# 總計畫/Main Project

## 1. Abstract

The project addresses the shifting health burden from infectious diseases to non-communicable diseases (NCDs), particularly in Taiwan, where aging, lifestyle changes, and urbanization have led to a rise in multimorbidity, defined as the coexistence of multiple chronic conditions. This increasing prevalence of multimorbidity, particularly in older populations, poses significant challenges for healthcare systems, particularly in managing both physical and mental health conditions simultaneously. Socioeconomic disparities further exacerbate the burden, with lower-income groups disproportionately affected.

The current status of multimorbidity research reveals several gaps. Studies have not adequately assessed the population health impact of multimorbidity clusters or incorporated its complexities into healthcare cost models. Existing forecasting models often overlook multimorbidity's super-additive effects, leading to inaccurate estimations of health and economic burdens. Furthermore, the fragmented treatment of mental and physical health issues and limited region-specific data, particularly in Asia, hinder comprehensive policy and planning.

This multidisciplinary project aims to address these gaps through five objectives: (1) quantifying the population health impact of multimorbidity across disease clusters and geography, (2) evaluating healthcare costs of multimorbidity across different socioeconomic groups, (3) assessing the impact of multimorbidity on future long-term care needs and evaluating policy interventions to address multimorbidity, (4) investigating mental-physical multimorbidity and potential interventions, and (5) projecting future health system costs under the burden of multimorbidity in Taiwan.

The project will have a significant impact on health system planning and policy development in Taiwan, advancing academic research across epidemiology, health economics, and public policy. By providing a more accurate assessment of healthcare needs and costs, the findings will guide future healthcare and long-term care policies, particularly as Taiwan's population continues to age.

## 2. Background, Current Status, Outstanding Problems, Objectives, and Impact of the Project

### Background, current status and outstanding problems

The conjure of health burden is undergoing a rapid transformation, shifting from infectious diseases to non-communicable diseases (NCDs) over the past 30 years. This shift is particularly evident in Taiwan, where a rapid aging population, lifestyle changes, and urbanization have led to a significant rise in multimorbidity—defined as the coexistence of two or more long-term conditions. Common chronic conditions such as hypertension, diabetes, cardiovascular disease, chronic kidney disease, and stroke present considerable challenges not only for patients but also for families and the health and long-time care systems. A recent systematic review suggested that the prevalence of multimorbidity varied substantially across age, sex, and countries, with a global prevalence of nearly 40% [1]. The World Health Organization (WHO) published a monograph on multimorbidity, calling for a system-based and multidisciplinary approach to respond to the rising challenge of multimorbidity [2]. In Taiwan, the prevalence of multimorbidity varies widely, with rates ranging from 21.76% among those aged 40-49 to 75.39% to 92.01% in individuals aged 60 and older [3].

Despite the mounting data on the prevalence and time trend of multimorbidity, current studies have not assessed the population health impact of specific disease clusters or that of total multimorbidity. Prevalence alone cannot be used to evaluate the population health impact of diseases, as the severity of different diseases and disease clusters can vary widely. The Global Burden of Disease (GBD) project, funded by the Gates Foundation, developed a standardized approach to measure population

health impact of diseases and risk factors. The disability-adjusted life years (DALY) metric measured in the GBD study has been used widely by international institutions (including the WHO) as a major index when comparing the population health impact of different diseases. Nonetheless, current GBD studies typically focus on single diseases, which is problematic given that multimorbidity is increasingly the norm. To date, there is a lack of clear methods and empirical evaluations for considering multimorbidity into disease burden estimates [4].

Similarly, existing models for assessing healthcare costs and long-term care needs primarily focus on single diseases, ignoring critical coexisting conditions or multimorbidity. Recent evidence from countries such as the USA, UK, and New Zealand indicates that the effects of multimorbidity or comorbidity are not merely additive but often super-additive. This highlights significant concerns regarding equity and relevance in our current single-disease approach to health financing, especially as multimorbidity becomes increasingly prevalent. While several studies have attempted to quantify the healthcosts associated with multimorbidity, most focus on a limited range of diseases and fail to adequately consider the interaction effects among multiple conditions.

