. When the

screening intervals were 2-yearly, 3-yearly, 4-year, or 6-yearly, the severe cases reduction

compared to no screen was by 54% (95% CI: 45-62%), 43% (95% CI: 32-52%), 35%

(95% CI: 23-45%), and 25% (95% CI: 12-36%), respectively.
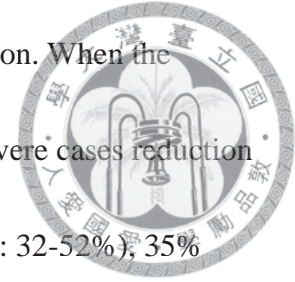
5.3.2 Results of deterministic cost-effectiveness and cost-utility analysis

The results from deterministic Markov decision analysis for the cost-effectiveness

and cost-utility analysis given a hypothetical cohort of 10,000 peoples aged 60 with 20

years follow-up are presented in Table 5-3.2. The incremental cost-effectiveness ratios

(ICER) of PD screening with different inter-screening intervals compared to no screen

ranged from $1169 to $1804 per life-year gained. The incremental cost-utility ratio ranged

from $1715 to $2606 per quality-adjusted life-year gained. Lower attendance rate (60%)

resulted in slightly small ICER and ICUR but the trend with changing inter-screening

intervals had the same trend. For higher attendance rate (100%), the absolute vales of

ICER and ICUR elevated a bit and still remained the same trend with different inter-

screening intervals.

Table 5-3-3 showed the distribution of cost and effectiveness, and net monetary

benefit from Monte Carlo simulation. The cost was $1050 for no screen, and increased

with more frequent inter-screening intervals, ranging from $1075 for triennial screen to

$1115 for annual screen. For life-year gained and QALY gained (QALYG), no screen had

the least gains, and this figure increased with more intensive inter-screening interval.

Considering the net monetary benefit with cost-effectiveness analysis given WTP at

$20,000, annual screen had the greatest NMB ($280,687) in terms of life-year gained,

followed by biennial ($280,511), triennial ($280,416) screen, and no screen ($280,113).

Under the cost-utility analysis, the trend was still the same, the most net monetary benefit

was for annual screen ($275,620), followed by biennial ($275,484), triennial ($275,438)

screen, and no screen ($275,272).

5.3.3 Results of probabilistic cost-effectiveness and cost-utility analysis

The probabilistic cost-effectiveness analysis was conducted to compare the results

in different screening intervals and attendance rate for Parkinson disease screening

strategies. Given 10000 first-order trials and 1000 second-order parameter samples in

Monte Carlo simulation, the scattered incremental cost-effectiveness analysis for

population-based screening program are shown in Figure 5-3-1~5-3-12. The results

demonstrated the 65-78% simulations were cost-effective. Taking the attendance rate with

triangular distribution, under the willing-to-pay of $20,000, the probability of cost-

effectiveness were 78.4%, 71.4%, and 67.3% for 1-year, 2-year, and 3-year respectively

when compared with no screening policy. To monitor the robustness of CEA by screening

attendance rate, the 100% and 60% attendance rate were applied to simulate compared

with no screening. Given attendance rate of 100%, the probability of being cost-

effectiveness was 79.2%, 75.8%, and 69.0% for screening interval with 1-year, 2-year, and

3-year compared with no screening, respectively (Figure 5-3-5~5-3-7). The acceptability

curve of cost-effectiveness analysis is shown in Figure 5-3-8. Given of attendance rate of

60%, the probability of being cost-effectiveness was 74.4%, 64.9%, and 64.4% for

different screening intervals (Figure 5-3-9~5-3-11).

The scattered incremental cost-utility analysis for different screening intervals for

population-based Parkinson disease screening compared with no screening were

demonstrated in Figure 5-3-13~5-3-24. Regardless the different screening intervals

chosen, approximate 59-69% simulations were cost-effective. Given the willing-to-pay of

$20,000, the probability of being cost-utility was 68.8%, 62.6%, and 59.0% for inter-

screening interval with 1-year, 2-year, and 3-year compared with no screening,

respectively. The acceptability curves by different screening intervals were demonstrated

in Figure 5-3-16.

To examine the cost-utility difference by screening attendance rate, we simulated

based on 100% and 60% with different screening interval scenarios to estimate the CUA.

Given screening attendance rate at 100%, it was about 63-70% simulations were cost-

effective. Given the willing-to-pay of $20,000, the probability of being cost- effectiveness

was 70.2%, 66.3%, and 62.6% for inter-screening interval with 1-year, 2-year, and 3-year

compared with no screening, respectively (Figure 5-3-17~5-3-20). Furthermore, given on

attendance rate with 60%, the probability of being cost- effectiveness was 62.6%, 61.0%, and 58.2% (Figure 5-3-21~5-3-24). The acceptability curve of cost-utility analysis was shown in Figure 5-3-24. The probability of being cost-effectiveness given 100% attendance rate was greater than 60%.
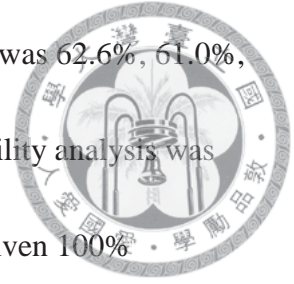
Chapter 6 Discussion

6.1 Part I: Compare the two detection methods for active detecting Parkinson's disease

In this study, we first demonstrate an evaluation of the relative efficacy of the active and passive detection methods of PD screening in a massive screening program which provided a natural experimental design (random assignment). The random screening in 2001 seemed to balance the population. The active method detected approximately 1.8-fold of the PD cases of the passive method. The active method detected more early H-Y stage (stage I and II) PD cases than did the passive method. The active method reduced 49% of PD cases diagnosed at H-Y stage III or higher, compared to the passive method. The method used to detect PD has been considered to account for the large variation in the estimates of IPD prevalence and incidence of many epidemiological studies.[8-14] In one systematic review of Parkinson's disease in Asia,[9] the prevalence ranged from 35.8 to 68.3 per 10^5 person-years in record-based studies and ranged from 51.3 to 176.9 per 10^5 person-years in door-to-door surveys. In door-to-door surveys, the standardized incidence rates were 8.7 per 10^5 person-years; in record-based studies, it ranged from 6.7 to 8.3 per 10^5 person-years. These discrepancies are due to different case-finding methods, different

age distributions in the population, different diagnosis criteria, and different genetic and environmental factors. Although door-to-door survey seemed to yield higher prevalence and incidence rates than record-based studies, no study has directly elucidated the differences between case-finding methods and none of the previous studies compared different methodologies of determining PD prevalence. Our study directly proved that the active method is able to detect approximately 1.8-fold the IPD cases of the passive method. In addition, our pseudo-experimental design was able to overcome the potential discrepancies of previous epidemiological studies such as age distributions, genetic, or environmental factors.

Two previous door-to door surveys estimated the prevalence of IPD in Taiwan. Liu et al. found that the prevalence rates of Parkinson's disease in Kinmen was 587 per 10^5 person-years among those aged 50 years or older in a single-phase door-to-door survey by neurologists.[34] A two-stage door-to door survey in Ilan county, Taiwan found a crude IPD prevalence rate of 367.9 per 10^5 person-years and an incidence rate of 30.1 per 10^5 person-years among subjects aged 40 years or older.[33] The age-adjusted prevalence rate for all age groups was 130.1 per 10^5 person-years and the age-adjusted incidence rate was 28.7 per 10^5 person-years after being adjusted to 1970 US census in Ilan county. The crude prevalence rate was 1,520 per 10^5 person-years in our study of adults aged 40 years or older. The age-adjusted prevalence rate was 552.5 per 10^5 person-years. If compared to the

previous results from Ilan county, our active method detected four times the PD cases of those found in the two-stage door-to door survey.
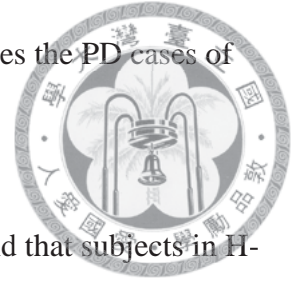
Early detection of PD is important because a previous study found that subjects in H-Y stage I may have the same life expectancy as the general population.[18] Early detection and treatment of PD may increase life expectancy.[3, 93-95] Liou et al. found that PD cases detected early showed a 74% reduction in the incidence of stage III or greater PD and a 26% reduction in mortality.[18] Our result suggest that the active detection method identified more stage I and II PD cases than did an examination of the health insurance claims record (80.4% vs. 61.5%, p=0.04). We also showed that the active detection method could reduce 49% of the incidence of PD at H-Y stage III or greater at diagnosis.

The active screening method is more time consuming and requires more resources than the passive detection method. However, delayed diagnosis of PD may result in rapid progress in H-Y stage and much greater medical costs to deal with the many complications that accompany the progression of this disease.[85, 96, 97] The relative cost effectiveness and benefit of the active and passive detection methods need further evaluation.

Although we demonstrated that the active method detected almost two times the PD cases of the passive method, the present study had several limitations. First, the participants in our study were adults who attended a community-based integrated screening program rather than a nationally representative sample. The incidence and

prevalence rates may not represent those of the national population. However, the aim of

the study was to compare two methods of PD detection, not determine national rates.

Secondly, we did not review all the H-Y stages of the PD cases due to resource limitations

and sampled 65 of 233 PD cases to determine H-Y staging data through the medical

records. However, our sample was sufficient to suggest that active detection is superior in

detecting early stage PD.

6.2 Part II: Natural History of Parkinson's Disease by Hoehn-Yahr Stage

The current thesis is the first study to model the natural history of PD with the

concept of classifying PD into SD phase and CD phase as a result of population-based

survey and screening for PD as did in the first part of a community-based active survey for

PD.

The results show an individual aged 60 year or older who is susceptible to PD and

entered the SD phase would progress to CD, on average around two years. The median

time progression to CD for those entering into the SD was 1.2 years. Such information is

very useful for the surveillance of PD staying in the SD through active survey.

The result of five-state model suggest once PD advanced to H-Y stage III and more

severe, the presence of symptoms and signs enabling one to seek for medical care was

almost certain as the transition rate was so large. However, if screening strategy (such as

inter-screening interval) is appropriate, it is still possible to detect early H-Y (H-Y stage

I&II) in the SD in order to stop subsequent progression to late H-Y in the presence of

symptoms and signs. Based on our findings, screening with 3-year inter-screening interval

might reduce 43% advanced disability, compared with no screening regime during 12-year

follow up.
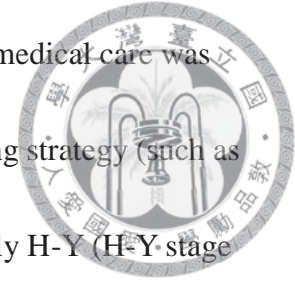
Hoehn-Yahr stage was used to model the disease progression of PD. Previous

studies had focused on the progression rate of each stage. Hoehn and Yahr proposed that

mean duration of each stage of PD was 3.0, 6.0, 7.0, 9.0, and 14.0 years in stage I, II, III,

IV and V, respectively.[98] Liou et al. used PD cases from two community-based program to

calculate step-by-step annual progression rate of each stage. They found the mean sojourn

time staying in H-Y stage I and stage II were 2.83 years and 6.62 years, respectively.[15]

There was no model available currently using the concept of screening for the natural

history of PD. Our finding suggests that the mean sojourn time staying in the SD phase

was around 1.7 years, which seemed shorter if we compared the mean duration time with

H-Y stage I and II in previous two studies. However, our population was older than the

previous two studies. Older age was associated with faster progression rate in previous

study report.[50] Though the previous two studies might not be compatible with ours, the

mean sojourn time for staying in SD phase might be shorter in the older age group

compared to younger one.
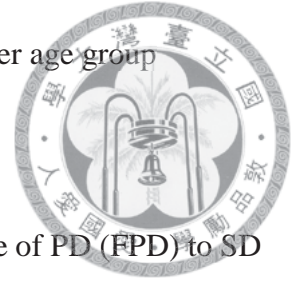
The 5-year cumulative risk of a person aged 60 or older from free of PD (FPD) to SD

and CD phase were 1.1% and 2.7%, respectively. The cross-over of the two curves in

figure 5-2-2 was at 2.8 years or so, which suggest an inter-screening interval would not be

beyond 2.8 years. It is also supportive by the figure 5-2-3 that once the person when

entered to SD phase, there was 96.7% that he/she would become clinical detectable in 5

years.

In our study, we extended the three-state model to five-state model according to the

H-Y stage. This gave more information on the natural history based on H-Y stage. For a

person who was 60 years or older, the annual incident rate of being susceptible to PD was

780 per 100,000 person-years (Table 5-2-4). This was close to the previous studies which

reported the incident rate of PD in older age groups (age above 55 or 65 years) were

between 410 and 529 per 100,000 person-years.[11, 27, 28] Then annual transition rate from

early H-Y to severe H-Y in the SD was 0.25 per year. In competing with the deterioration

from early H-Y to late H-Y stage, annual progression from the SD to the CD for early H-Y

was around 0.40. This implied that once the person entered to the early SD phase, he/she

had stronger potential to progress to early CD phase. Finally, annual progression rate from

the SD to the CD for late H-Y was 2.12. It suggested that once the person entered to the

late SD phase, the presence of symptoms and signs enabling one to seek for medical care was almost certain.

In addition to the temporal disease natural history, we also elucidate the effect of patient-specific covariates on the multiple progression involved in the disease progression for PD. The results show that elderly age by 10 years had higher risk of developing PD and faster transition from HY I/II to HY III+ before surfacing to CD phase. Low level of uric acid also played the role of risk factor on the incidence of PD. High level of education strongly affected the transition from HY I/II to HY III+ before surfacing to CD phase. This approach not only provided the role of risk factors for specific personal attributes for PD, but also elucidated which stage the covariates took effect on. In this thesis, we found that high level of education had higher risk of progression to late stage in the SD stage, but had no significant effect on incidence of SD stage PD.

As far as methodology is concerned, we developed the likelihood functions for the natural history of H-Y stage-based in a non-standard case-cohort design. Chen et al. used a similar approach for the estimation of disease natural history of adenoma-carcinoma and *de novo* carcinoma.[44]. In their study, they had data from a cross-sectional hospital-based cohort. In this thesis, data are heterogeneous different screening rounds (prevalent and follow-up) and uncensored mode. This method was proved as valid with consistent estimates of the complete data analysis and sampled data analysis for the three-state

Markov model. The advantages of this approach are two-fold. First, the successful

derivation for the likelihood functions of the multi-state Markov model allows the

estimation for disease natural history with an efficient case-cohort design. Second, this

approach can solve the problem of missing information, such as H-Y stage for PD patients

in this thesis, once the missing mechanism is not informative or systematic.

There were some limitations of this thesis. In the current analysis, we applied the

time-homogeneous Markov model for the three-state and five-state Markov model. It may

be argued that the incidence rate is hardly remain constant across different age groups.

Similarly, it is reasonable to expect that the transition from SD to CD in early stage should

reduce with time. Figure 6-2-1 shows the predicted 20-year risk of PD by Hoehn-Yahr

stage with the four transition rates following the Weibull distribution with shape

parameters of 1.2, 1.08, 0.8, and 1.08, respectively. Note that shape parameters greater

than one indicates the increasing risk by time, and shape parameters less than one

indicates decreasing risk by time. Based on this set of parameters, the pattern of the

predicted cumulative risk of H-Y III+ PD was similar to our results in Figure 5-2-7, except

the crossing point for SD, H-Y I&II to the two states of CD was delayed, because we

assumed the transition to CD stages was slower in the early period and arise in the later

period. Estimation based on time-non-homogeneous Markov model is worthwhile to do in

the future with a larger cohort. Nevertheless, the further application of the estimated

results for decision analysis was not age-dependent. Namely, we did not assess time-related parameters for different strategies. Such a limitation would not affect the results of applications for cost-effectiveness analysis or cost-utility analysis. Second, we did not do sensitivity analysis in the current thesis, which the model power was not validate, either. Third, covariate like elderly age had higher risk of developing PD and faster transition from HY I/II to HY III+ before surfacing to CD phase but had no effect on transition from SD phase HY III+ to CD phase III+. That meant there might be some competing risks should be considered in the model. Mortality information needed to be incorporated in the natural history model to solve this problem in the future.
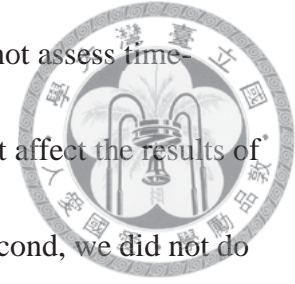
The present study model the natural history of PD and suggested that the screening interval of PD may not longer than 3 years in order to detect early H-Y stage in the SD phase and to stop subsequent progression to late H-Y stage.

6.3 Part III Cost-effectiveness Analysis of screening of PD

This current analysis showed that a population-based early detection of PD would like to be considered cost-effective compared with no screening. The incremental cost-effectiveness ratios (ICER) of PD screening with different inter-screening intervals compared to no screen ranged from $1169 to $1804 per life-year gained. The incremental cost-utility ratio ranged from $1715 to $2606 per quality-adjusted life-year gained. In

probabilistic analysis, the probability of being cost-effective at $20,000 WTP was 64-74%

given 100% attendance rate. The simulation cohort of different screening regimen result

also showed that if the intensive screening for PD offered, the large the reduction in late

H-Y PD could be achieved.
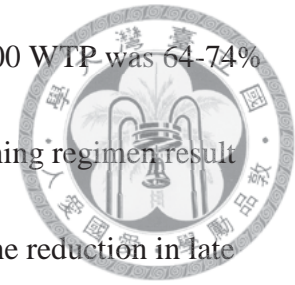
Johnson et al incorporated the data including dementia rate, direct and indirect costs

and health utility by H-Y stage into a model to evaluate possible economic consequences

of slowing progression of PD. They reported that reducing PD progression rate could

produce significant economic benefit.[82] This also implied that the disease burden would be

improved if the proportion of the severe H-Y stage could be reduced. In previous study,

Liou et al. simulate a community cohort age 40 years and older and found that different

screening intervals with 10-, 5-, and 1-year could reduce 58%, 74% and 84% of PD with

H-Y stage III or more severe at diagnosis.[15] Our result showed that with different inter-

screening intervals from 6 years to 1 year, the percentage of H-Y stage III or more severe

at diagnosis reduced from 25% to 71% (table 5-3-1). Though our result showed less

reduction of the H-Y stage III or more severe at diagnosis in different screen regiment, our

simulated cohort based on 60 years and older community cohort, which may be more cost-

effective compared to the previous study.

There had been lacking cost-effectiveness analysis (CEA) of the screening of PD up

to date. A recent CEA of opportunistic dementia screening program was done in South

Korea.[99] In that study, screening showed that cost ranged from $24,150 to 35,661 per

QALY gained depending on different age group (65 years old to over 80). The probability

of being cost-effective for screening for dementia was highest in the group over 75 years

old range from 60% with WTP $20,000 to 80% with WTP $80,000. In my thesis, given

the WTP $20,000, the probability of being cost-effective for screening of PD were 69-79%

and 64-74% with 100% and 60% attendance rate with various inter-screening intervals.

When compared the CEA screening for other disease, like cancer screening, Lee et

al. showed that it was around 0.03 per life year gain when using first or second prevention

compared to no intervention. The ICER for once-only chemoprevention at age 30 years

versus no screening was $17,044 per life-year gained.[100] Compared to our study result, the

ICER for annual screening was $1949 per life-year gained and the ICUR was 2808 per

QALY gain under 100% attendance rate. It is more cost-effective compared to the gastric

cancer prevention. Kawasaki et al used a Markov model with a probabilistic cohort

analysis to calculate incremental costs per QALY gained by implementing a screening

program detecting diabetic retinopathy in Japan.[101] They reported that the ICER was $

11,857 per QALY under the annual screening program.

Johnson et al proposed a 25-year Markov model based on the Hoehn and Yahr scale,

which compared a base case PD patient to an identical patient whose rate of progression

was slowed by a hypothetical disease-modifying therapy.[82] Ten studies of progression of

H-Y stage were reviewed, average time across H-Y stages I to V were 2.69, 5.04, 3.58,

and 2.2 years, respectively. Overall, the expected time to progress from H-Y I to V was

13.4 years. In that study, the four hypothetical disease slowing scenarios are identical to

the base case, but with the likelihood of progression to a severe PD stage reduced by 10%,

20%, 50% and 100%. Slowing disease progression by 10% and 20% would have net

monetary benefit of $29,001and $ 60,657, respectively. In my thesis, the result of cost

effectiveness analysis showed that the inter-screening interval of two years of PD

detection were cost-effectiveness.
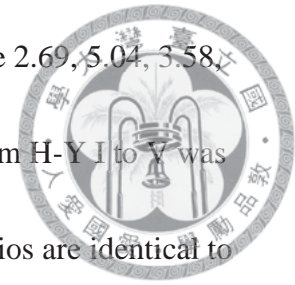
In current study, we assume that the patients who are diagnosed at the beginning

stage will continue the treatment according to the disease stage until death. This will

underestimate the cost and overestimate the effectiveness. It is because the treatment will

be different when the disease progressed. The medical cost in current study was based on

the reimbursement from NHIA, it is dynamic if the long term insurance is changed in our

national policy.