Better understanding of the impact of multimorbidity has crucial implication on the planning and delivery of long-term care. The prevalence of multimorbidity has shown to increase rapidly with age both in high-income and lower-and-middle income settings [5]. As populations age, multimorbidity is becoming a dominant challenge in long-term care settings, resulting in higher care needs, medication use (“polypharmacy”), and resource consumption. While the field is still developing, some healthcare systems and research initiatives are using forecasting models and population health data to guide care planning for individuals with multiple chronic conditions. One such example is the Scottish Multimorbidity Model. The data from this model is used to forecast future healthcare needs and resource allocation for long-term-care facilities. By identifying areas with higher burdens of multimorbidity, the government has been able to direct more resources to regions where long-term care services are most needed [6]. Much research is needed to explore how the population health data and forecasting results on multimorbidity to inform long-term care in Asian settings.

Among the various disease conditions considered under the multimorbidity framework, mental health disorders present a unique challenge and opportunity. Multimorbidity frequently involves a combination of physical illnesses (such as diabetes, heart disease, or arthritis) and mental health disorders (like depression and anxiety) [7]. Studies have shown that mental health conditions significantly exacerbate the management and outcomes of physical diseases, leading to increased healthcare utilization and poorer quality of life [5]. However, there is a critical knowledge gap in understanding how these conditions interact over time, especially in diverse socio-economic subpopulations. Most research still focuses on managing individual diseases, and there is limited evidence on integrated care models that address both mental and physical aspects of multimorbidity [8]. Moreover, existing healthcare systems often treat mental and physical health in silos, leading to fragmented care and suboptimal treatment outcomes. More research is needed to explore effective, holistic strategies that consider the psychological, social, and physical dimensions of multimorbidity.

A critical area of multimorbidity research is forecasting. Given the increasing life expectancy and population ageing globally, it is anticipated that the burden of multimorbidity will increase in most settings. A quantitative assessment of the future burden of multimorbidity will assist health policymaking and help the healthcare system to prepare for the prevention and management of multimorbidity. Nonetheless, the current status of forecasting the burden of multimorbidity is still evolving. While models have improved with the use of advanced machine learning, epidemiological data, and large health datasets, several gaps remain. First, multimorbidity often involves diverse chronic conditions, making it difficult to develop universally applicable forecasting models. Second,

there's limited access to long-term datasets that track multiple conditions across time. Third, existing models struggle to account for individual variations like lifestyle and socio-economic factors. More research is needed to improve data integration, model adaptability, and the inclusion of non-clinical factors (like social determinants).

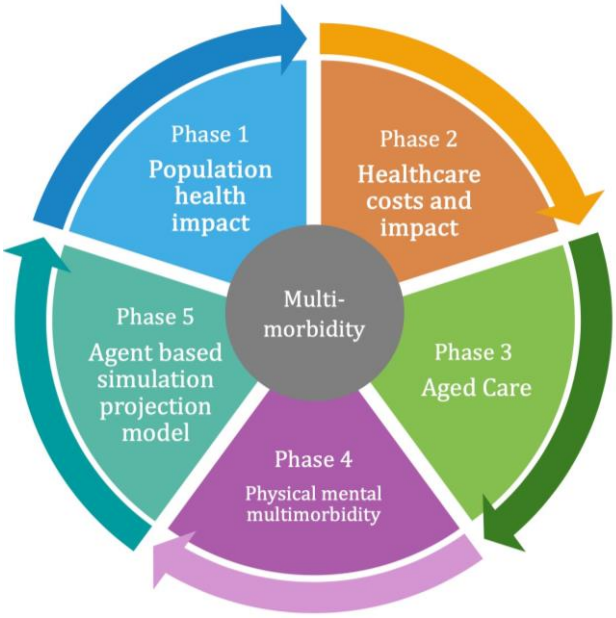
Last but not the least, the prevalence of multimorbidity is highly socioeconomic patterned with lower-income groups disproportionately affected, exacerbating existing health disparities. Local variations in health system factors further influence access to care and outcomes, highlighting the urgent need for a comprehensive understanding of these dynamics as Taiwan's population continues to age. Like other high-income countries with aging populations, Taiwan's healthcare costs are driven by NCDs, especially in individuals with multimorbidity. Addressing this issue requires a nuanced approach that considers socioeconomic factors and local variations.

In sum, there are several important knowledge gaps regarding multimorbidity in Taiwan and globally. Current assessment of the epidemiology of multimorbidity fails to capture its burden on population health impact. Similarly, healthcare cost models do not account for the interactions between multiple conditions, leading to inaccurate assessments of the real economic burden. Forecasting models, though improving, still struggle with the complexity and diversity of multimorbidity, particularly in resource-limited settings where long-term datasets and individualized variations are lacking. Mental health conditions, which often co-occur with physical illnesses, further complicate disease management, but healthcare systems typically treat them separately, resulting in fragmented care. Additionally, there is a significant lack of region-specific data in Asia including Taiwan, where research on how multimorbidity affects healthcare systems and long-term care planning remains limited. These gaps highlight the need for more comprehensive, integrated research to inform healthcare policy and planning.