The diagnosis of the PD is based on the clinical diagnosis by the neurologist. The

screening program performed by the neurologist might have some benefit such as the low

refuse rate and the high accuracy of disease diagnosis. However, the manpower to perform

the community screening may costly when a community-based screening is conducted.

In this part, our study shows that screen for PD with different inter-screening

intervals is cost-effective than no screen.

Chapter 7 Conclusion

The conclusions about the current finding are:

1. Active detection method through a community-based survey and screening is able to detect around two times the PD cases in comparison with passive method.

2. Temporal natural history of H-Y stage between the SD and the CD was model by using data from a community-based survey, which provide available information on disease progression of PD in the absence of intervention.

3. Our study shows that screen for PD with different screening intervals is cost-effective than no screen at all.

Figure 3-1 Simulated randomized controlled trial study design
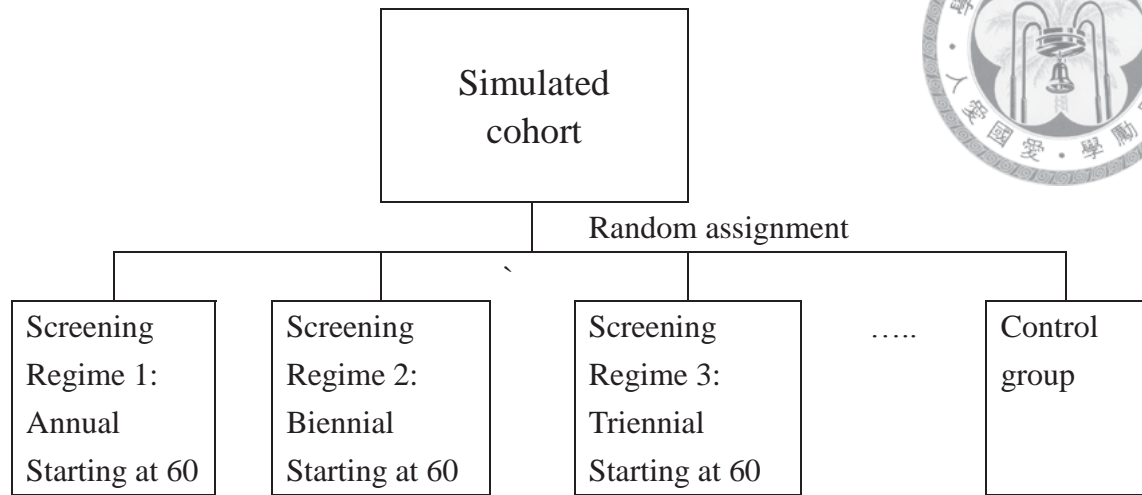
Figure 3-2-1 Decision tree of Parkinson's disease screening

PD screening

1y_start at 60 y/o [+]

2y_start at 60 y/o [+]

3y_start at 60 y/o [+]
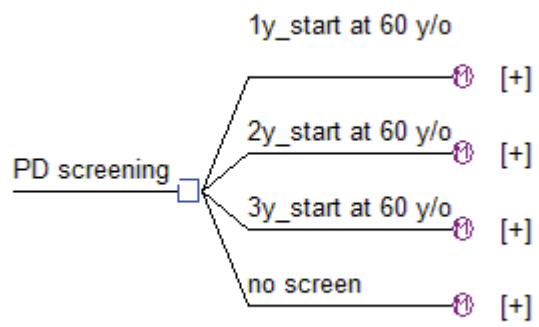
no screen [+]

Figure 3-2-2 Decision tree of Parkinson's disease screening (continue)
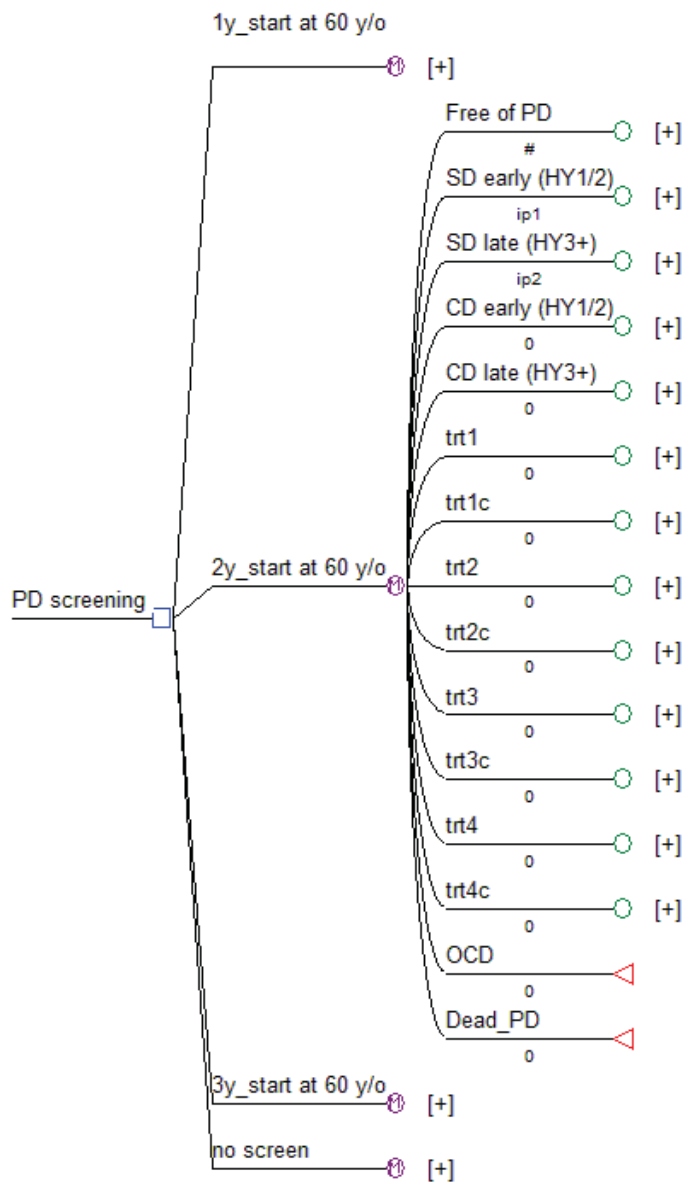
Figure 3-2-3 Decision tree of Parkinson's disease screening (continue)
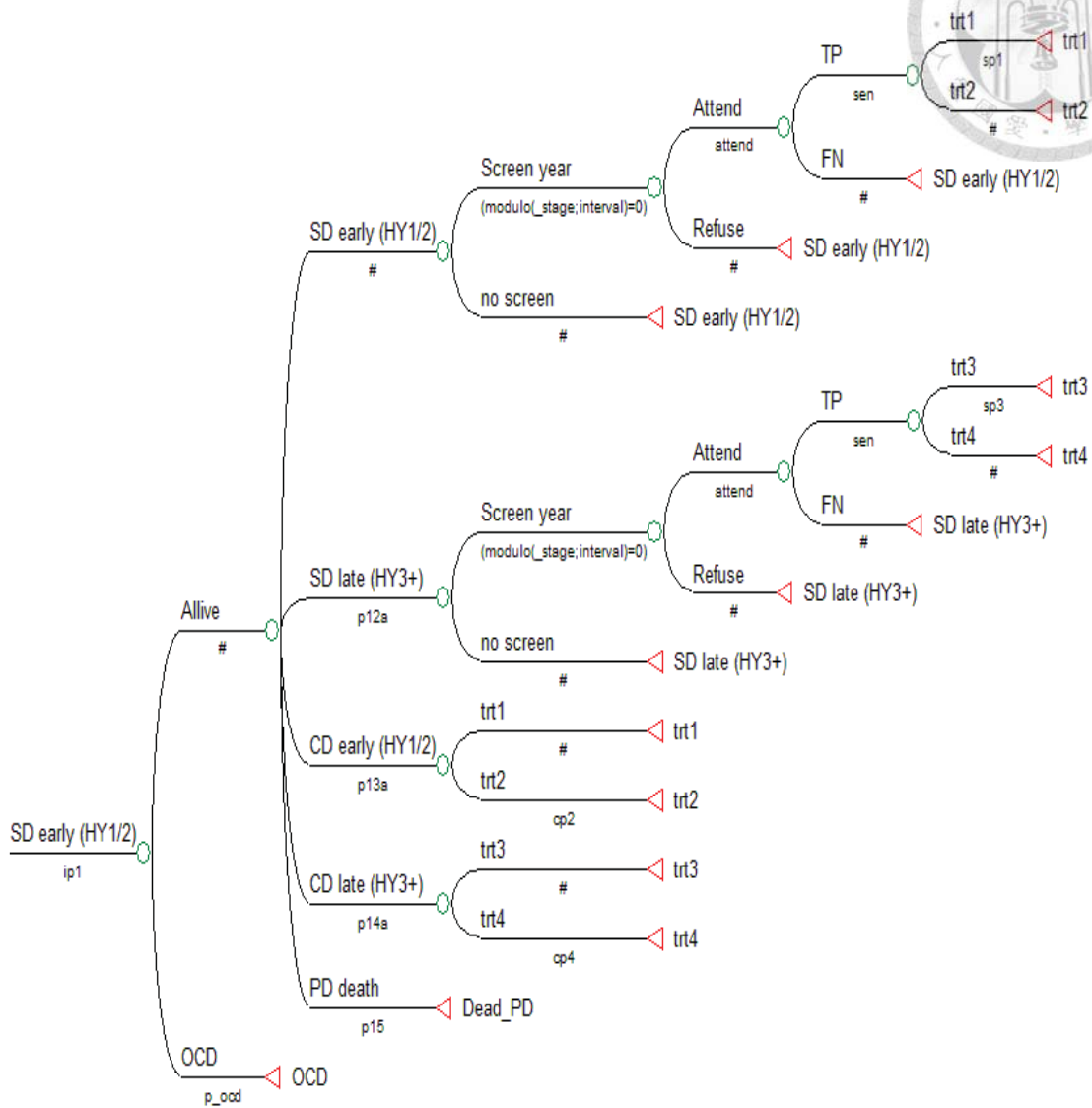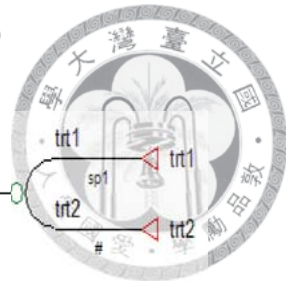
Figure 5-1-1 Study Flow Chart

KCIS 2001

KCIS 2001
N=20,951

← Random selection

Active method
N=11,332

Passive method
N=9,619

88 PD cases
diagnosed
before 2001 ←

59 PD cases
→ diagnosed
before 2001

PD case
N=58

Non-PD case in 2001
survey
N=11,186

N=9,560

PD case after survey
2001 N=34
2002 N=42
2003 N=27
2004 N=31
Total=134

PD case in follow-up
2001 N=16
2002 N=29
2003 N=17
2004 N=27
Total=89
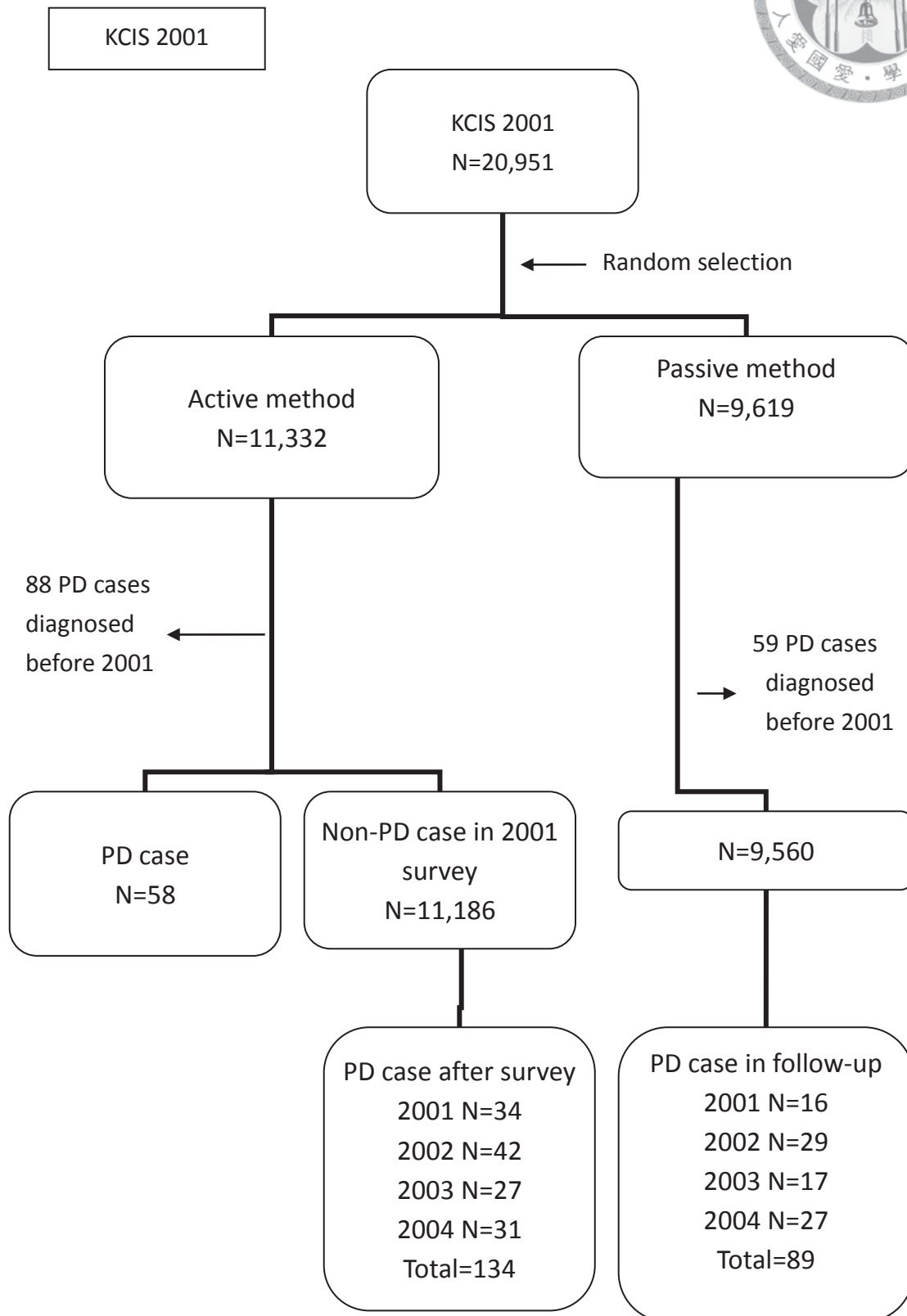
Figure 5-1 2 Cumulative detection rate of two methods of detecting Parkinson's disease.
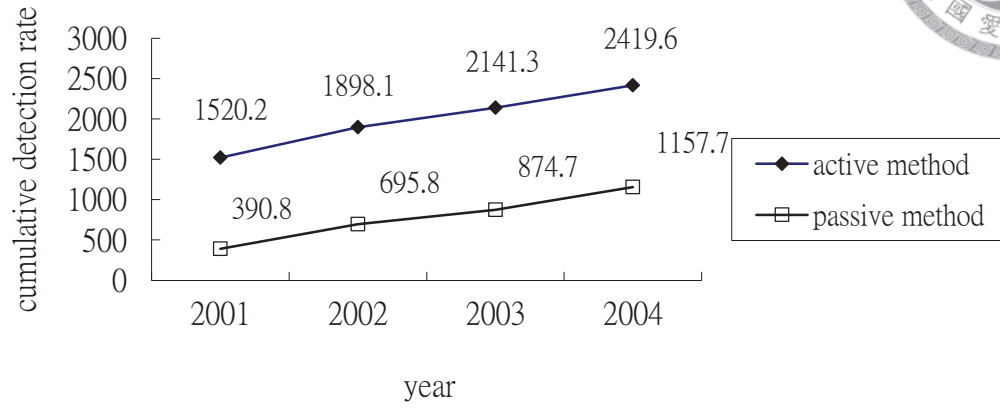
Figure 5-2-1 Study flow chart include participants age 60 and older for analysis.
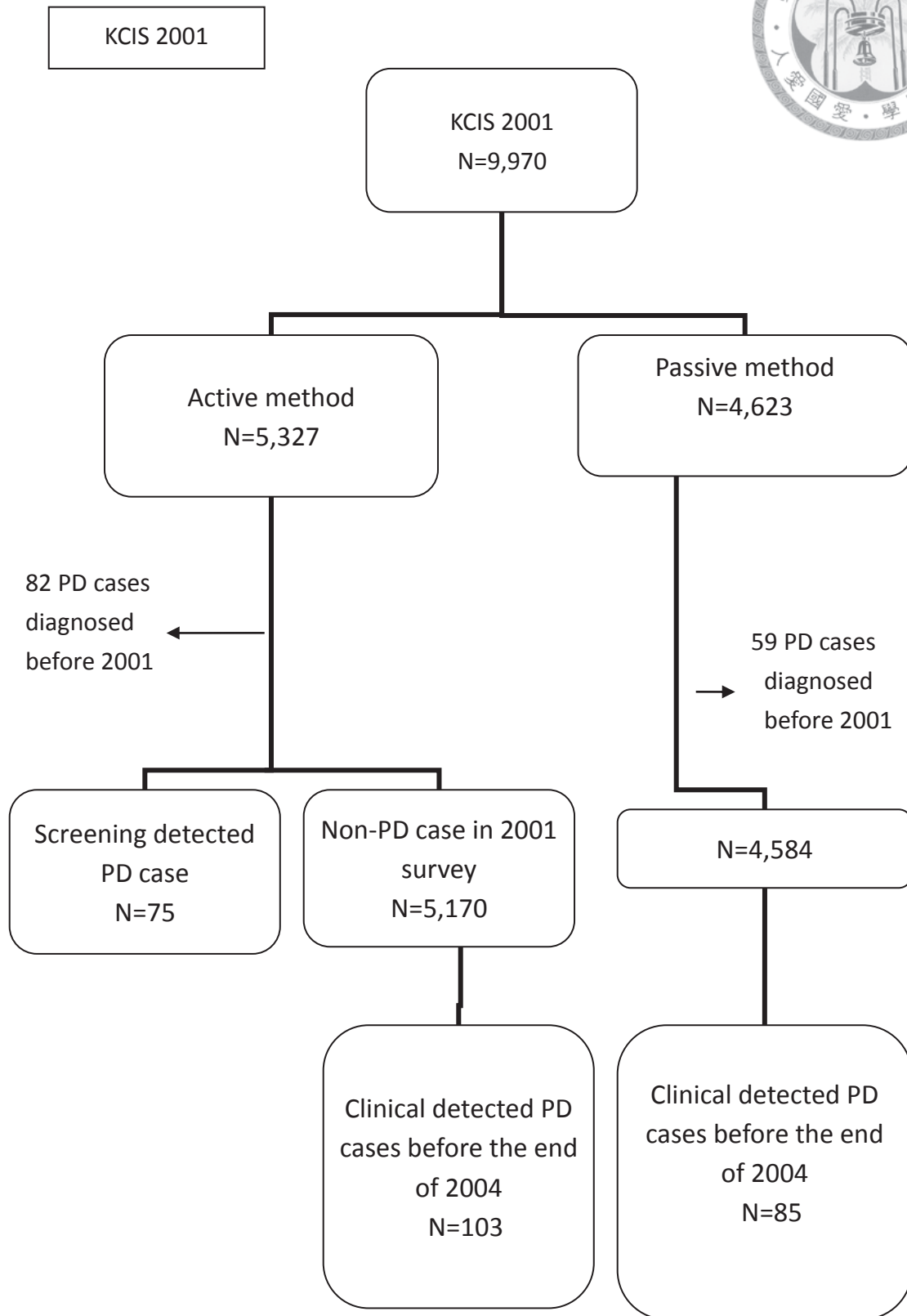
Figure 5-2-2 Cumulative risk for the SD and CD from free of PD in three-state model
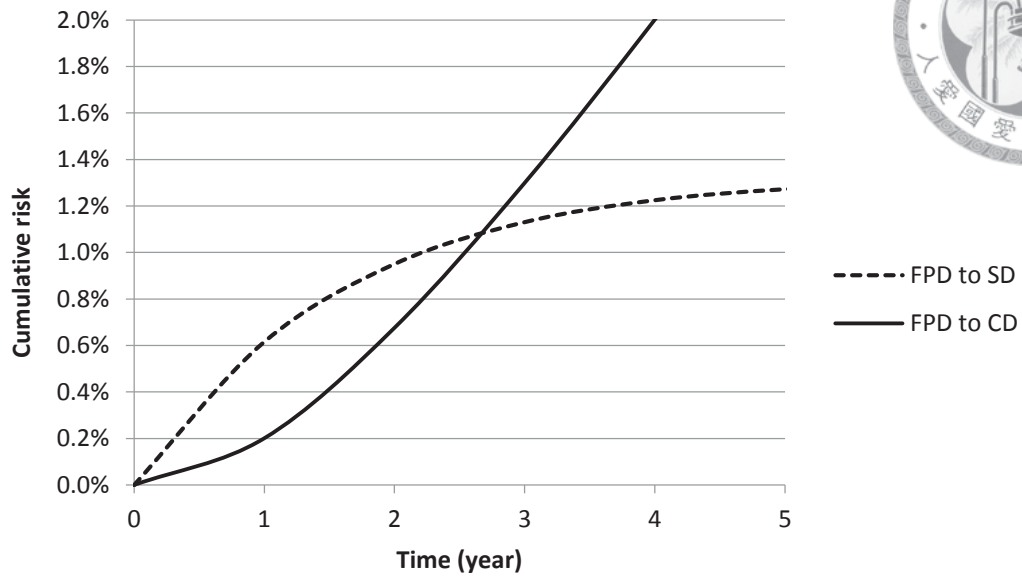
Figure 5-2-3 Cumulative risk of surfacing to the CD from the SD in three-state model
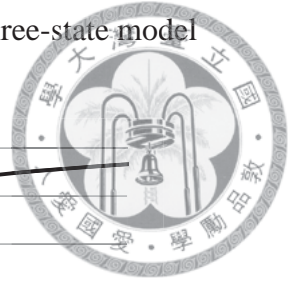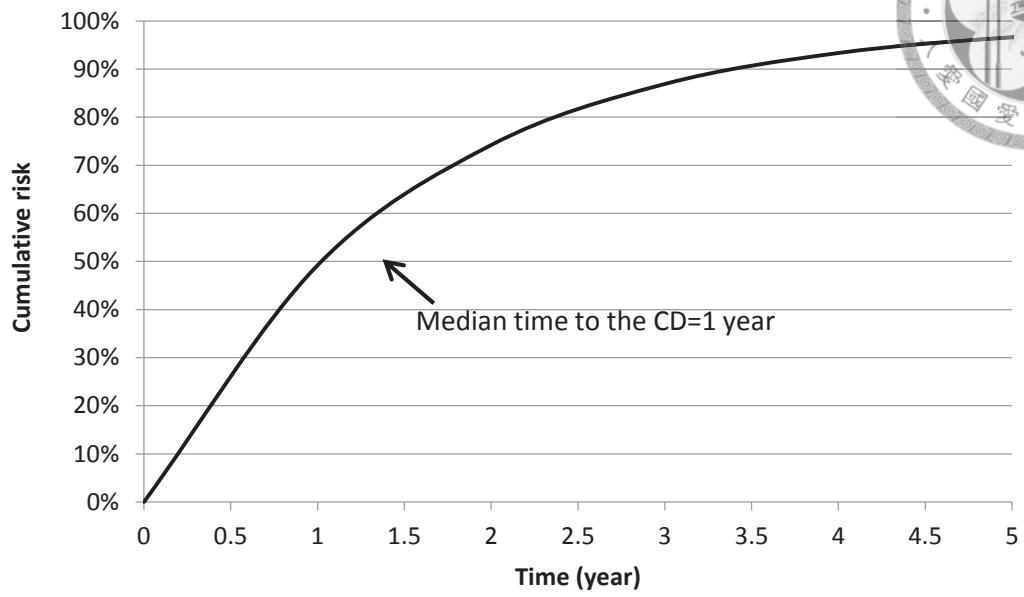
Figure 5-2-4 Cumulative risk for the SD and CD from free of PD in three-state model (sampling fraction)
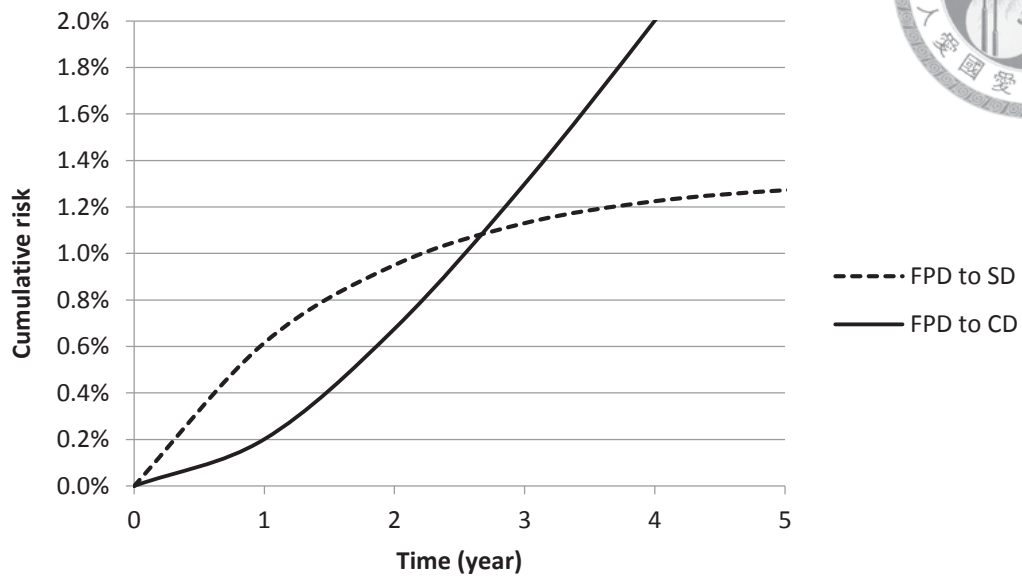
Figure 5-2-5 Cumulative risk of surfacing to the CD from the SD in three-state model (sampling fraction)