**Objectives and impact of the project**

In light of the pressing need to comprehensively understand and evaluate the current and future burden and impact of multimorbidity on population health and health expenditure, and to translate the findings from the quantitative assessment to long-term care policymaking, we propose a multidisciplinary integrated project with the following research objectives:

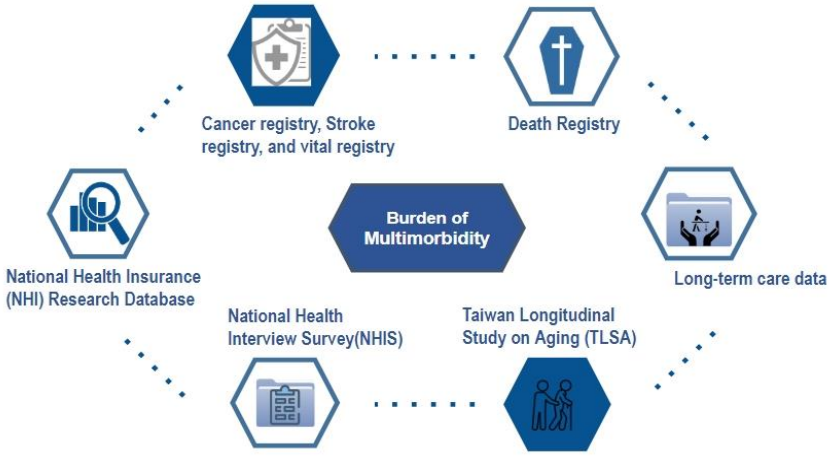
[Subproject 1] To quantify the population health impact of multimorbidity in Taiwan across disease clusters, geography (at the township level), and time, using the standardized approach in the GBD study.
[Subproject 2] To evaluate the healthcare costs of multimorbidity, particularly the combined effects of multiple chronic conditions, rather than focusing on single diseases, nationally and across different geographical and populations subgroups.
[Subproject 3] To assess the impact of multimorbidity on current and future long-term care needs, based on quantitative assessments from Subprojects 1-2, and evaluate policy interventions to address these needs.
[Subproject 4] To investigate the burden, impact, and associated factors of mental-physical multimorbidity and potential interventions.
[Subproject 5] To project the future population health and health system costs burden of multimorbidity in Taiwan, accounting for the effect of rapid population ageing and ongoing trend of major risk factors as well as diseases.




This project will have substantial impacts on both health system planning and policy development in Taiwan. By integrating multimorbidity into estimates of population health impact and understanding the socioeconomic disparities in health system utilization, the project will provide critical insights into Taiwan's future healthcare needs.

## 3. **Integrative Concept and Project Approach**

The proposed research leverages the high-quality health information system in Taiwan. The study builds on the success of our previous 核心研究計畫 through which Taiwan Burden of Disease Center (TBDC) was established in NTU. In brief, TBDC collected and collated detailed information on risk factors, disease occurrence, health expenditure, and vital status at the national and subnational level (Figure below). Data linkage at the individual level was also done in the secure data center of Ministry of Health and Welfare.




Using the high-quality health data we assembled, we will conduct the core research activities of estimating the population health impact of multimorbidity in Taiwan over the past 20 years,

including the population health impact of major disease clusters. In the same vein, we will use this data to evaluate the health system costs of multimorbidity, in particular examining the presence of any super-additive effect in disease clusters. Building on the analysis results on disease epidemiology, population health impact, and health system expenditure, we will construct an agent-based model that represents the population structure in Taiwan. The model will be calibrated to the distribution of social and individual determinants of health, disease incidence and progression, and vital experiences in Taiwan. The agent-based model will then be used to forecast the future burden of multimorbidity on population health and health expenditure. See Figure below for the interplay of different aims in the proposed research

Building on research outputs from the core research activities above, we will further explore the policy implication of quantifying the burden of multimorbidity on long-term care needs for now and in the near future. In particular, we will assess the incremental impact of multimorbidity in combination with frailty on the prevalence of dementia and the growing demand for long-term care services over time. We will also address the complex interplay between mental and physical health issues using the results generated from the core activities.

4. **Description of the Teamwork:**

Subproject 1, focusing on quantifying the population health burden of multimorbidity and assessing geographic distribution of small areas in Taiwan, will be conducted by Professor Hsien-Ho Lin. Dr. Lin is a Distinguish Professor and Director of Institute of Epidemiology and Preventive Medicine and is an expert in burden of disease research. He established Taiwan Burden of Disease Center, which will be a major source of data for this integrated project.

Subproject 2, The costing analysis subproject will be led by Associate Professor John Tayu Lee, a world-renowned health economist recognized for his work on NCDs and multimorbidity. Currently a Mount Jade Young Scholar at NTU, Dr. Lee will carry out a comprehensive analysis of healthcare costs related to comorbidities and multimorbidity

Subproject 3, evaluating long-term care needs and utilization, will be led by Professor Ya-Mei Chen, a prominent researcher on long-term care planning and service delivery in Taiwan.

Subproject 4, quantifying the impact and burden of comorbidities of mental and physical disorders and the long-term prognosis of mental-physical multimorbidity, will be led by Professor Shu-Sen Chang, Professor and Director of Institute of Health Behavior and Community Sciences. Prof. Chang is a psychiatrist with long-term experiences of investigating the interplay between mental and physical health.

Subproject 5, forecasting the future burden of multimorbidity through agent-based modeling, will be led by Associate Professor Tsung-Ren Huang from Department of Psychology at National Taiwan University and Stanford University. Prof Huang is a leading expert in AI and computational modeling for behavioral sciences. Because of his interdisciplinary research, Prof. Huang is also affiliated with seven other teaching/research units at NTU, primarily related to mathematics, statistics, and artificial intelligence.

It is evident from Section 3 that this project is truly integrative. The Subprojects 1 & 2 will generate the population health and health system burden estimations across age, sex, geographies, socioeconomic groups, and time. The resulting informaiton will then be used by Subprojects 3, 4, and 5 for long-term care planning, understanding the interaction of physical and mental illnesses, and forecasting. The team members will therefore work closely from the very beginning to ensure seamless integration of the subprojects. Several investigators of this project have been working in previous integrated projects, including our previous 核心研究計畫. We anticipate that communication and collaboration across team members will be very smooth.

## 5. Long-Term Goals, Originality and Innovation, and the Impact on the Community of the Project

This project will have substantial impacts on both health system planning and policy development in Taiwan. By integrating multimorbidity into standardized burden of disease estimates and understanding the socioeconomic disparities in health system utilization, the project will provide critical insights into Taiwan's future healthcare needs. Additionally, it will allow for a more accurate estimation of health system costs, enabling more efficient resource allocation. The findings on long-term care needs will also inform policies on long-term care, which is increasingly critical as Taiwan's population ages.

The multidisciplinary study will have significant academic value, with a novel concept that advances current approaches to assessing the burden of multimorbidity and comorbidity. The investigators of the team are highly accomplished with outstanding publication records, well-prepared to tackle the complex challenges posed by this research. The study will contribute to multiple disciplines such as epidemiology, social welfare, health economics, and public policy.

## 6. References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## 7. Keywords in Chinese and English (list five keywords)

多重慢性疾病, 疾病負擔, 醫療系統成本, 預測, 長照

Multimorbidity, disease burden, health system costs, forecasting, long-term care

# 國立臺灣大學核心研究群研究計畫申請書

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| 子計畫一<br>Subproject 1 | 子計畫名稱 | 量化台灣多重慢性疾病的群體健康影響 | 主持人<br>Co-PI | 林先和<br>Hsien-Ho Lin |
| | Title of Project | Quantifying population health impact of multimorbidity in Taiwan | | |

**1. Specific Objectives of this Subproject**

As mentioned in the main project, most of existing studies on multimorbidity reported on the prevalence of multimorbidity without explicitly assessing their potential impact on population health. There is also a lack of clear methods and empirical evaluations for considering multimorbidity into disease burden estimates, including the Global Burden of Disease (GBD) study. The overall goal of Subproject 1 is to quantify the population health burden of multimorbidity using a standardized approach. In order to achieve this goal, we propose three interrelated objectives for this study.