Median time to the CD= 1.2 year
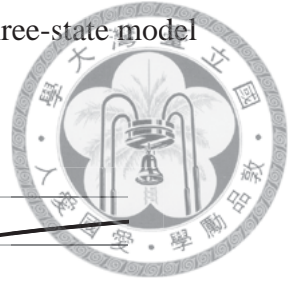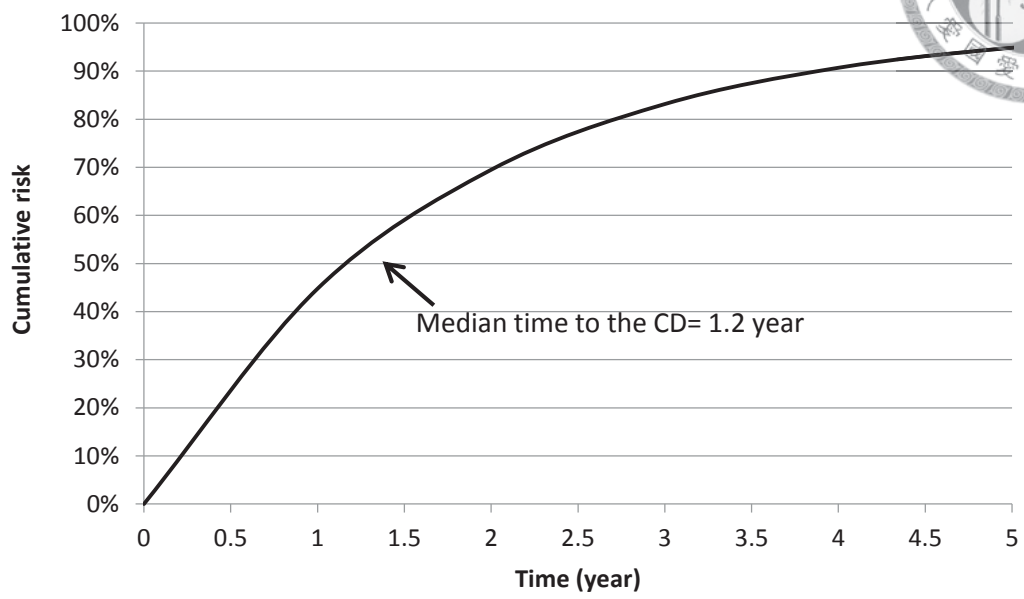
Figure 5-2-6 Predict 20-year risk of being early and advanced H-Y stage
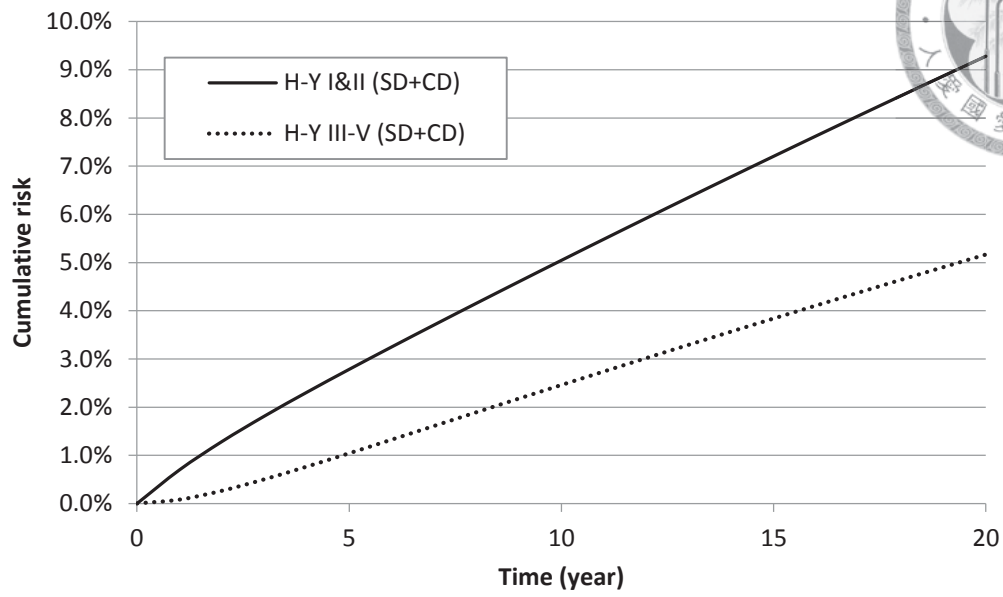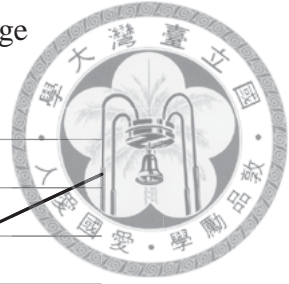
Figure 5-2-7 The predicted 20-year risk of PD by Hoehn-Yahr stage
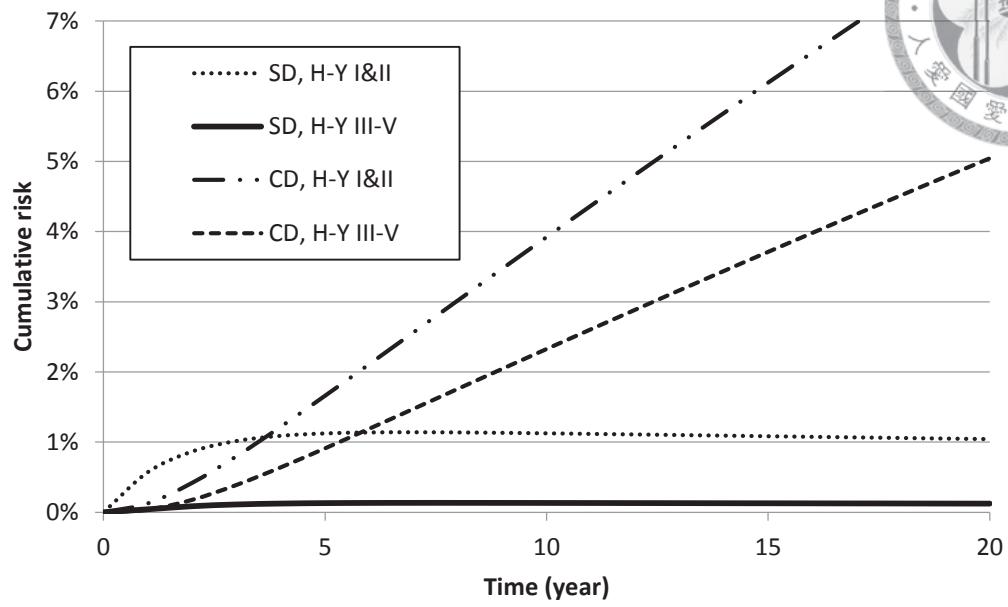
Figure 5-3-1 Scattered incremental cost-effectiveness analysis for 1-year vs. no screening
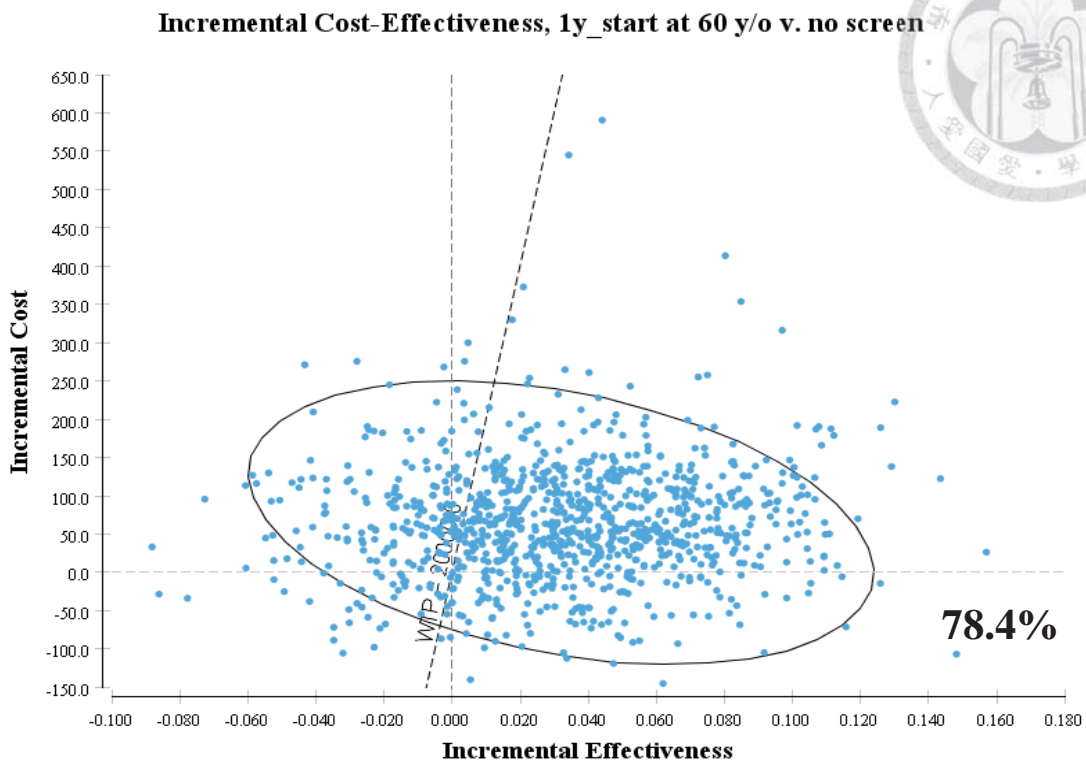
Figure 5-3-2 Scattered incremental cost-effectiveness analysis for 2-year vs. no screening.
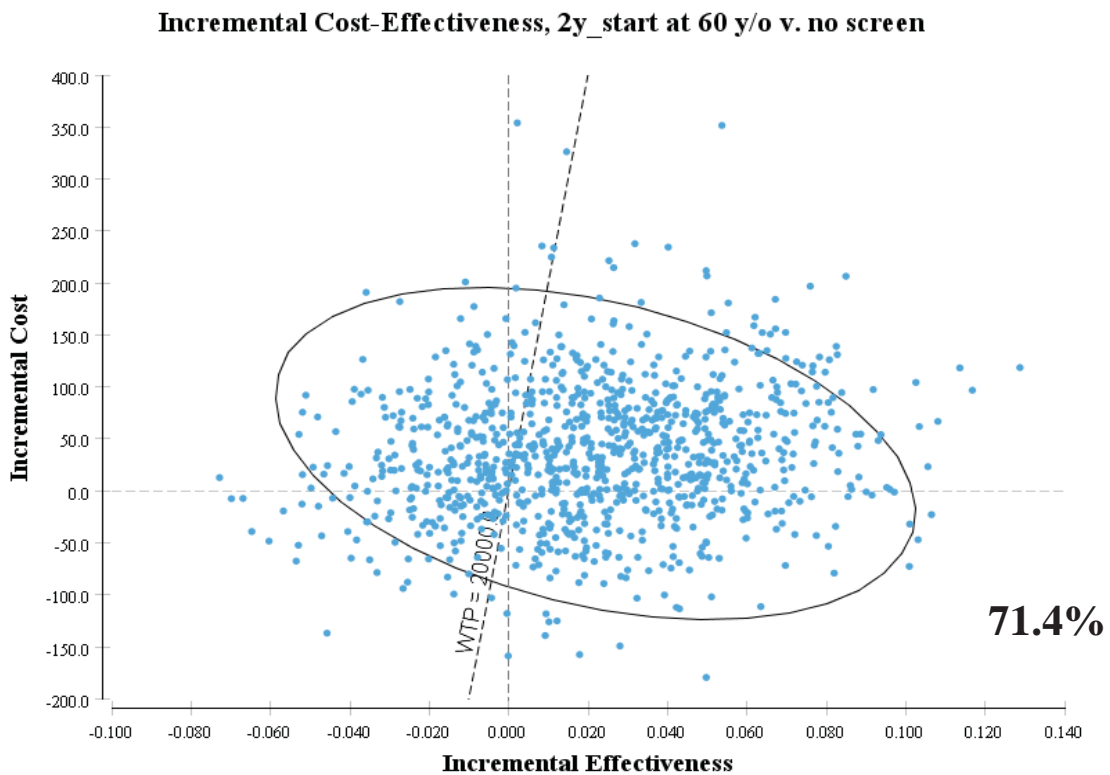
Figure 5-3-3 Scattered incremental cost-effectiveness analysis for 3-year vs. no screening.

Incremental Cost-Effectiveness, 3y_start at 60 y/o v. no screen

67.3%
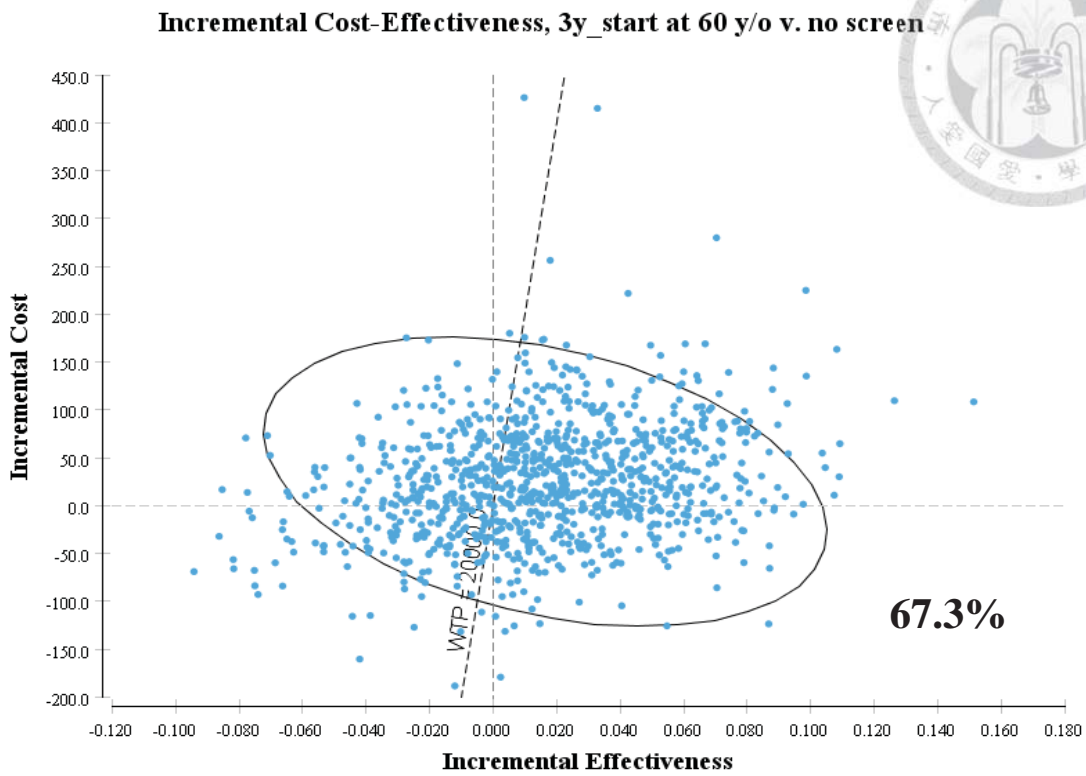
Figure 5-3-4 Acceptability curve for cost-effectiveness analysis for various inter-screening intervals

Cost- effectiveness acceptability curves of screening for Parkinson's disease
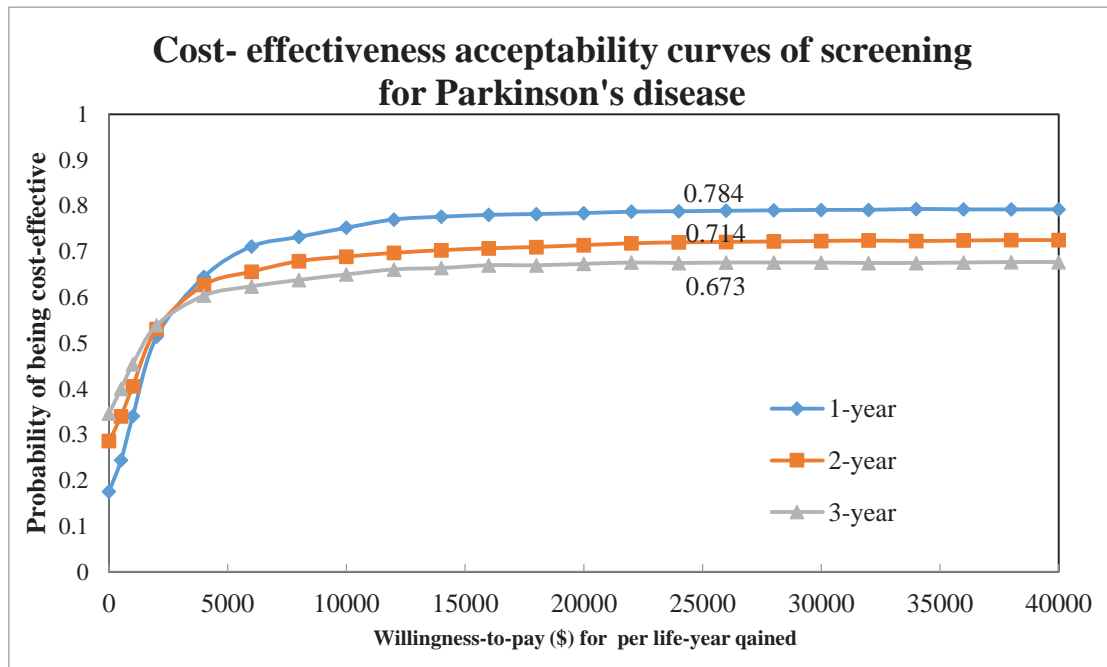
Figure 5-3-5 Scattered incremental cost-effectiveness analysis for 1-year with 100% attendance rate vs. no screening.

Incremental Cost-Effectiveness, 1y_start at 60 y/o v. no screen

79.2%
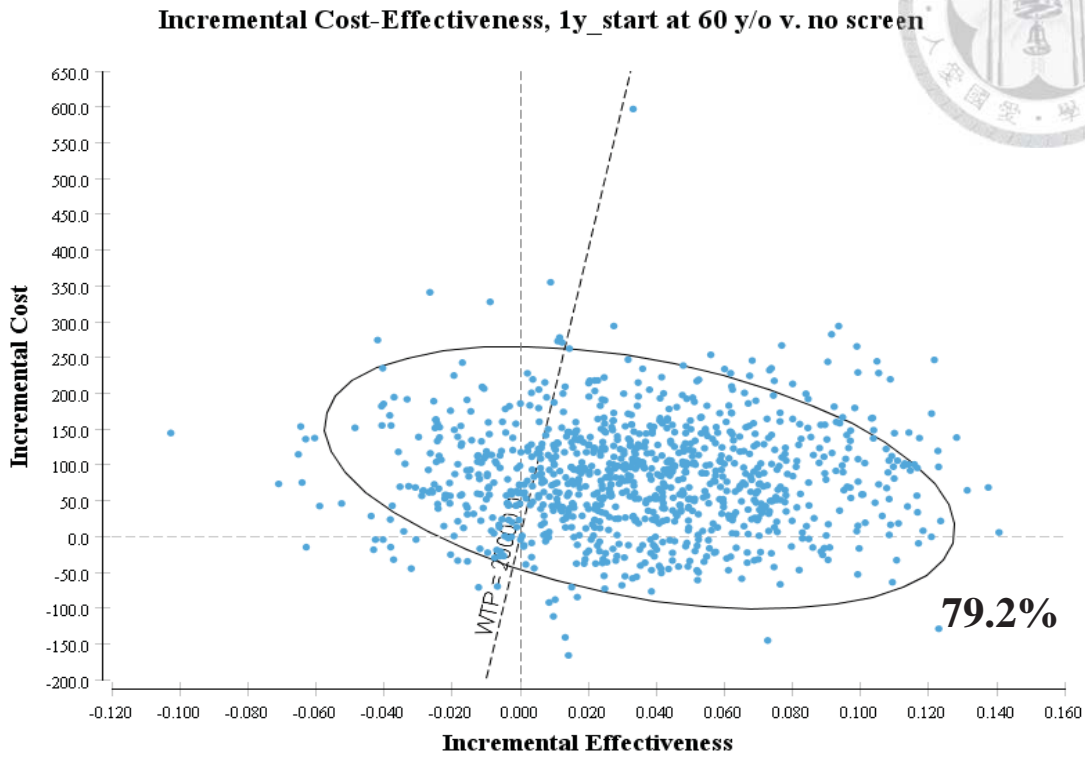
Figure 5-3-6 Scattered incremental cost-effectiveness analysis for 2-year with 100% attendance rate vs. no screening.

Incremental Cost-Effectiveness, 2y_start at 60 y/o v. no screen

75.8%
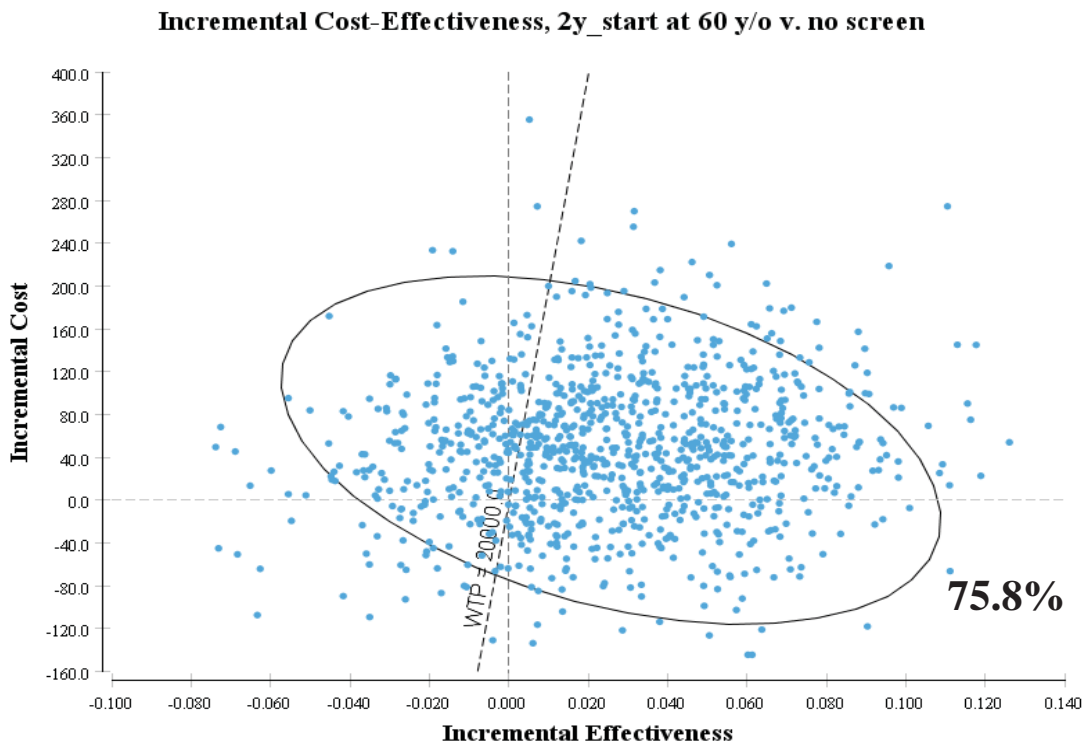
Figure 5-3-7 Scattered incremental cost-effectiveness analysis for 3-year with 100% attendance rate vs. no screening.
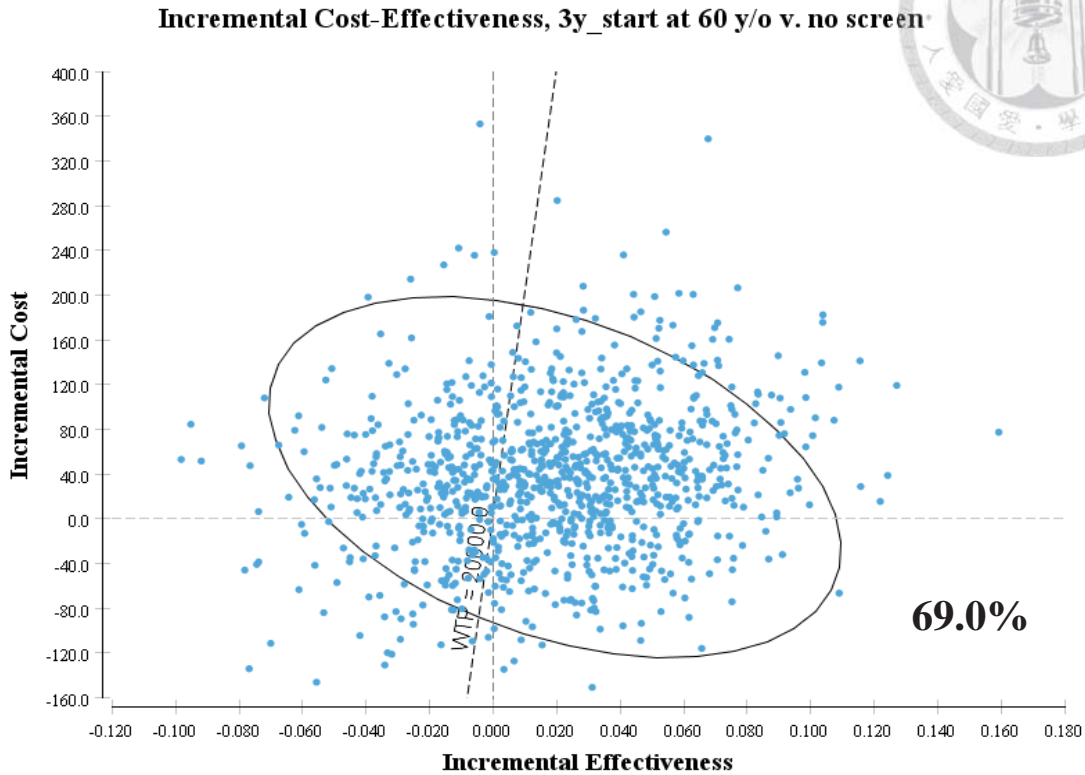
Figure 5-3-8 Acceptability curve for cost-effectiveness analysis for various inter-screening intervals with 100% attendance rate.
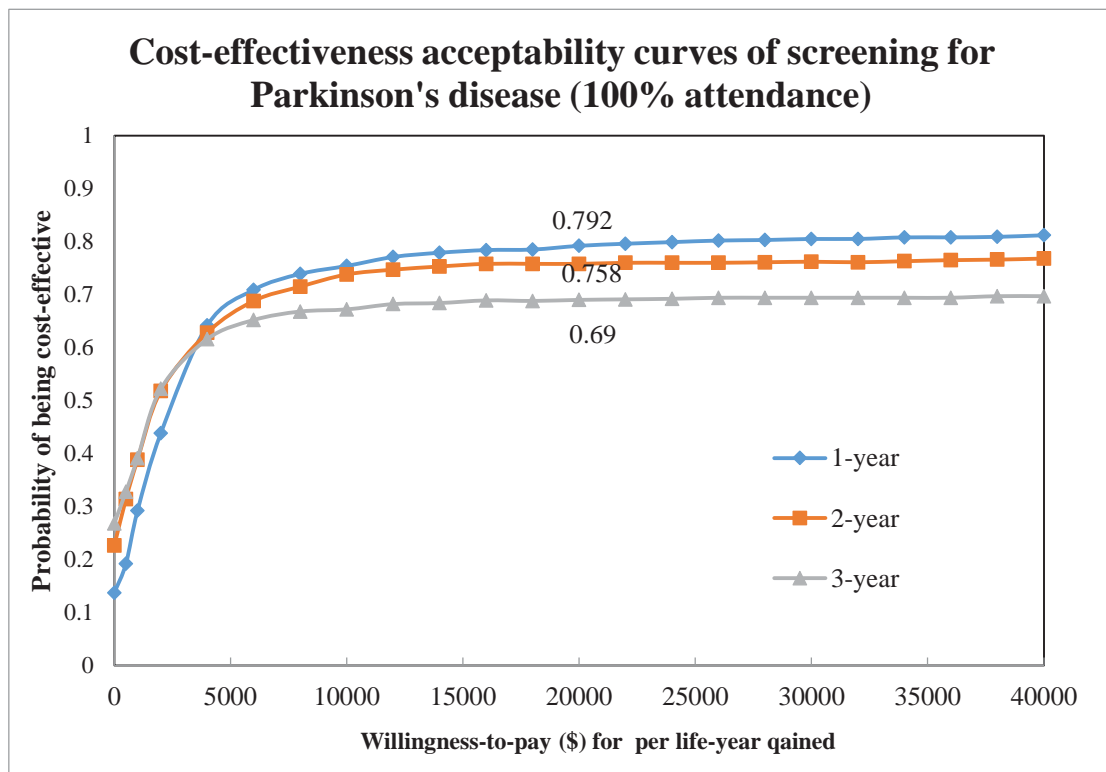
Figure 5-3-9 Scattered incremental cost-effectiveness analysis for 1-year with 60% attendance rate vs. no screening.

Incremental Cost-Effectiveness, 1y_start at 60 y/o v. no screen

74.4%
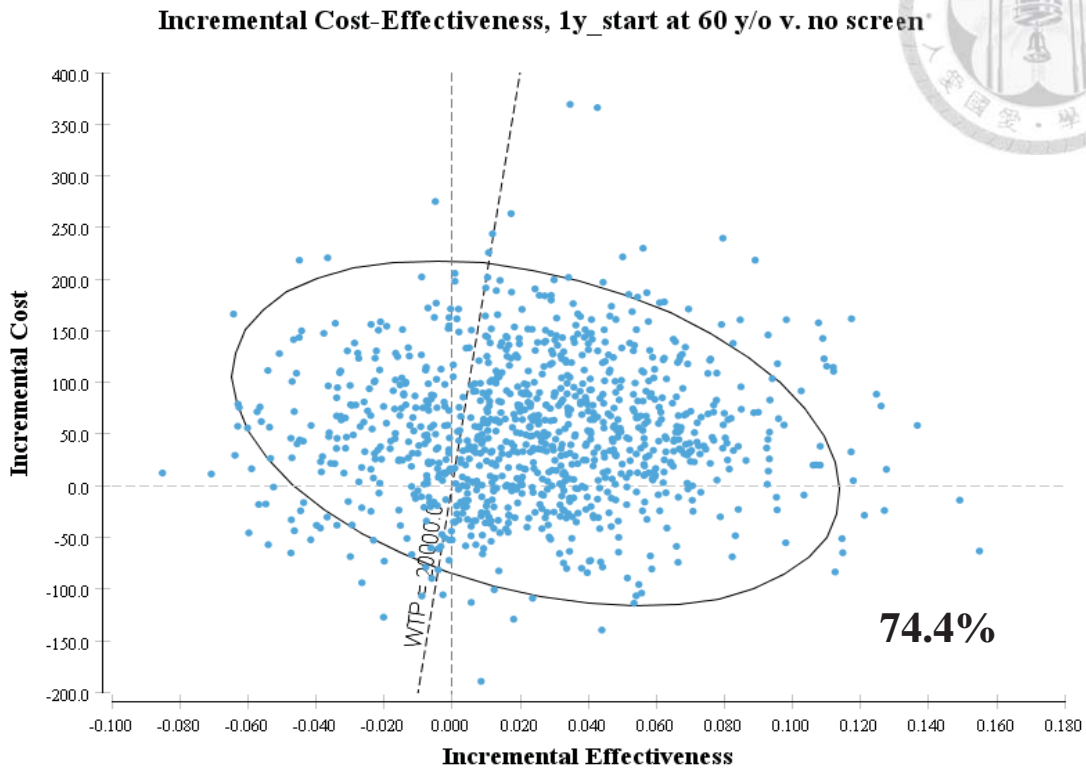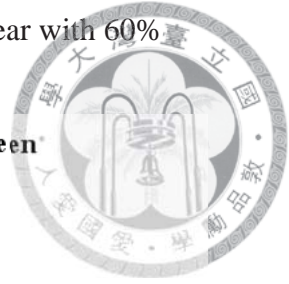
Figure 5-3-10 Scattered incremental cost-effectiveness analysis for 2-year with 60% attendance rate vs. no screening.