Objective 1: To estimate the trend and patterns in multimorbidity over time
Objective 2: To estimate the population health burden (measured by years lived with disability, YLD) of multimorbidity
Objective 3: To estimate the joint of multimorbidity on health

**2. Contribution of this Subproject to the Synergic Integration**

This subproject will be one of the building blocks of the main project. The estimated population health burden of multimorbidity will be joined by the burden on health system expenditure from Subproject 2 to delineate the big picture of the burden of multimorbidity on different dimensions, which can be used further for the planning of long-term care in Taiwan (Subproject 3). The trend and patterns of multimorbidity obtained from this subproject will be used to inform and parameterize the agent-based model in Subproject 5.

**3. Methods and Approach**

**Past achievement of the co-PI**

The co-PI (as well as the PI for the main project) has pioneered the work of burden of disease estimation over the past 14 years. With colleagues from NTU College of Public Health and supported by the NTU Core Consortium Project (核心研究計畫), they established Taiwan Burden of Disease Center to estimate the impact of fatal and nonfatal diseases on population health and health expenditures (see supplement for the final project report from our previous Core Consortium Project). The results from the previous project have been published and used by health administration units in Taiwan, including the Health Promotion Administration, Health Insurance Administration, and local health authorities in Kaohsiung and Hsinchu. The data pipeline and results from the previous study laid a solid foundation for the proposed research activities in this subproject as well as the main project.

**Selection of diseases for multimorbidity**

We will use the following criteria to determine which diseases will be eligible for selection into the multimorbidity assessment. First, we will identify the top 40 diseases (List A) causing the largest burden of years lived with disability (YLD) based on the results from Taiwan Burden of Disease Center (see below for past achievement). The list of disease corresponds to the diseases that contributed most to nonfatal population health loss in Taiwan from a single disease perspective. Second, we will identify the top 40 diseases (List B) with the highest health system

expenditure in the National Health Insurance, also based on the results from Taiwan Burden of Disease Center. The final list of diseases under consideration will be the union of List A and List B. The same list of diseases will be used for Subproject 2 (Health system cost analysis).

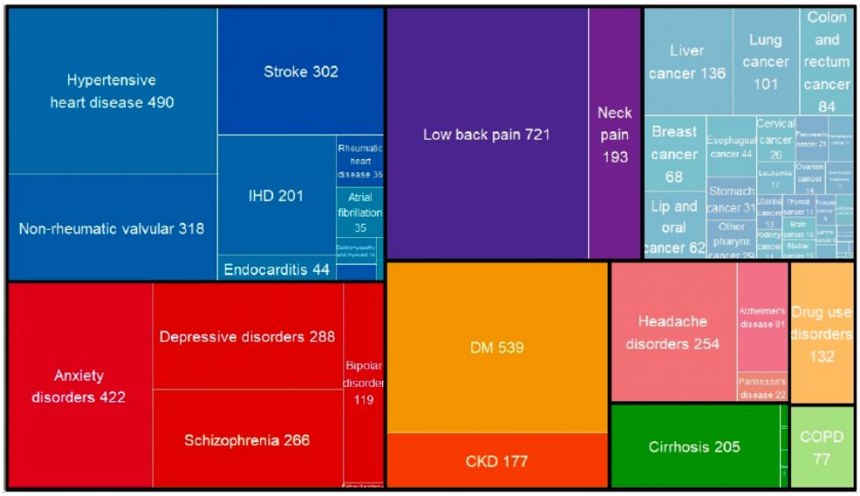


**Figure.** Tree map of the magnitude of population health impact (measured by years lived with disability, YLD per 100,000) by single diseases. Results based on the previous work by Taiwan Burden of Disease Center.

**Objective 1. Trend and patterns of multimorbidity**

We will include all adult population in Taiwan and will analyze the national health insurance database, cancer registry, stroke registry, and vital registry to estimate the incidence, prevalence, and mortality of single diseases (see above for the disease list) using a longitudinal follow-up design. While the prevalence indicator is the main outcome measure in this subproject, the incidence and mortality indicators will be used to inform the agent-based model. For prevalence estimation of most noncommunicable diseases (e.g., stroke, heart diseases, diabetes), we will assume that the disease will be life-long. For prevalence of diseases that are recurrent in nature (e.g., depression, bipolar diseases), we will account for the episodic nature of the disease following the approach by GBD [1]. In brief, an assumed duration of disease will be applied based on the natural history of each disease. For cancers, we will also account for the natural history by incorporating the duration of different stages (diagnosis and treatment, remission, cure, metastatic and terminal) of each cancer, following the GBD standard [2].