Incremental Cost-Effectiveness, 2y_start at 60 y/o v. no screen

64.9%
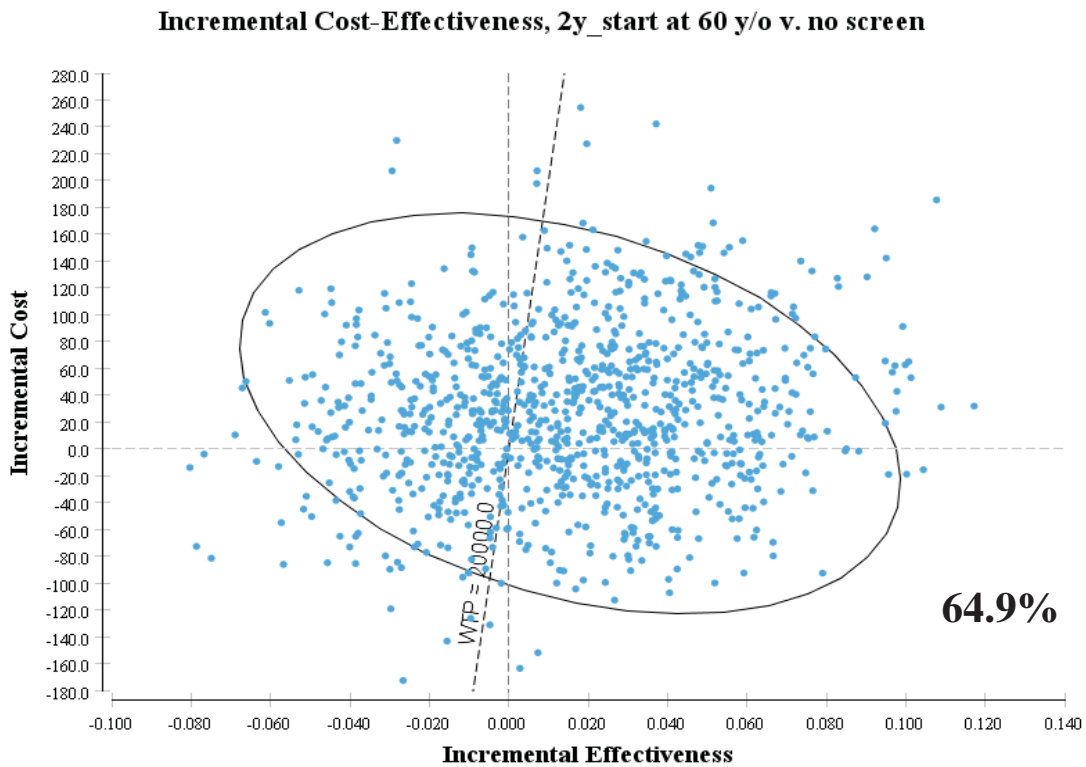
Figure 5-3-11 Scattered incremental cost-effectiveness analysis for 3-year with 60% attendance rate vs. no screening.
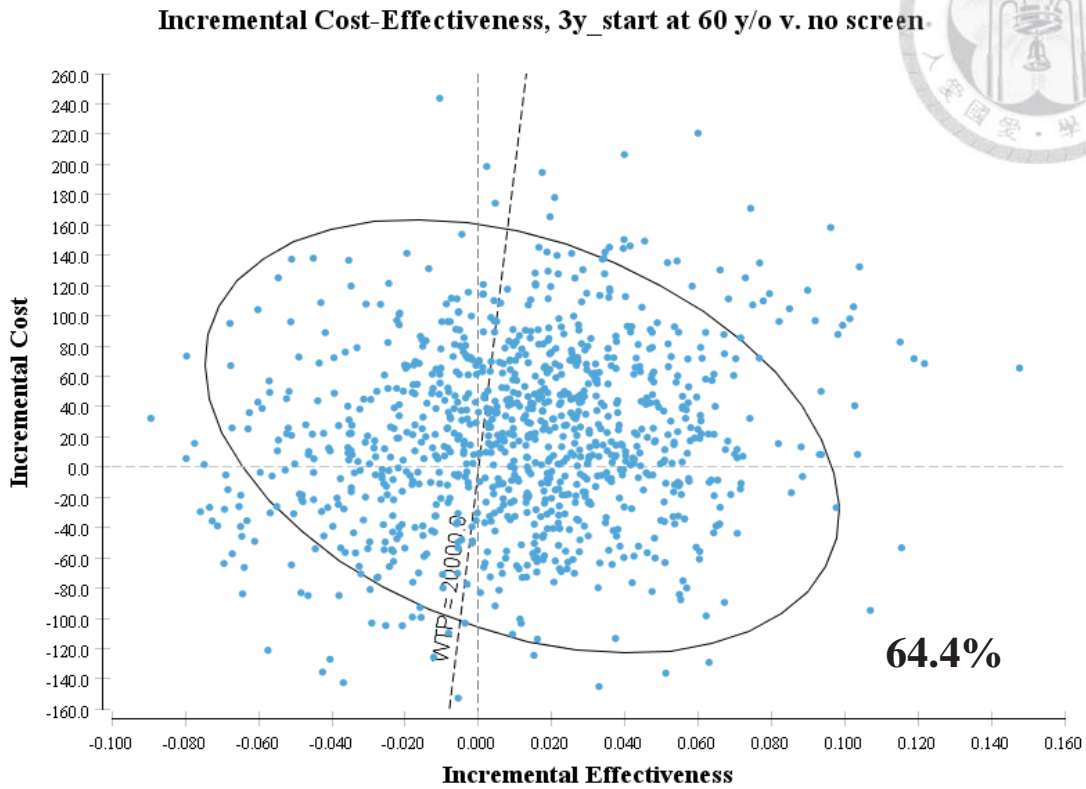
Figure 5-3-12 Acceptability curve for cost-effectiveness analysis for various inter-screening intervals with 60% attendance rate.
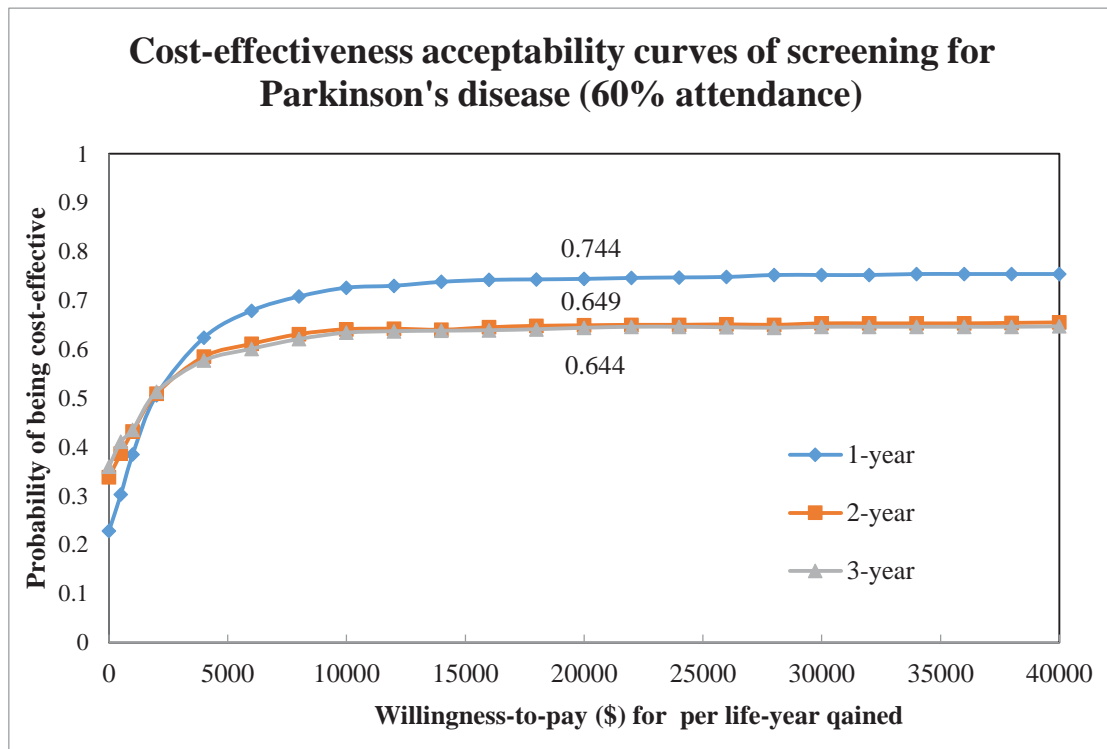
Figure 5-3-13 Scattered incremental cost-utility analysis for 1-year vs. no screening.

Incremental Cost-Utility, 1y_start at 60 y/o v. no screen
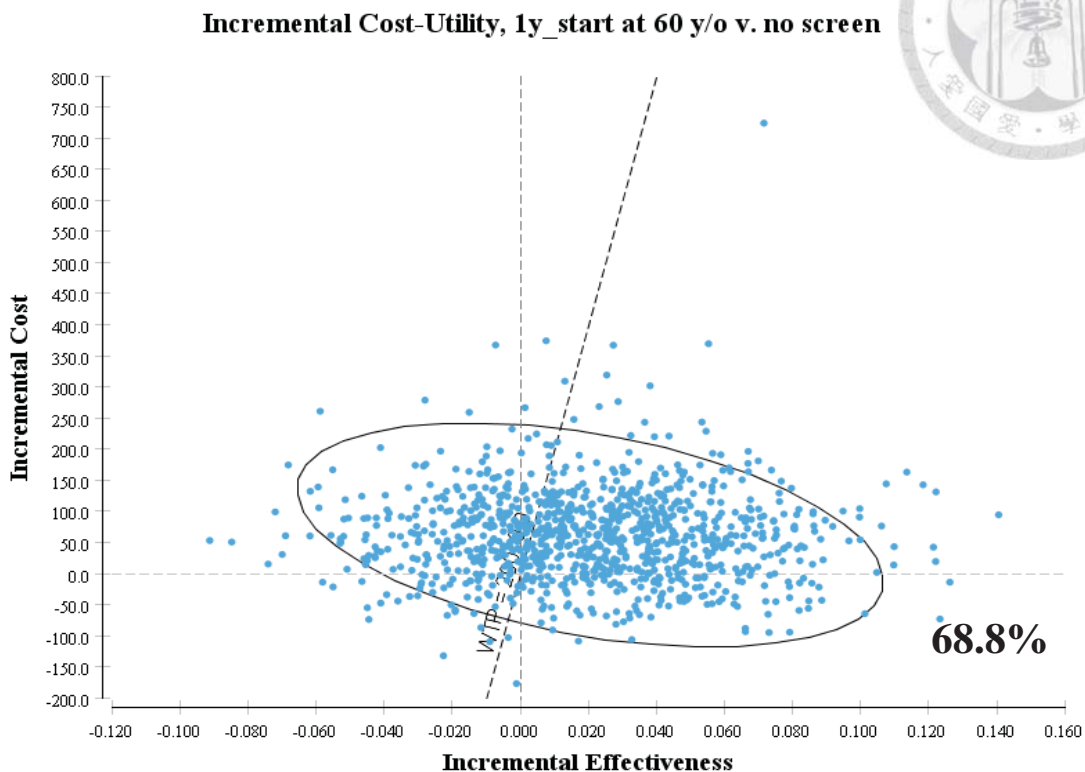
Figure 5-3-14 Scattered incremental cost-utility analysis for 2-year vs. no screening.

Incremental Cost-Cost-Utility, 2y_start at 60 y/o v. no screen
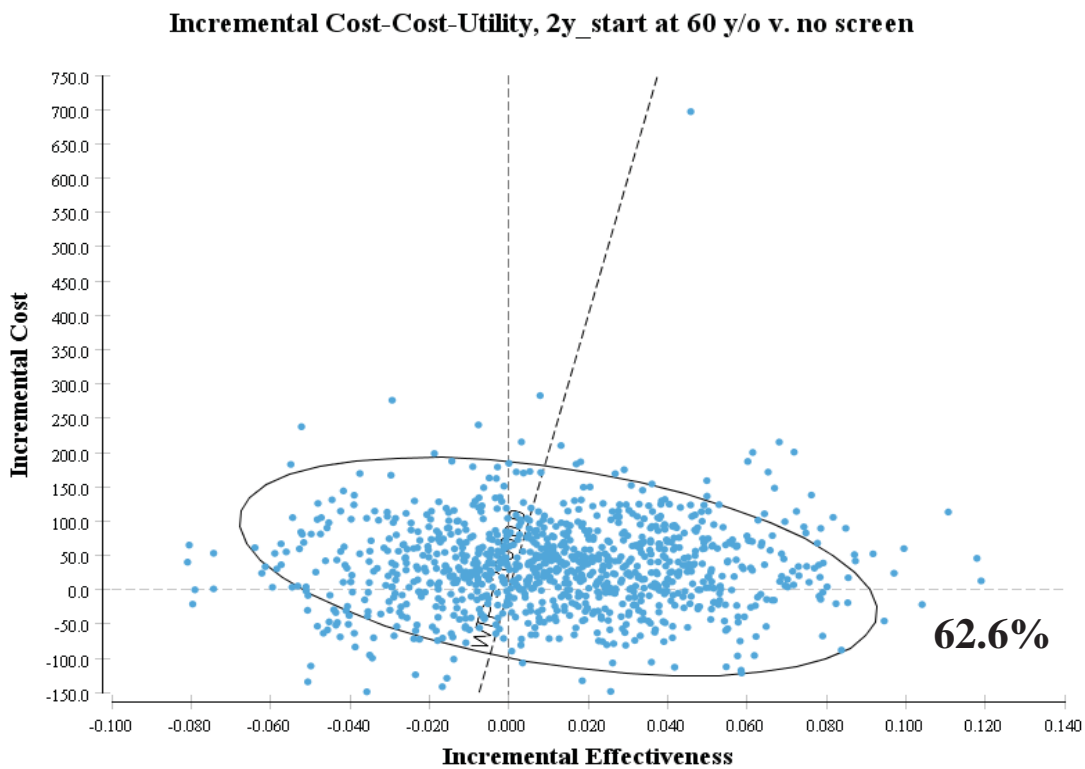
Figure 5-3-15 Scattered incremental cost-utility analysis for 3-year vs. no screening

Incremental Cost-Cost-Utility, 3y_start at 60 y/o v. no screen
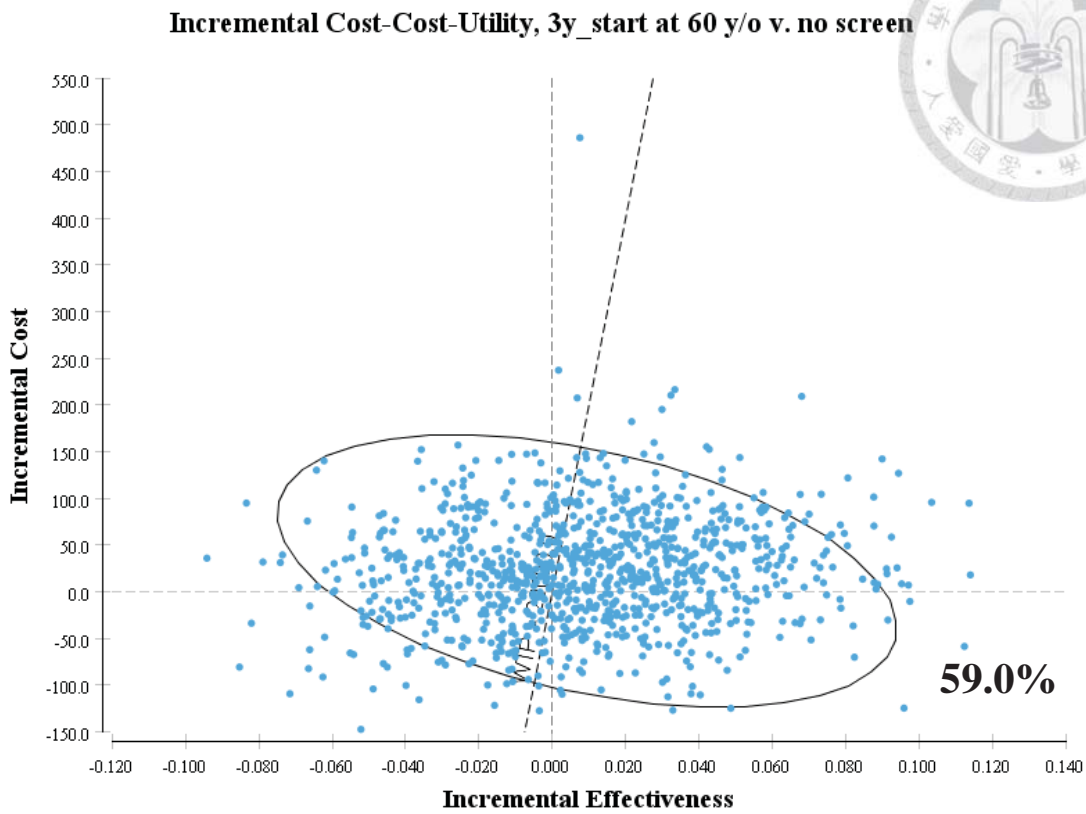
Figure 5-3-16 Acceptability curve for cost-utility analysis for various inter-screening intervals
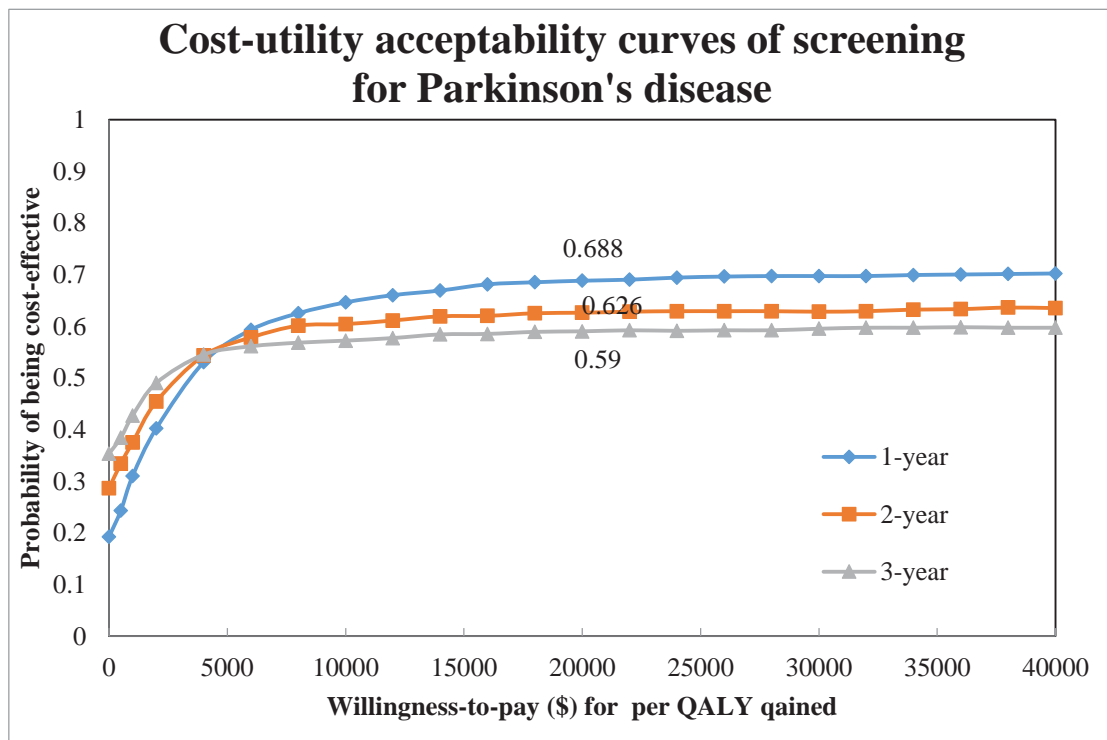
Figure 5-3-17 Scattered incremental cost-utility analysis for 1-year with 100% attendance rate vs. no screening.

Incremental Cost-Utility, 1y_start at 60 y/o v. no screen
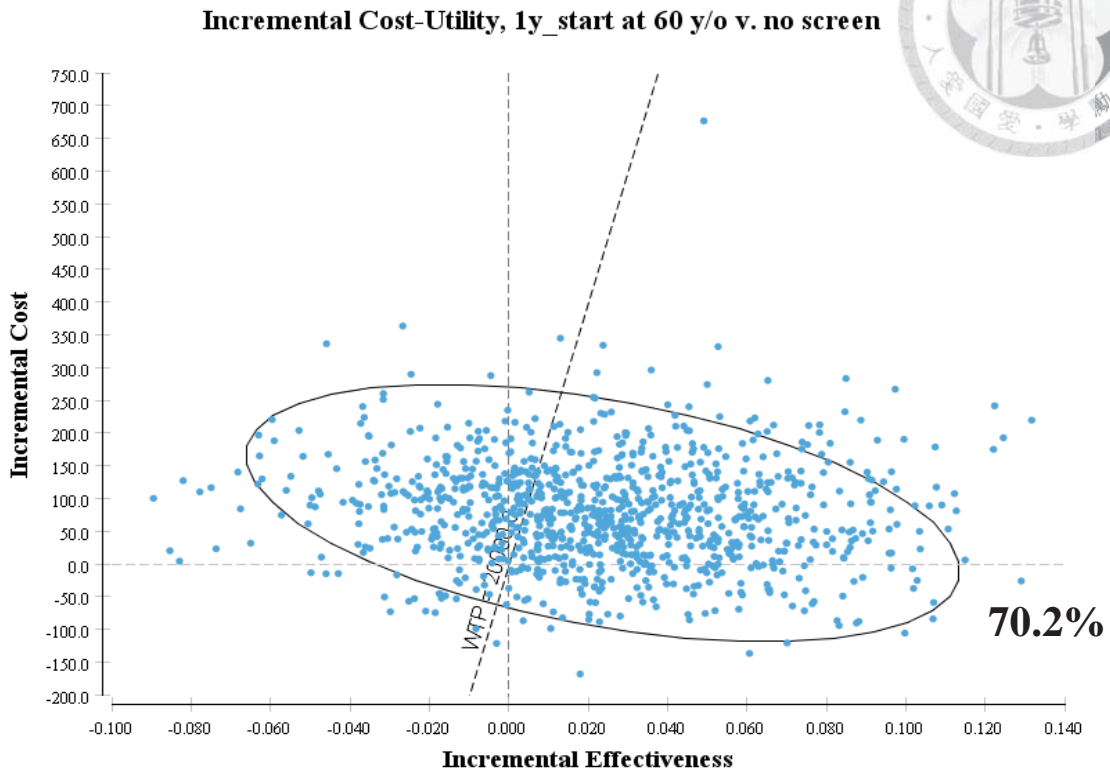
Figure 5-3-18 Scattered incremental cost-utility analysis for 2-year with 100% attendance rate vs. no screening.