Once the disease status (for all target diseases) of each individual is ascertained, we will estimate the prevalence of comorbidity in the following ways. First, we will estimate the proportion of population with 2, 3, 4, or more diseases in the total population as well as by age, sex, geography (township), and socioeconomic status (based on insurance levels). We will look at the temporal trend of multimorbidity in the crude and age-standardized analysis. Second, we will estimate the two-disease joint distribution of all combinations of the target diseases. This analysis will reveal the disease pairs with higher prevalence in the total population and in subgroups. Importantly, we will also examine the pairwise association for all disease combinations, using odds ratios (OR) as the measurement of association. The pairwise association can be either positive (OR>1), neutral (OR=1), or negative (OR<1). Positive associations of diseases indicate potentially higher burden from multimorbidity and should be the focus of future research.

**Objective 2. Population health burden of multimorbidity**

We will estimate the non-fatal burden of multimorbidity using the years lived with disability (YLD) index, following the GBD study approach [3]. The key advantage of using the YLD metric

is the comparability with other single diseases as well as with previous studies (such as those conducted by the GBD team). The YLD estimation requires information on the prevalence of disease clusters and the associated health impact measured by disability weight. The disability weighting system is the measure developed by the GBD to determine the level of health loss form non-fatal outcomes, based on valuation and preferences from the general population [4]. Based on the results from the Objective 1, we will select the leading 100 disease pairs with the highest joint prevalence. The disability weights of single diseases have been evaluated by our Taiwan Burden of Disease Center. In brief, the disability weight tables from the GBD were used to determine the health loss of each distinct health state [3], and the severity distribution within each disease was further informed by local data (e.g., prescription patterns for COPD, and modified ranking scale [mRS] from the stroke registry for stroke, EQ-5D-5L for low back pain). Using the disability weights of single diseases, we will determine the disability weight of specific disease pair under three alternative assumptions [5]:
A. Additive assumption: $DW_{i,j} = DW_i + DW_j$ (but no more than 1)
B. Multiplicative assumption: $DW_{i,j} = 1- (1-DW_i)*(1- DW_j)$
C. Maximum limit assumption: $DW_{i,j} = \max (DW_i , DW_j)$

While the GBD has been using the multiplicative assumption when doing the co-morbidity adjustment, there is no empirical evidence behind this assumption. We will present the YLD results of disease pair ranking under three alternative assumptions, and observe whether different assumptions will lead to different ranking results. It should be noted that estimating the mortality burden (usually using the metric “years of life lost”, or YLL) is not feasible under the GBD framework, as the current YLL estimation is based one single underlying cause of death in the vital registry system. Further development in the cause of death methodology will be needed to quantify the mortality burden of multimorbidity.

**Objective 3. Joint impact of multimorbidity on health**

As described in the previous objective, empirical evidence on the joint impact of multimorbidity on health in terms of general health and activities has been very limited. In the third objective, we will explore the joint impact of disease pairs on health using the data from Taiwan. We will use the matched data of National Health Interview Survey (NHIS) and National Health Insurance (NHI). Through cross-matching, the disease status of participants of NHIS will be ascertained from the NHI. The participants of the NHIS did not provide direct information on disability weight, but they did provide information on functional health outcomes including GALI (Global Activity Limitation Indicator) and EQ-5D-5L. So the third objective will focus on these functional health indicators instead of YLD.

We will use multivariable regression models and generalized linear models (GLMs) to estimate the effect of individual diseases and their combinations on health outcomes (either categorically or as a binary variable), where the main effects are to estimate the impact of each disease on its own, and the interaction effects are to capture whether the combined impact is greater (superadditive) or less (subadditive) than the sum of individual disease impacts. The interaction terms in these models assess whether the combined effect of diseases is **subadditive** (less than the sum of the individual effects, suggesting that having multiple diseases does not fully compound the health burden) or **superadditive** (greater than the sum, indicating that multimorbidity amplifies health limitations more than expected). By comparing the outcomes from both GALI and EQ-5D-5L, the approach provides a comprehensive view of how multimorbidity impacts both general functional limitations and specific health dimensions. This allows for a better understanding of whether certain disease combinations lead to

disproportionately worse health outcomes than single diseases, influencing healthcare planning and resource allocation.