Incremental Cost-Utility, 2y_start at 60 y/o v. no screen
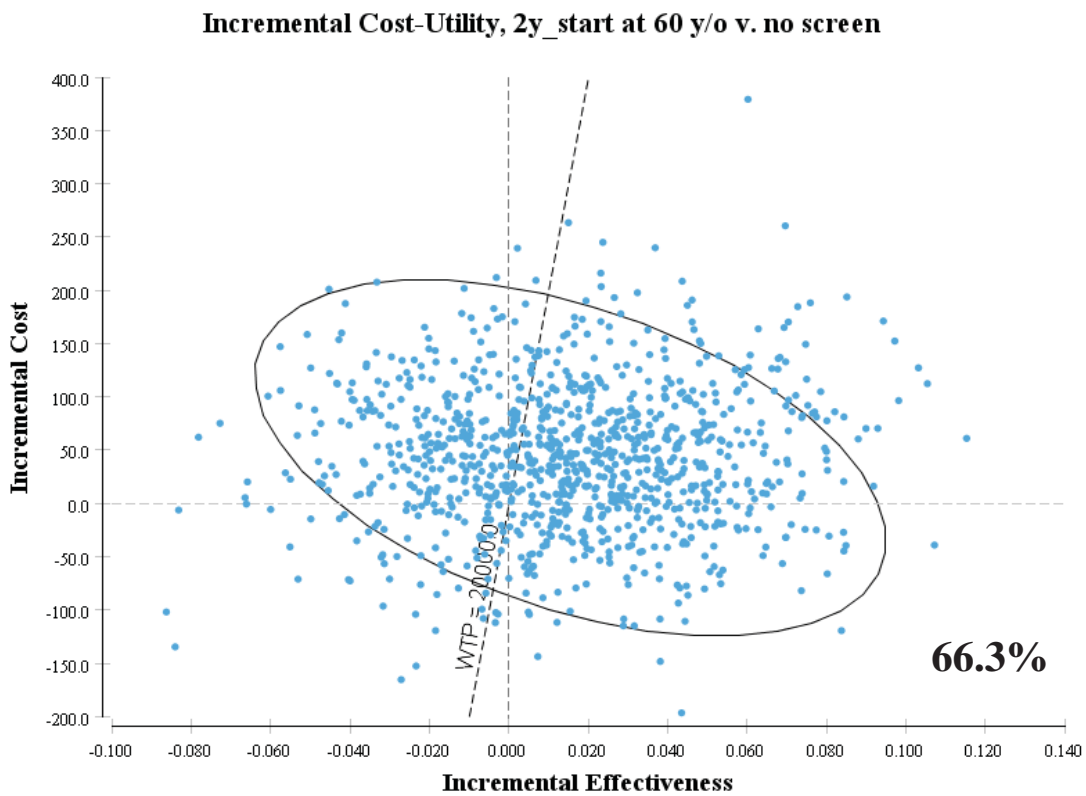
Figure 5-3-19 Scattered incremental cost-utility analysis for 3-year with 100% attendance rate vs. no screening.
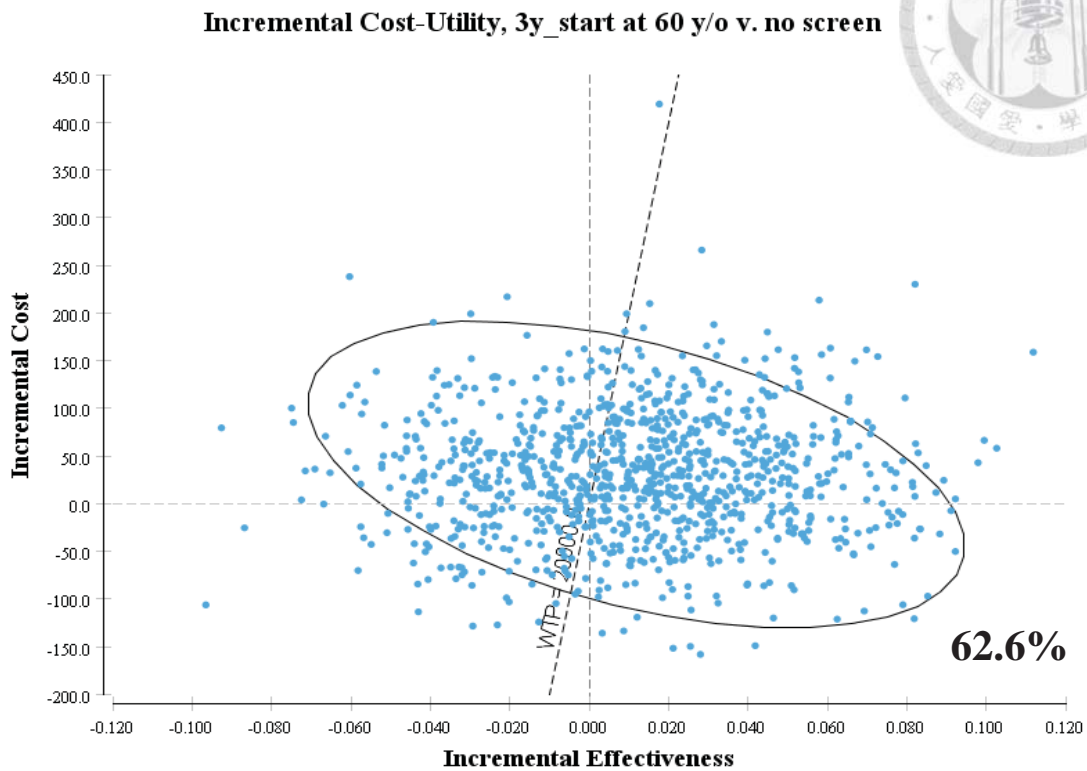
Figure 5-3-20 Acceptability curve for cost-utility analysis for various inter-screening intervals with 100% attendance rate.
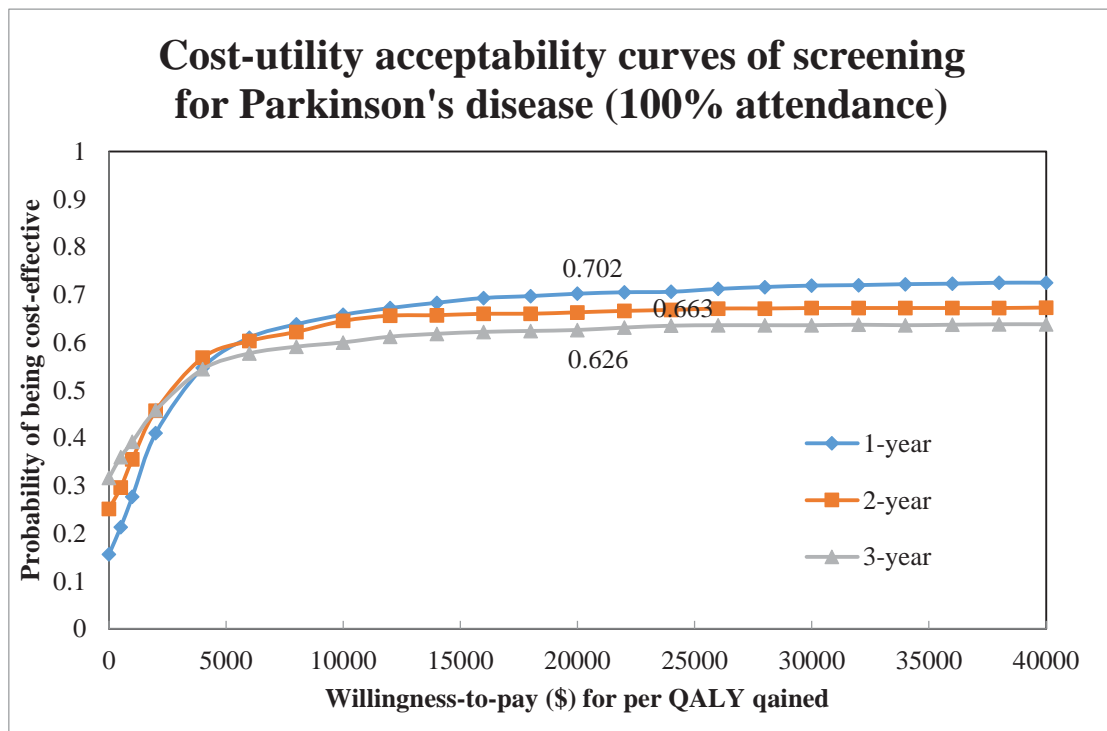
Figure 5-3-21 Scattered incremental cost-utility analysis for 1-year with 60% attendance rate vs. no screening.

Incremental Cost-Utility, 1y_start at 60 y/o v. no screen

62.6%
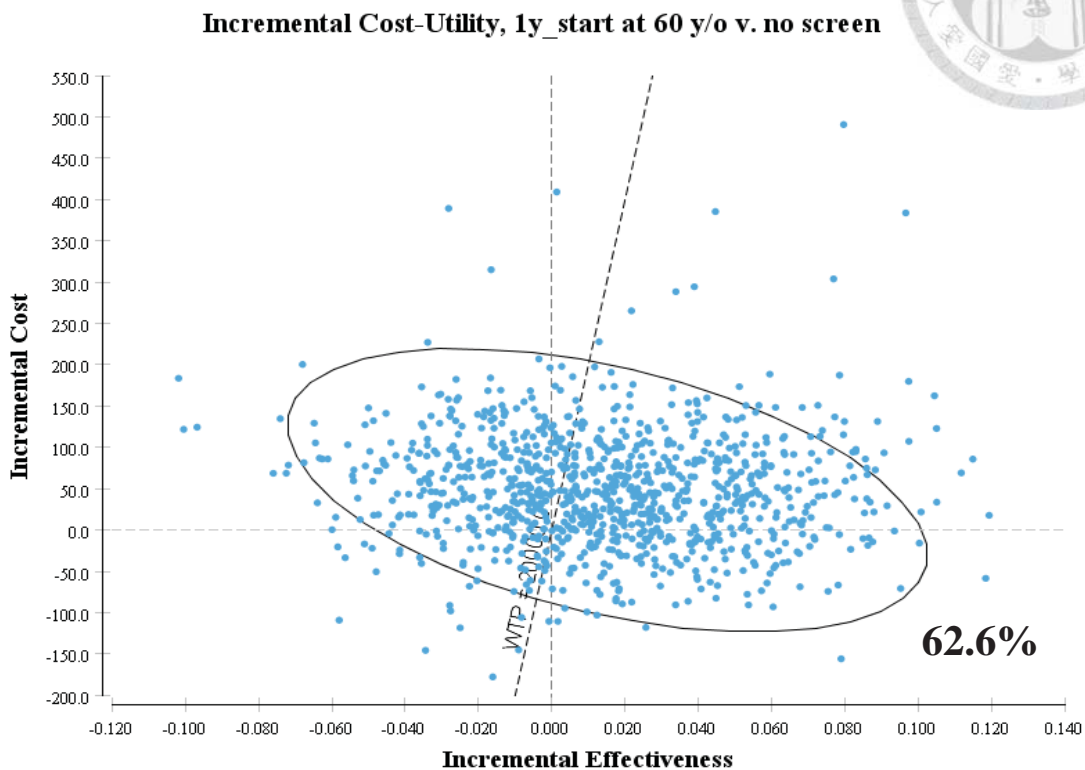
Figure 5-3-22 Scattered incremental cost-utility analysis for 2-year with 60% attendance rate vs. no screening.

Incremental Cost-Utility, 2y_start at 60 y/o v. no screen

61.0%
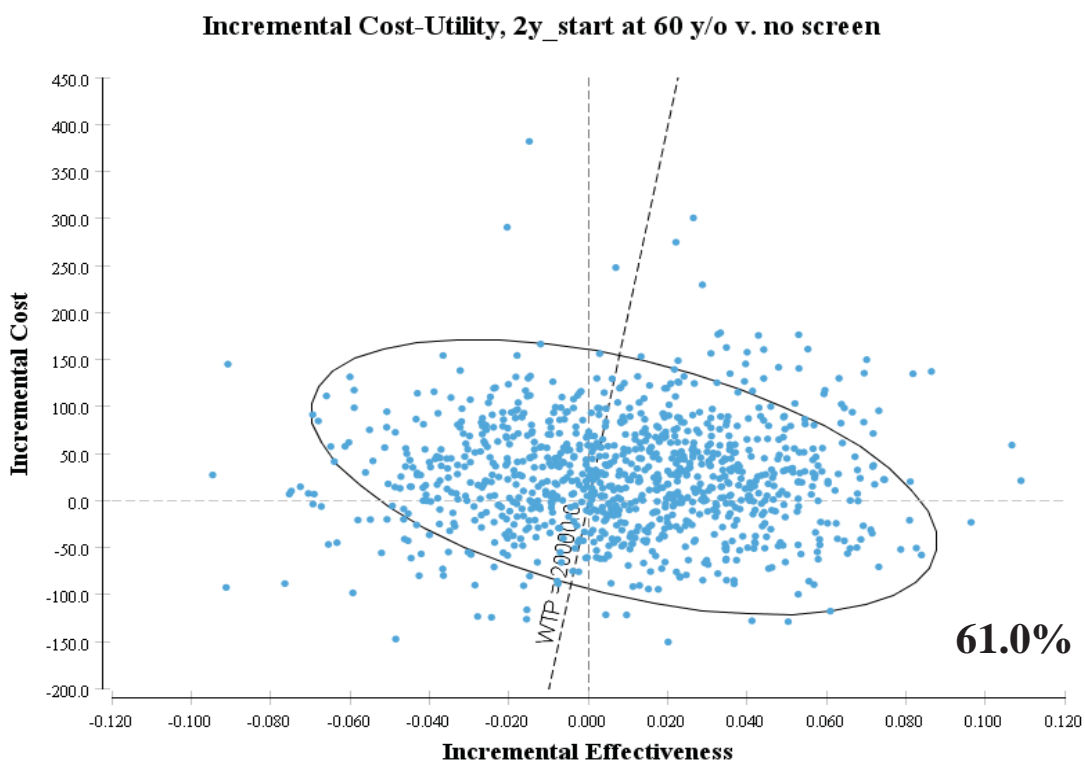
Figure 5-3-23 Scattered incremental cost-utility analysis for 3-year with 60% attendance rate vs. no screening.
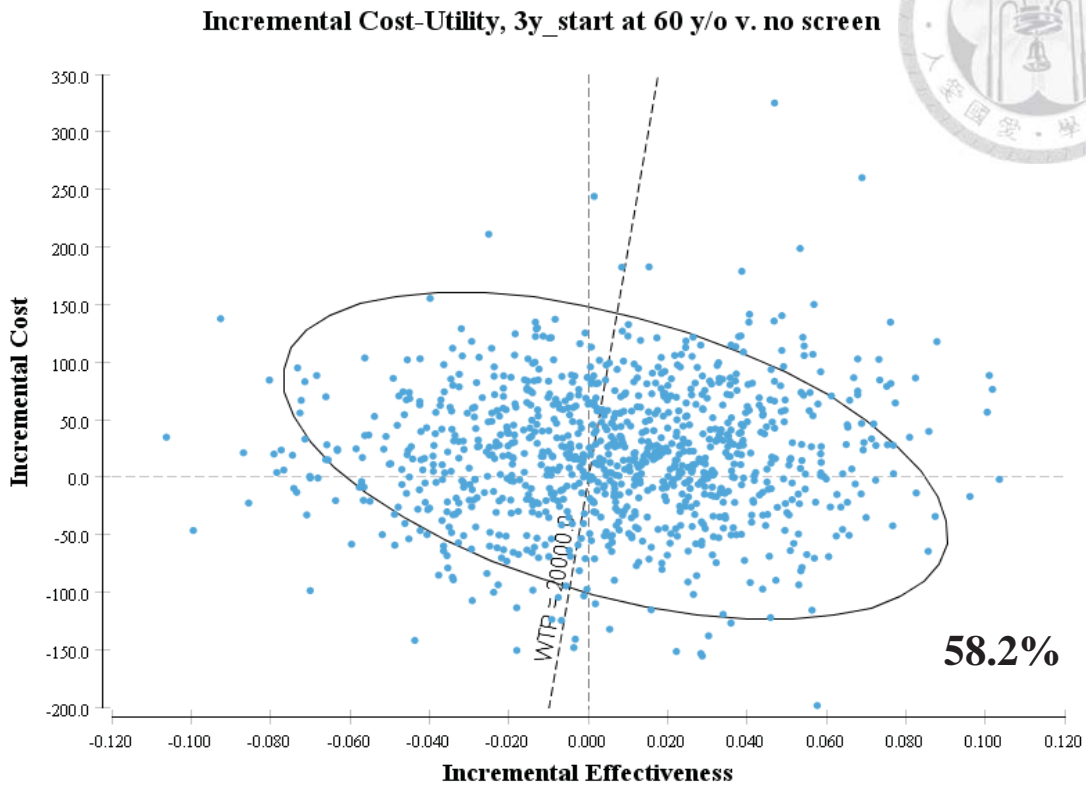
Figure 5-3-24 Acceptability curve for cost-utility analysis for various inter-screening intervals with 60% attendance rate.
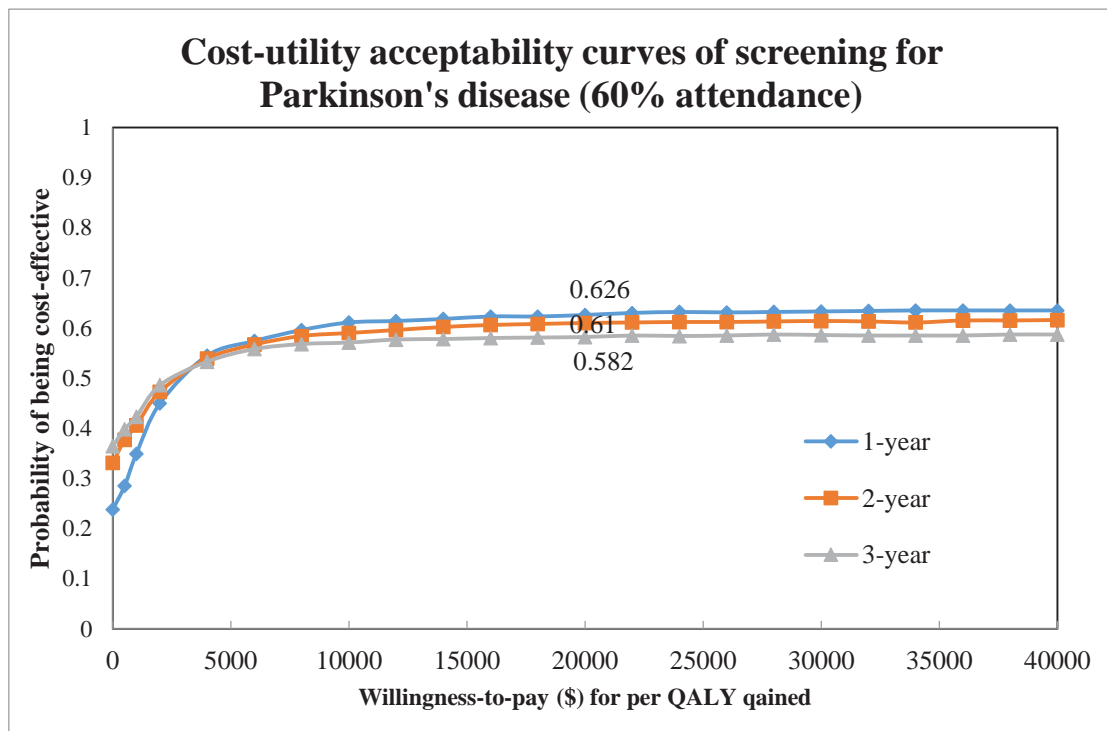
Figure 6-2-1 The predicted 20-year risk of PD by Hoehn-Yahr stage assuming Weibull distribution for transitions
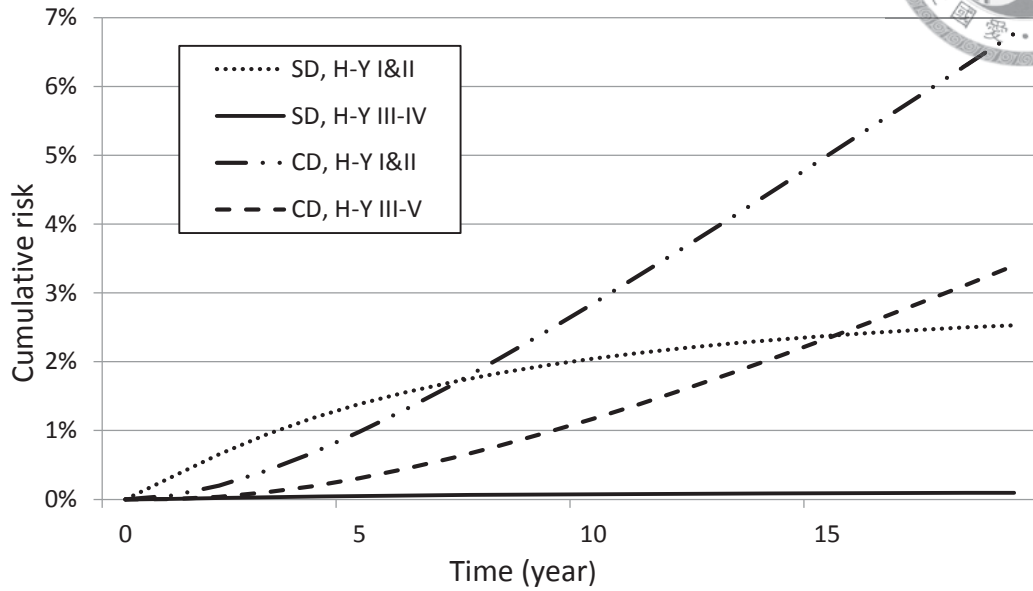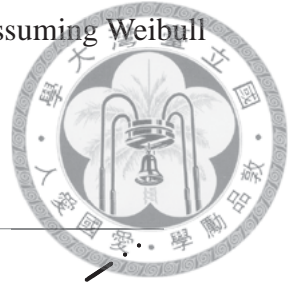
* The transitions from free of PD to SD H-Y I/II, from SD H-Y I/II to SD H-Y III+, from

SD H-Y I/II to CD H-Y I/II and from SD H-Y III+ to CD H-Y III+ were assume to follow

four Weibull distributions, Weibull(0.004, 1.2), Weibull(0.08, 1.08), Weibull(0.3982, 0.8),

and Weibull(2.1227, 1.08), respectively.

Table 4-6-1 Estimate and distribution of parameters

Item	Estimate (Range)	Distribution	References
Prevalence of each state (normal, SD early, SD late)		Dirichlet(9697, 118, 14)	KCIS
Transition rate (per year)			KCIS
Normal→ SD early	0.0078	Gamma(86, 11014)	
SD early→ SD late	0.2489	Gamma(20.6, 82.5)	
SD early→ CD early	0.3981	Gamma(30.3, 76.2)	
SD late→ CD late	2.1227	Gamma(6.66, 3.14)	
All-cause mortality			Life table (2001)
Sensitivity of physical examination, %	100		Liou et al.,2009
Specificity of physical examination, %	100		Liou et al.,2009
Mortality after treatment(per year)			Liou et al., 2009[18]
Stage I	0.0102		
Stage II	0.0485		
Stage III	0.0797		
Stage IV+	0.1989		
Annual transition rate after treatment (per year)			Zhao et al., 2010[102]
Stage I→II	0.5988		
Stage II→III	0.1379		
Stage III→IV	0.5000		
Stage IV→V	0.4608		
Utility			Shimbo 2001[91]
H-Y Stage I	0.708		
H-Y Stage II	0.678		
H-Y Stage III	0.622		
H-Y Stage IV+	0.547		
Treatment efficacy			
Relative Risk for progression to H-Y III+	0.76	Beta(76,24)	Liou, 2012[103]
Relative Risk for progression to H-Y III+	0.87	Beta(87,13)	Liou, 2012
Screen cost	8	Triangular (6,8,10)	Expert's opinion
Annual outpatient cost			KCIS,NHI
H-Y Stage I	259±281	lognormal(5.16,0.88)	
H-Y Stage II	286±346	lognormal(5.20,0.95)	
H-Y Stage III	329±289	lognormal(5.51,0.76)	
H-Y Stage IV+	393±299	lognormal(5.74,0.68)	
Annual hospitalization cost			Shimbo 2001
H-Y Stage III	3111	Triangular(2333,3111,3889)	

Item	Estimate (Range)	Distribution	References
Prevalence of each state (normal, SD early, SD late)		Dirichlet(9697, 118, 14)	KCIS
H-Y Stage IV+	4352	Triangular(3269,4352,5444)	
Admission rate			Hassan et al, 2013[92]
H-Y Stage III	40.9%	Beta (356, 515)	
H-Y Stage IV+	55.5%	Beta (152,122)	
Home care, per month	667		Market price
Discount, %	3	uniform(0,6)	

Table 5-1-1 Annual Incidence of PD in Active Detection Group

	Age(y)	40-49	50-59	60-69	70-79	80+	Total
2001	Population	3,514	2,482	2,724	2,054	412	11,186
	Person Year	1,847.39	1,360.93	1,495.64	1,122.76	225.2621	6,051.98
	PD	2	1	6	17	8	34
	Incidence	108.2607	73.47927	401.1657	1514.13	3551.418	561.7995
2002	Population	3,512	2,481	2,718	2,037	404	11,152
	Person Year	3,499.53	2,472.90	2,707.89	2,030.69	402.8556	11,113.86
	PD	2	2	9	19	10	42
	Incidence	57.15055	80.87677	332.3624	935.6445	2482.279	377.9066
2003	Population	3,510	2,479	2,709	2,018	394	11,110
	Person Year	3,497.99	2,472.08	2,705.69	2,027.84	398.809	11,102
	PD	0	2	4	16	5	27
	Incidence	0	80.90337	147.8365	789.0164	1253.733	243.1903
2004	Population	3,510	2,477	2,705	2,002	389	11,083
	Person Year	3,509.85	2,477.11	2,715.65	2,041.67	394.4011	11,139
	PD	1	1	6	20	3	31
	Incidence	28.49126	40.36964	220.9418	979.5902	760.647	278.3096

Table 5-1-2 Annual Incidence of PD in Passive Detection Group

	Age(y)	40-49	50-59	60-69	70-79	80+	Total
2001	Population	2,868	2,108	2,391	1,802	391	9,560
	Person Year	1,268.84	925.62	1,019.90	727.08	152.345	4,093.79
	PD	0	1	4	6	5	16
	Incidence	0	108.0353	392.1958	825.2155	3282.025	390.8361
2002	Population	2,868	2,107	2,387	1,796	386	9,544
	Person Year	2,858.18	2,099.74	2,378.27	1,789.92	383.0226	9,509.14
	PD	0	1	9	15	4	29
	Incidence	0	47.62488	378.426	838.0266	1044.325	304.9697
2003	Population	2,868	2,106	2,378	1,781	382	9,515
	Person Year	2,858.18	2,100.54	2,376.30	1,784.13	381.8042	9,501
	PD	0	1	6	8	2	17
	Incidence	0	47.6067	252.493	448.3988	523.8286	178.9292
2004	Population	2,868	2,105	2,372	1,773	380	9,498
	Person Year	2,866.04	2,105.49	2,384.47	1,795.95	388.742	9,541
	PD	0	1	8	13	5	27
	Incidence	0	47.49483	335.5046	723.8506	1286.2	282.9984

Table 5-1-3 Baseline characteristics of two groups of those with idiopathic Parkinson's disease by detection method.

	Active method n= 11,244	Passive method n= 9,560	p value
Age (years)	58.36±12.25	58.78±12.30	0.01
Height (cm)	157.30±8.24	157.10±8.25	0.15
Weight (kg)	62.05±10.81	61.48±10.73	<0.01
Waist Circumference (cm)	80.91±10.22	80.57±10.11	0.02
Hip Circumference (cm)	95.71±7.77	95.72±7.70	0.93
SBP (mmHg)	128.10±21.11	129.10±21.36	0.002
DBP (mmHg)	79.95±11.36	80.34±11.73	0.01
Male (%)	4312 (38.35%)	3588 (37.53%)	0.23
Current smoker (%)	2094 (18.64%)	1783 (18.89%)	0.65
Current drinker (%)	1922 (17.13%)	1662 (17.63%)	0.35
Current betelnut use (%)	234 (2.09%)	195 (2.07%)	0.93

SBP: systolic blood pressure

DBP: diastolic blood pressure

Table 5-1-4 Distribution of Hoehn-Yahr (H-Y) stage for cases of idiopathic Parkinson's disease (IPD) detected by the active or passive method.

H-Y stage	Active method in 2001	Active method group	Passive method group
	IPD case N(%)	IPD case N (%)	IPD case N (%)
I	13 (22.4)	14 (14.4)	1 (3.8)
II	41 (70.7)	64 (66.0)	15 (57.7)
III+	4 (6.9)	19 (19.6)	10 (38.5)
Total	58 (100)	97 (100)	26 (100)
Risk ratio of being stage III+	0.18	0.51	1.00
*stage III+ (95% CI)	(0.06-0.52)	(0.27-0.96)	

*active method versus passive method

Table 5-1-5 Crude and adjusted relative risk for active and passive detection methods for Parkinson's disease.

	relative risk (95%CI)	p value
Crude Estimate		
active vs passive method	1.82 (1.42-2.34)	<0.0001
Adjusted Estimate		
active vs passive method	1.95 (1.51-2.52)	<0.0001
age	1.18 (1.16-1.20)	<0.0001
weight	1.00 (0.98-1.02)	0.95
waist circumference	1.01 (0.99-1.03)	0.18
systolic blood pressure	0.99 (0.98-1.00)	0.05
diastolic blood pressure	1.01 (1.00-1.02)	0.14

Table 5-2-1 H-Y stage distribution in screen-detective case and clinical-detective case

| H-Y stage | Active detection | | Passive detection |
| | SD case | CD case | CD case |
	IPD case N (%)	IPD case N (%)	IPD case N (%)
I+II	57 (76.0)	18 (17.5)	16 (18.8)
III+	7 (9.3)	11 (10.7)	8 (9.4)
unknown	11(14.7)	74 (71.8)	61 (71.8)
Total	75 (100)	103 (100)	85 (100)
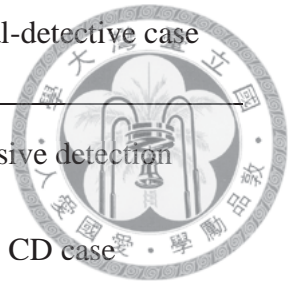
Table 5-2-2 Estimated transition rates with three-state model

Transitions/MST	Estimate	95%CI		
Normal-> SD (λ_1)	0.0076	0.0067	-	0.0086
SD->CD (λ_2)	0.6776	0.5303	-	0.8429
MST staying in SD (year)	1.48	1.212	-	1.886

MST: mean sojourn time
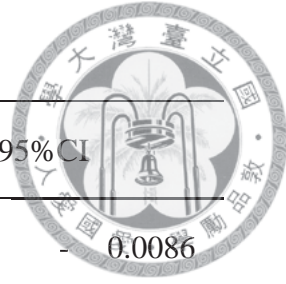
Table 5-2-3 Estimated transition rates with a three-state model using a case-cohort design sampling fraction

Transitions	Estimate	95%CI		
Normal-> SD (λ_1)	0.0082	0.0064	-	0.0100
SD->CD (λ_2)	0.5935	0.4330	-	0.7541
MST staying in SD (year)	1.68	1.326	-	2.309
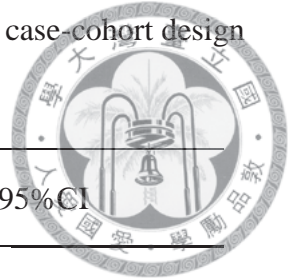
Table 5-2-4 Estimated transition rates with a five-state model using a case-cohort sampling fraction design

Transitions	Estimate	95%CI
Normal-> SD (λ_1) with H-Y I/II	0.0078	0.0062 - 0.0095
SD with H-Y I/II -> SD H-Y III+ (λ_2)	0.2498	0.1420 - 0.3576
SD with H-Y I/II -> CD with H-Y I/II+ (λ_3)	0.3982	0.2564 - 0.5399
SD with H-Y III+ -> CD with H-Y III+ (λ_4)	2.1227	0.5109 - 3.7346
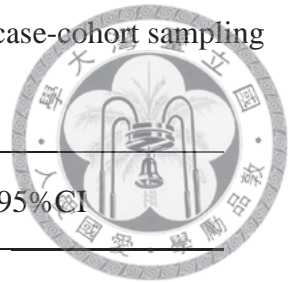
Table 5-2-5 Distribution of characteristics of subjects
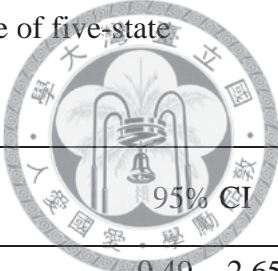
Covariate	Level	Non-PD		PD		Total	p-value
		n	%	n	%		
Gender							
	Female	5282	97.7%	124	2.3%	5406	0.0095
	Male	4284	96.9%	139	3.1%	4423	
Age group							
	60-69	5063	98.8%	61	1.2%	5124	<0.0001
	70-79	3742	96.3%	144	3.7%	3886	
	80-89	718	93.2%	52	6.8%	770	
	90+	43	87.8%	6	12.2%	49	
Education level							
	<=6 years	7616	97.3%	210	2.7%	7826	0.9264
	>6 years	1950	97.4%	53	2.6%	2003	
BMI							
	>=22	7659	97.5%	199	2.5%	7858	0.7877
	<22	1907	96.8%	64	3.2%	1971	
Ever smokers							
	No	6847	97.5%	177	2.5%	7024	0.1594
	Yes	2656	97.0%	83	3.0%	2739	
Ever drinker							
	Never	7551	97.4%	203	2.6%	7754	0.575
	Ever	1947	97.2%	57	2.8%	2004	
Serum uric acid, mg/dl							
	>=5.5	5381	97.6%	132	2.4%	5513	0.0518
	<5.5	3749	96.9%	118	3.1%	3867	
Less meat intake							
	No	5498	97.6%	137	2.4%	5635	0.0887
	Yes	3985	97.0%	123	3.0%	4108	
Less fruit intake							
	No	7755	97.5%	202	2.5%	7957	0.0983
	Yes	1735	96.8%	58	3.2%	1793	
Less vegetable intake							
	No	7383	97.4%	200	2.6%	7583	0.7475
	Yes	2111	97.2%	60	2.8%	2171	
Less coffee intake							
	No	9367	97.4%	254	2.6%	9621	0.2495
	Yes	109	95.6%	5	4.4%	114	

Table 5-2-6 Relative risk on transition rate of normal to SD early phase of five-state Markov model of Parkinson's disease
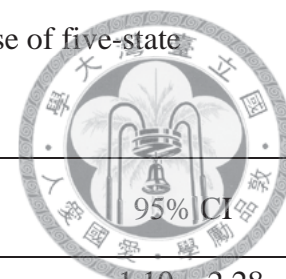
Variable	Regression coefficient	SD	RR	95% CI
Gender (Male vs. female)	0.46	0.19	1.58	1.10 - 2.28
Age , per 10 years increased	0.63	0.13	1.88	1.47 - 1.47
BMI<22 vs. 22+	0.71	0.20	2.02	1.38 - 2.97
Low uric acid (<5.5 vs. 5.5+ mg/dl)	0.43	0.19	1.54	1.07 - 2.22
Educated >6 vs. <=6 year)	-0.22	0.24	0.80	0.50 - 1.30
Ever smoker	0.42	0.19	1.52	1.05 - 2.22
Ever alcohol drinker	0.37	0.21	1.45	0.96 - 2.18
Less meat intake	0.38	0.18	1.46	1.02 - 2.09
Less fruit intake	0.36	0.22	1.44	0.94 - 2.19
Less vegetable intake	0.21	0.21	1.23	0.81 - 1.86
Less coffee intake	0.41	0.28	1.51	0.88 - 2.59

Table 5-2-7 Relative risk on transition rate of SD early to SD late phase of five-state Markov model of Parkinson's disease

Variable	Regression coefficient	SD	RR	95% CI
Gender (Male vs. female)	0.13	0.43	1.14	0.49 - 2.65
Age , per 10 years increased	0.81	0.43	2.25	0.97 - 5.21
BMI<22 vs. 22+	-0.43	0.46	0.65	0.27 - 1.58
Low uric acid (<5.5 vs. 5.5+ mg/dl)	-0.96	0.43	0.38	0.17 - 0.89
Educated >6 vs. <=6 year)	1.81	0.50	6.09	2.28 - 16.26
Ever smoker	0.01	0.43	1.01	0.43 - 2.35
Ever alcohol drinker	0.09	0.46	1.10	0.44 - 2.72
Less meat intake	-0.69	0.41	0.50	0.22 - 1.12
Less fruit intake	0.45	0.46	1.58	0.64 - 3.90
Less vegetable intake	-0.39	0.49	0.68	0.26 - 1.77
Less coffee intake	-1.12	0.52	0.33	0.12 - 0.90

Table 5-2-8 Relative risk on transition rate of SD early to CD early phase of five-state Markov model of Parkinson's disease
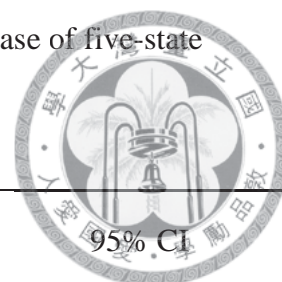
Variable	Regression coefficient	SD	RR	95% CI
Gender (Male vs. female)	-0.79	0.33	0.45	0.24 - 0.87
Age , per 10 years increased	-1.01	0.27	0.36	0.21 - 0.62
BMI<22 vs. 22+	-0.87	0.37	0.42	0.20 - 0.87
Low uric acid (<5.5 vs. 5.5+ mg/dl)	0.16	0.35	1.17	0.59 - 2.31
Educated >6 vs. <=6 year)	-0.07	0.43	0.94	0.41 - 2.16
Ever smoker	-0.72	0.36	0.49	0.24 - 0.99
Ever alcohol drinker	-0.03	0.38	0.97	0.46 - 2.03
Less meat intake	-0.45	0.32	0.64	0.34 - 1.20
Less fruit intake	-0.07	0.40	0.93	0.43 - 2.03
Less vegetable intake	-0.50	0.40	0.61	0.28 - 1.32
Less coffee intake	-0.59	0.45	0.55	0.23 - 1.33

Table 5-2-9 Relative risk on transition rate of SD late to CD late phase of five-state Markov model of Parkinson's disease
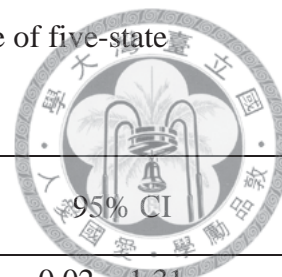
Variable	Regression coefficient	SD	RR	95% CI
Gender (Male vs. female)	-1.80	1.05	0.17	0.02 - 1.31
Age , per 10 years increased	-1.34	0.54	0.26	0.09 - 0.76
BMI<22 vs. 22+	-0.84	0.74	0.43	0.10 - 1.85
Low uric acid (<5.5 vs. 5.5+ mg/dl)	0.21	0.86	1.24	0.23 - 6.68
Educated >6 vs. <=6 year)	-1.18	0.75	0.31	0.07 - 1.33
Ever smoker	-1.03	0.75	0.36	0.08 - 1.56
Ever alcohol drinker	-0.31	0.83	0.73	0.14 - 3.72
Less meat intake	-0.09	0.75	0.91	0.21 - 3.97
Less fruit intake	-0.41	0.84	0.66	0.13 - 3.41
Less vegetable intake	0.25	1.08	1.28	0.15 - 10.55
Less coffee intake	0.37	0.82	1.45	0.29 - 7.28

Table 5-2-10 Multivariate analysis on transition rate of normal to SD early phase

Variable	Regression coefficient		Relative risk	
	estimate	SD	estimate	95% CI
Age , per 10 years increased	0.59	0.13	1.80	1.40 - 2.32
Gender (Male vs. female)	0.27	0.22	1.31	0.86 - 2.00
BMI<22 vs. 22+	0.56	0.20	1.75	1.19 - 2.59
Ever smoker	0.21	0.22	1.23	0.80 - 1.90
Age , per 10 years increased	0.59	0.13	1.81	1.41 - 2.33
Gender (Male vs. female)	0.28	0.21	1.33	0.88 - 1.99
BMI<22 vs. 22+	0.57	0.20	1.77	1.20 - 2.62
Ever alcohol drinker	0.24	0.23	1.27	0.81 - 1.98
Age , per 10 years increased	0.55	0.13	1.74	1.35 - 2.23
Gender (Male vs. female)	0.42	0.19	1.52	1.04 - 2.22
BMI<22 vs. 22+	0.57	0.20	1.77	1.21 - 2.61
Educated >6 vs. <=6 year)	-0.40	0.25	0.67	0.41 - 1.11
Age , per 10 years increased	0.56	0.13	1.75	1.35 - 2.27
Gender (Male vs. female)	0.46	0.19	1.58	1.08 - 2.31
BMI<22 vs. 22+	0.49	0.20	1.64	1.10 - 2.45
Low uric acid (<5.5 vs. 5.5+ mg/dl)	0.53	0.19	1.70	1.16 - 2.49
Age , per 10 years increased	0.58	0.13	1.78	1.38 - 2.28
Gender (Male vs. female)	0.35	0.19	1.42	0.98 - 2.05
BMI<22 vs. 22+	0.54	0.20	1.72	1.17 - 2.55
Less fruit intake	0.31	0.21	1.36	0.89 - 2.07
Age , per 10 years increased	0.57	0.13	1.77	1.38 - 2.27
Gender (Male vs. female)	0.34	0.19	1.41	0.98 - 2.03
BMI<22 vs. 22+	0.56	0.20	1.76	1.19 - 2.59
Less vegetable intake	0.13	0.21	1.13	0.75 - 1.71
Age , per 10 years increased	0.55	0.13	1.73	1.35 - 2.23
Gender (Male vs. female)	0.38	0.19	1.46	1.01 - 2.11
BMI<22 vs. 22+	0.56	0.20	1.75	1.18 - 2.58
Less meat intake	0.32	0.19	1.38	0.96 - 1.99

Multivariate analysis on transition rate of normal to SD early phase (continued)

Variable	Regression coefficient		Relative risk	
	estimate	SD	estimate	95% CI
Age , per 10 years increased	0.57	0.13	1.76	1.37 – 2.27
Gender (Male vs. female)	0.34	0.19	1.41	0.97 – 2.04
BMI<22 vs. 22+	0.57	0.20	1.77	1.19 – 2.61
Less coffee intake	-15.67	77.31	0.00	0.00 - -