## 4. Originality and Innovation of the Proposal and the Impact on the Community

The proposed study is significant for its comprehensive approach to understanding the **population health burden of multimorbidity**, an area often overlooked in existing studies. By analyzing national health insurance claims data and using functional health outcomes such as **GALI** and **EQ-5D-5L**, the research will provide novel insights into the **joint effects of multimorbidity clusters** on health. This originality is reflected in the study's comparison of subadditive and superadditive effects of disease combinations, advancing knowledge in multimorbidity research. The **innovative methodological approach,** using regression models to capture interaction effects between diseases, offers a nuanced understanding of how **multimorbidity amplifies health limitations**. These findings will have a direct impact on **healthcare planning, resource allocation**, and the development of targeted interventions for populations with complex health needs, significantly benefiting the broader community by addressing the growing burden of chronic conditions.

## 5. Research Budget (Please list the sum)： Funds include personnel expenses, consumable & miscellaneous expenses, travel expenses, and equipment expenses.

| Project Year<br><br>Budget Categories (NT$) | First year from 01/25 to 12/25 (MM/YY) | Second year from 01/26 to 12/26 (MM/YY) | Third year from 01/27 to 12/27 (MM/YY) | Total for the entire term of the Consortium Project |
|---|---|---|---|---|
| personnel expenses | 880,000 | 900,000 | 920,000 | 2,700,000 |
| consumable & miscellaneous expenses (including data) | 220,000 | 150,000 | 160,000 | 530,000 |
| travel expenses | 0 | 120,000 | 120,000 | 240,000 |
| equipment expenses | 100,000 | 30,000 | 0 | 130,000 |
| Subtotal(s) for Each Year | 1,200,000 | 1,200,000 | 1,200,000 | 3,600,000 |

## 6. References


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# 國立臺灣大學核心研究群研究計畫申請書

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| 子計畫 Subproject | 子計畫名稱 | **共病與多重慢性疾病的成本分析：特徵，權重與指數** | 主持人 Co-PI | 李達宇 副教授 John Tayu Lee Associate Prof. |
| | Title of Project | **Costing for Comorbidity and Multimorbidity: Patterns, Weights, and Index** | | |

## SPECIFIC OBJECTIVES OF THE SUBPROJECT

Research Gaps and Novelty

Accurate estimates of the costs associated with NCDs and comorbidities are critical components for healthcare financing and planning. The costs of health conditions are not only integral to payment models, such as Diagnosis-Related Groups (DRG) and bundled payments, but also essential for economic evaluation of health interventions and cost-effectiveness analyses. Despite the fact that most patients with chronic diseases present with more than one condition, existing observational studies on costs of NCDs in Taiwan predominantly focus on individual diseases, neglecting the increasing prevalence of comorbidity[1] [2]. There is a dearth of evidence on the costs of multimorbidity, which hinders adjustments to payment models for comorbid conditions[3]. Moreover, patients with comorbidities are frequently excluded from clinical trials, limiting the applicability of findings to broader patient populations.

Another limitation of the literature is the over-reliance on cross-sectional data and the use of simple counts of NCDs, without applying weights that reflect the relative importance of each condition and patient heterogeneity in healthcare costs. Established multimorbidity indices, such as the Charlson Comorbidity Index (CCI)[4] and the Health Resource Use Index for Medicare and Medicaid in the US[5], are widely used. However, their weights are based on health systems that differ significantly from Taiwan, making them unsuitable for local health payment models. While countries like India and the UK are developing their own multimorbidity indices, Taiwan has yet to initiate similar efforts.

Furthermore, existing studies have not adequately examined how healthcare utilization for a single disease changes when considering the influence of comorbid conditions, including potential additional or reduced spending related to other chronic illnesses. Recent analyses in the USA[6] and New Zealand[7] revealed the 'super additive effects' of comorbid conditions, highlighting the needs for considering comorbid conditions in estimating healthcare costs.

Another major limitation of cross-sectional studies is their inadequate representation of the temporal dynamics of healthcare utilization and costs over an individual's lifespan. As a result, there is a significant gap in evidence on how healthcare expenditures evolve as patients progress from having no noncommunicable diseases (NCDs) to developing NCDs and multimorbidity across different life stages.