Table 5-2-11 Multivariate analysis on transition rate of SD early phase to SD late phase

| Variable | Regression coefficient | | Relative risk | |
	estimate	SD	estimate	95% CI
Age , per 10 years increased	0.71	0.44	2.03	0.86 - 4.82
Gender (Male vs. female)	0.08	0.55	1.09	0.37 - 3.22
BMI<22 vs. 22+	-0.32	0.49	0.72	0.28 - 1.90
Ever smoker	0.01	0.53	1.01	0.35 - 2.88
Age , per 10 years increased	0.82	0.47	2.27	0.91 - 5.66
Gender (Male vs. female)	-0.04	0.51	0.96	0.36 - 2.59
BMI<22 vs. 22+	-0.31	0.50	0.74	0.28 - 1.95
Ever alcohol drinker	0.42	0.56	1.53	0.51 - 4.57
Age , per 10 years increased	1.02	0.47	2.78	1.11 - 6.96
Gender (Male vs. female)	-0.51	0.55	0.60	0.21 - 1.76
BMI<22 vs. 22+	0.04	0.55	1.04	0.36 - 3.03
Educated >6 vs. <=6 year)	2.32	0.63	10.15	2.94 - 35.02
Age , per 10 years increased	0.76	0.47	2.14	0.85 - 5.43
Gender (Male vs. female)	-0.18	0.48	0.83	0.33 - 2.11
BMI<22 vs. 22+	-0.42	0.51	0.66	0.24 - 1.79
Low uric acid (<5.5 vs. 5.5+ mg/dl)	-1.07	0.48	0.34	0.13 - 0.87
Age , per 10 years increased	0.80	0.45	2.22	0.92 - 5.35
Gender (Male vs. female)	0.07	0.48	1.07	0.42 - 2.73
BMI<22 vs. 22+	-0.43	0.51	0.65	0.24 - 1.75
Less fruit intake	0.67	0.52	1.95	0.71 - 5.37
Age , per 10 years increased	0.69	0.44	1.99	0.84 - 4.70
Gender (Male vs. female)	0.19	0.48	1.21	0.47 - 3.12
BMI<22 vs. 22+	-0.32	0.49	0.72	0.28 - 1.90
Less vegetable intake	-0.36	0.54	0.70	0.24 - 2.01
Age , per 10 years increased	0.90	0.45	2.47	1.01 - 6.00
Gender (Male vs. female)	-0.10	0.48	0.90	0.35 - 2.32
BMI<22 vs. 22+	-0.13	0.50	0.88	0.33 - 2.34
Less meat intake	-0.97	0.50	0.38	0.14 - 1.00

Table 5-2-12 Multivariate analysis on transition rate of SD early phase to CD early phase

Variable	Regression coefficient		Relative risk		
	estimate	SD	estimate	95% CI	
Age , per 10 years increased	-0.93	0.27	0.39	0.23 -	0.68
Gender (Male vs. female)	-0.49	0.40	0.62	0.28 -	1.35
BMI<22 vs. 22+	-0.82	0.39	0.44	0.20 -	0.95
Ever smoker	-0.22	0.43	0.80	0.35 -	1.85
Age , per 10 years increased	-0.91	0.28	0.40	0.23 -	0.69
Gender (Male vs. female)	-0.65	0.37	0.52	0.25 -	1.09
BMI<22 vs. 22+	-0.85	0.40	0.43	0.20 -	0.93
Ever alcohol drinker	0.13	0.43	1.14	0.49 -	2.67
Age , per 10 years increased	-0.91	0.27	0.40	0.24 -	0.68
Gender (Male vs. female)	-0.61	0.35	0.54	0.27 -	1.08
BMI<22 vs. 22+	-0.77	0.39	0.46	0.22 -	0.99
Educated >6 vs. <=6 year)	0.16	0.46	1.18	0.48 -	2.90
Age , per 10 years increased	-0.90	0.29	0.41	0.23 -	0.72
Gender (Male vs. female)	-0.62	0.35	0.54	0.27 -	1.07
BMI<22 vs. 22+	-0.86	0.40	0.42	0.19 -	0.94
Low uric acid (<5.5 vs. 5.5+ mg/dl)	-0.08	0.36	0.92	0.46 -	1.86
Age , per 10 years increased	-0.91	0.27	0.40	0.23 -	0.69
Gender (Male vs. female)	-0.57	0.34	0.56	0.29 -	1.09
BMI<22 vs. 22+	-0.85	0.40	0.43	0.20 -	0.94
Less fruit intake	0.19	0.41	1.21	0.54 -	2.71
Age , per 10 years increased	-0.92	0.27	0.40	0.23 -	0.68
Gender (Male vs. female)	-0.50	0.34	0.60	0.31 -	1.17
BMI<22 vs. 22+	-0.82	0.39	0.44	0.20 -	0.95
Less vegetable intake	-0.44	0.40	0.65	0.30 -	1.41
Age , per 10 years increased	-0.85	0.27	0.43	0.25 -	0.72
Gender (Male vs. female)	-0.63	0.34	0.54	0.27 -	1.04
BMI<22 vs. 22+	-0.78	0.39	0.46	0.21 -	0.99
Less meat intake	-0.35	0.34	0.70	0.36 -	1.38

Multivariate analysis on transition rate of SD early phase to CD early phase (continued)

Variable	Regression coefficient		Relative risk	
	estimate	SD	estimate	95% CI
Age , per 10 years increased	-0.94	0.28	0.39	0.23 - 0.67
Gender (Male vs. female)	-0.61	0.34	0.55	0.28 - 1.06
BMI<22 vs. 22+	-0.78	0.40	0.46	0.21 - 1.00
Less coffee intake	9.44	93.80	12629.72	0.00 - -

Table 5-2-13 Multivariate analysis on transition rate of SD late phase to CD late phase

Variable	Regression coefficient		Relative risk	
	estimate	SD	estimate	95% CI
Age , per 10 years increased	-1.31	0.57	0.27	0.09 - 0.82
Gender (Male vs. female)	-1.88	1.09	0.15	0.02 - 1.30
BMI<22 vs. 22+	-0.90	0.80	0.41	0.09 - 1.93
Ever smoker	-0.10	0.80	0.91	0.19 - 4.37
Age , per 10 years increased	-1.29	0.57	0.28	0.09 - 0.84
Gender (Male vs. female)	-2.06	1.11	0.13	0.01 - 1.12
BMI<22 vs. 22+	-0.91	0.78	0.40	0.09 - 1.84
Ever alcohol drinker	0.46	0.91	1.58	0.27 - 9.40
Age , per 10 years increased	-1.37	0.57	0.25	0.08 - 0.77
Gender (Male vs. female)	-1.54	1.14	0.21	0.02 - 2.02
BMI<22 vs. 22+	-0.87	0.81	0.42	0.08 - 2.06
Educated >6 vs. <=6 year)	-0.78	0.87	0.46	0.08 - 2.53
Age , per 10 years increased	-1.22	0.63	0.30	0.09 - 1.02
Gender (Male vs. female)	-1.67	1.22	0.19	0.02 - 2.04
BMI<22 vs. 22+	-1.30	0.89	0.27	0.05 - 1.55
Low uric acid (<5.5 vs. 5.5+ mg/dl)	0.27	1.00	1.31	0.18 - 9.33
Age , per 10 years increased	-1.34	0.59	0.26	0.08 - 0.83
Gender (Male vs. female)	-1.87	1.14	0.15	0.02 - 1.45
BMI<22 vs. 22+	-0.87	0.80	0.42	0.09 - 2.03
Less fruit intake	-0.24	0.92	0.78	0.13 - 4.79
Age , per 10 years increased	-1.33	0.55	0.27	0.09 - 0.79
Gender (Male vs. female)	-2.03	1.12	0.13	0.01 - 1.18
BMI<22 vs. 22+	-1.01	0.79	0.36	0.08 - 1.72
Less vegetable intake	0.89	1.18	2.44	0.24 - 24.78
Age , per 10 years increased	-1.30	0.60	0.27	0.08 - 0.88
Gender (Male vs. female)	-1.96	1.22	0.14	0.01 - 1.55
BMI<22 vs. 22+	-0.84	0.80	0.43	0.09 - 2.07
Less meat intake	-0.33	0.79	0.72	0.15 - 3.38

Multivariate analysis on transition rate of SD late phase to CD late phase (continued)

Variable	Regression coefficient		Relative risk	
	estimate	SD	estimate	95% CI
Age , per 10 years increased	-1.31	0.57	0.27	0.09 - 0.82
Gender (Male vs. female)	-1.92	1.06	0.15	0.02 - 1.18
BMI<22 vs. 22+	-0.89	0.79	0.41	0.09 - 1.94
Less coffee intake	8.05	82.75	3135.27	0.00 - -

Table 5-2-14 Covariate in transition of five state model with hypothesis testing

Covariate		Normal to SD early (λ_1)	SD early to SD late (λ_2)	SD early to CD early (λ_3)	SD late to CD late (λ_4)	Net force coefficient (NFC)	p value
Gender (male vs. female)	estimate	0.34	0.22	-0.44	-1.28	-0.61	0.61
	RR	1.40	1.25	0.64	0.28		
	95% CI	0.92-2.15	0.52-3.02	0.31-1.32	0.04-1.92		
Age, per 10 years increased	estimate	0.61	0.99	-0.52	-0.45	1.06	0.15
	RR	1.84	2.69	0.59	0.64		
	95% CI	1.38 - 2.45	1.30 - 5.58	0.34 - 1.04	0.22 - 1.82		
BMI<22 vs. 22+	estimate	0.57	-0.21	-0.39	-0.40	-0.21	0.85
	RR	1.76	0.81	0.68	0.67		
	95% CI	1.11 - 2.79	0.32 - 2.03	0.31 - 1.47	0.14 - 3.20		
Low UA <5.5 vs. 5.5+ (mg/dl)	estimate	0.48	-0.67	0.53	0.05	-1.14	0.35
	RR	1.61	0.51	1.70	1.05		
	95% CI	1.04 - 2.48	0.21 - 1.27	0.79 - 3.64	0.17 - 6.47		
Education >6 vs. <= 6 years	estimate	-0.06	1.74	0.14	-0.81	0.80	0.48
	RR	0.94	5.71	1.15	0.45		
	95% CI	0.55 - 1.61	1.90 - 17.20	0.33 - 4.06	0.10 - 2.06		

Covariate		Normal to SD early (λ_1)	SD early to SD late (λ_2)	SD early to CD early (λ_3)	SD late to CD late (λ_4)	NFC	p value
Ever smoke	estimate	0.31	0.11	-0.41	-0.61	-0.09	0.94
	RR	1.36	1.11	0.66	0.55		
	95% CI	0.87 - 2.12	0.47 - 2.67	0.30 - 1.45	0.12 - 2.55		
Ever alcohol use	estimate	0.48	0.35	0.32	-0.04	0.00	1.00
	RR	1.62	1.43	1.37	0.96		
	95% CI	1.01 - 2.58	0.55 - 3.72	0.61 - 3.10	0.19 - 5.01		
Less meat intake	estimate	0.25	-0.55	-0.27	0.01	-0.27	0.79
	RR	1.28	0.58	0.77	1.01		
	95% CI	0.83 - 1.96	0.24 - 1.39	0.37 - 1.57	0.23 - 4.43		
Less fruit intake	estimate	0.52	0.74	0.36	0.00	0.38	0.74
	RR	1.68	2.10	1.43	1.00		
	95% CI	1.04 - 2.71	0.79 - 5.58	0.59 - 3.45	0.18 - 5.40		
Less vegetable intake	estimate	0.06	-0.30	-0.46	0.42	0.58	0.69
	RR	1.06	0.74	0.63	1.52		
	95% CI	0.64 - 1.76	0.27 - 2.01	0.27 - 1.48	0.17 - 13.74		
Less coffee intake	estimate	0.19	-1.15	-0.70	0.44	-0.01	0.99
	RR	1.21	0.32	0.49	1.55		
	95% CI	0.67 - 2.20	0.09 - 1.08	0.15 - 1.66	0.31 - 7.74		
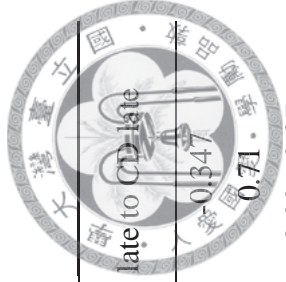
Table 5-2-15 Multivariate analysis for the multiple transition in the five-state Markov model

Covariate		Normal to SD early	SD early to SD late	SD early to CD early	SD late to CD late
Age, per 10 years increased	estimate	0.584	1.626	-0.454	-0.347
	RR	1.79	5.08	0.63	0.71
	95% CI	1.32 -2.44	1.94 -13.29	0.35-1.15	0.22 - 2.27
Gender (male vs. female)	estimate	0.338	-0.736	-0.362	
	RR	1.40	0.48	0.70	
	95% CI	0.90 - 2.19	0.15 - 1.54	0.35 - 1.40	
Low UA <5.5 vs. 5.5+ (mg/dl)	estimate	0.431	-0.933		
	RR	1.54	0.39		
	95% CI	1.04 - 2.28	0.13 - 1.19		
BMI<22 vs. 22+	estimate	0.359		-0.501	
	RR	1.43		0.61	
	95% CI	0.90 - 2.27		0.28 - 1.31	
Education >6 vs. <= 6 years	estimate		2.685		
	RR		14.65		
	95% CI		3.94 - 54.53		

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Table 5-2-16 Multivariate analysis for the multiple transition in the five-state Markov model with further adjustment of vegetable and fruit intake

Covariate		Normal to SD early	SD early to SD late	SD early to CD early	SD late to CD late
Age, per 10 years increased	estimate	0.603	1.642	-0.425	-0.419
	RR	1.83	5.16	0.65	0.66
	95% CI	1.34 - 2.50	1.94 - 13.76	0.35 - 1.21	0.16 - 2.74
Gender (male vs. female)	estimate	0.355	-0.693	-0.350	
	RR	1.43	0.50	0.70	
	95% CI	0.91 - 2.24	0.15 - 1.70	0.34 - 1.45	
Low UA <5.5 vs. 5.5+ (mg/dl)	estimate	0.426	-0.917		
	RR	1.53	0.40		
	95% CI	1.03 - 2.28	0.13 - 1.23		
BMI<22 vs. 22+	estimate	0.330		-0.545	
	RR	1.39		0.58	
	95% CI	0.87 - 2.23		0.26 - 1.29	
Education >6 vs. <= 6 years	estimate		2.725		
	RR		15.26		
	95% CI		3.96 - 58.76		

Multivariate analysis for the multiple transition in the five-state Markov model with further adjustment of vegetable and fruit intake (continued)

Covariate		Normal to SD early	SD early to SD late	SD early to CD early	SD late to CD late
Less vegetable intake	estimate		-0.619		-0.480
	RR		0.54		0.62
	95% CI		0.16 - 1.80		0.30 - 1.28
Less fruit intake	estimate		0.437		0.415
	RR		1.55		1.51
	95% CI		0.48 - 4.96		0.67 - 3.42

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Table 5-3-1 The simulated results of PD cases by HY stage at diagnosis with 1-, 2-, 3-, 4-, and 6-yearly screening in 12 years for a hypothetical cohort of 9829 elderly people aged 60 at entry
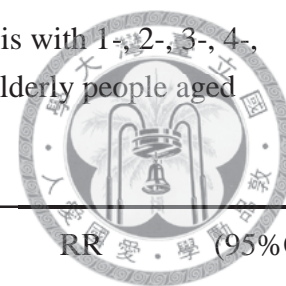
Screening interval	SD, HYI&II	SD, HY III+	CD, HY I&II	CD, HY III+	Proportion of HY III+	RR	(95%CI)
1	755.56	61.14	140.74	41.11	10.2%	0.2904	(0.2330, 0.3620)
2	602.97	62.15	234.51	98.92	16.1%	0.4575	(0.3797, 0.5513)
3	498.69	55.59	298.59	145.67	20.2%	0.5717	(0.4808, 0.6798)
4	425.51	48.94	343.56	180.53	23.0%	0.6519	(0.5520, 0.7698)
6	333.74	39.18	399.95	225.68	26.5%	0.7523	(0.6415, 0.8824)
No screen	107.59	12.71	538.93	339.33	35.3%	1.0000	

Table 5-3-2 Incremental cost-effectiveness ratio (ICER) and cost-utility ratio (ICUR) among screening strategies by attendance rate

Attend-ance	Strategy	COST,$	Incr. Cost	LYG	Incr. LYG	ICER	QALYG	Incr. QALYG	ICUR
~ Triangular (0.6,0.8,1)									
	No screening	1052.3	baseline	14.054	baseline	baseline	13.813	baseline	baseline
	Triennially	1070.8	18.6	14.070	0.016	1169	13.824	0.011	1715
	Biennially	1080.5	28.3	14.075	0.021	1367	13.828	0.014	1995
	Annually	1107.5	55.2	14.084	0.031	1804	13.835	0.021	2606
60%									
	No screening	1052.3	baseline	14.054	baseline	baseline	13.813	baseline	baseline
	Triennially	1066.2	13.9	14.066	0.012	1151	13.822	0.008	1689
	Biennially	1073.3	21.1	14.070	0.016	1316	13.824	0.011	1924
	Annually	1093.2	40.9	14.079	0.025	1652	13.831	0.017	2395
100%									
	No screening	1052.3	baseline	14.054	baseline	baseline	13.813	baseline	baseline
	Triennially	1075.5	23.3	14.073	0.020	1188	13.827	0.013	1742
	Biennially	1087.7	35.5	14.079	0.025	1416	13.831	0.017	2065
	Annually	1121.9	69.7	14.090	0.036	1949	13.838	0.025	2808

Table 5-3-3 The distribution of cost, effectiveness, and net monetary benefit

Outcome	Strategy	Mean	SD	2.50%	97.50%
Cost,$					
	Annually	1114.8	201.6	833.1	1597.7
	Biennially	1086.1	194.6	811.0	1553.6
	Triennially	1075.2	194.0	785.5	1511.7
	No screen	1050.2	183.6	758.2	1475.0
Effectiveness, life year gained(LYG)					
	Annually	14.090	0.055	13.976	14.196
	Biennially	14.080	0.053	13.973	14.181
	Triennially	14.075	0.057	13.959	14.181
	No screen	14.058	0.053	13.951	14.156
Effectiveness, QALY gained(QALYG)					
	Annually	13.836	0.069	13.694	13.966
	Biennially	13.828	0.067	13.693	13.958
	Triennially	13.825	0.069	13.682	13.959
	No screen	13.815	0.067	13.681	13.942
Net Monetary Benefit (NMB) given on WTP=20,000 $ per LYG					
	Annually	280687	1186	278265	282919
	Biennially	280511	1136	278180	282724
	Triennially	280416	1219	278064	282667
	No screen	280113	1151	277798	282216
Net Monetary Benefit (NMB) given on WTP=20,000 $ per QALYG					
	Annually	275620	1458	272484	278366
	Biennially	275484	1425	272633	278279
	Triennially	275438	1467	272468	278215
	No screen	275272	1427	272375	277982

Note. Simulated 1,000 samples with sample size of 10,000

Abbreviation Note

BMI: body mass index

CD: clinical detectable

CD HY I/II: clinical detectable phase Hoehn-Yahr stage I/II

CD HY III+: clinical detectable phase Hoehn-Yahr stage III+

CEA: cost-effectiveness analysis

CE plane: cost-effectiveness plane

CP: clinical phase

FPD: free of Parkinson's disease

HRQoL: health related quality of life

H-Y: Hoehn-Yahr

ICER: incremental cost-effectiveness ratios

ICUR: incremental cost-utility ratios

KCIS: Keelung community-based integrated screening program

MCMC: Markov Chain Monte Carlo

NFC: net force coefficient

NMB: net monetary benefit

OCD: other causes of death

PCDP: preclinical screen detective disease

PD: Parkinson's disease

QALY: quality-adjusted life-year

SD: screening detectable

SD HY I/II: screening detectable phase Hoehn-Yahr stage I/II

SD HY III+: screening detectable phase Hoehn-Yahr stage III+

UPDRS: unified Parkinson's disease rating scale
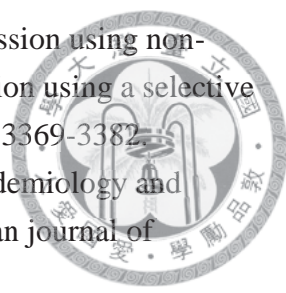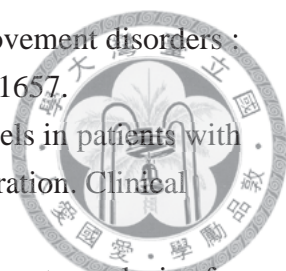
WTP: willingness-to-pay

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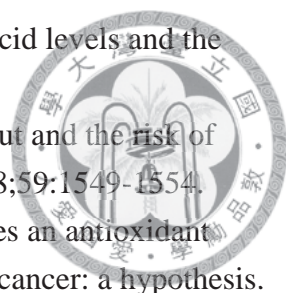
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