Specific Objectives

The proposed study will be the most comprehensive costing analysis of comorbidity and multimorbidity, both in Taiwan and internationally. Leveraging a longitudinal national health insurance administrative claims dataset of 2 million individuals, this study aims to: (1) establish a comprehensive catalogue of costs associated with NCDs and comorbid conditions; (2) develop a multimorbidity weights index for health service costs; (3) investigate the relative importance of NCDs on healthcare costs; and (4) examine how healthcare costs vary by health states over time for patients with multimorbidity. The specific objectives, study phases, and key outputs are as follows:

| Phase | Objectives | Key Activities/ Outputs |
|---|---|---|
| Phase 1: Detailed Costs Analysis for Single NCDs and Comorbidities | (1) Quantify costs attributable to individual NCDs | Activities: Analyzing expenditures associated with specific NCDs such as cardiovascular disease, cancer, and diabetes<br>Outputs: Comprehensive cost catalogue for specific NCDs |
| | (2) Examine costs by number of NCDs | Activities: Investigate how costs vary across different counts of NCDs (0,1,2,3,4, etc.)<br>Outputs: Report detailing cost variations by NCD count, and build predictive model based on number and types of NCDs |
| Phase 2: Cluster Analysis | (3) Assess spending by key NCD clusters | Activities: Identify and evaluate expenditure associated with clusters of related NCDs<br>Outputs: Analysis report on expenditures associated with NCD clusters |
| | (4) Evaluate spending on single NCDs and their comorbid conditions | Activities: Compare costs for individuals with a single NCD versus those with comorbidities<br>Outputs: Incremental cost analysis for single vs comorbid conditions |
| Phase 3: Multimorbidity Index | (5) Generate a multimorbidity index for healthcare costs | Activities: Develop a formula for assigning weights to various NCDs based on their impact on healthcare costs<br>Outputs: Multimorbidity weights index |
| | (6) Estimate the relative importance of NCDs on costs | Activities: Assess how different NCDs contribute to overall healthcare expenditures<br>Outputs: Analysis of relative contributions of NCDs to patients' annual healthcare expenditures |
| | (7) Estimate temporal cost analysis | Activities: Track changes in healthcare costs over time as individuals transition between different health states and develop additional NCDs<br>Outputs: Longitudinal analysis report tracking cost changes over time |
| Subgroup Analysis: Demographic and Geographic Analysis | Investigate demographic differences | - Analysis of how demographic factors (age, gender, socioeconomic status) influence healthcare costs. |
| | Assess geographic variation | -Analysis of regional variations (geographic remoteness, metro, non-metro status, health system readiness and availability factors) in healthcare costs |

## CONTRIBUTION OF THIS SUBPROJECT TO THE SYNEGIC INTEGRATION

This subproject focuses on economic analysis, focusing on costs associated with comorbidity and multimorbidity. The parameters estimated from this study can be used as inputs to complement the epidemiological data informing the overall forecasting model. The analysis of NCD clusters will yield detailed cost information across various physical-mental health

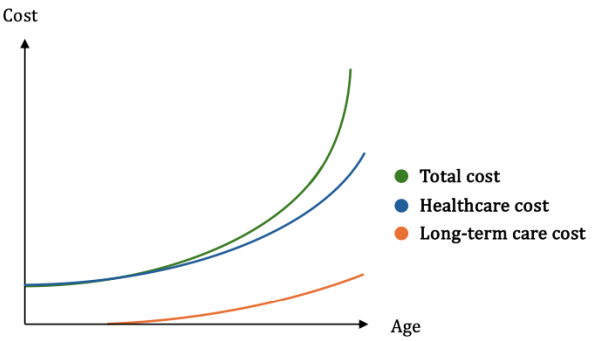


**Figure 1. Health and aged care cost across lifetime**

combinations and socioeconomic groups. These healthcare cost estimates will be further integrated with aged care costs to provide estimate for the total health and aged care service costs (please see Figure 1).

## METHODS AND APPROACH

Data and Sample: We will conduct a retrospective observational cohort study of adult patients with NCDs using National Health Insurance (NHI) administrative claims data from January 1, 2010, to December 31, 2020. This extensive database includes over 2 million NHI members and offers a nationally representative sample of the Taiwanese population, includes comprehensive information on patient enrollment, inpatient and outpatient medical claims, and pharmacy claims. Patient records will be linked using a unique identifier, with additional integration of mortality and cancer registries. All data handling will comply with National Health and Welfare requirements and receive approval from the NTU Institutional Review Board (IRB).

NCD Measures and Outcomes: Patients aged 18 years or older with NCDs will be identified through a combination of medical history (e.g. ICD-9-CM and ICD-10-CM), medication records, and inpatient and outpatient care data. To avoid statistical noise and resulting spurious findings in the models, we excluded disease with prevalence of <2%. Outcomes of interest will be derived from claims files associated with ambulatory, inpatient care and emergency department utilization and expenditures, along with prescription record, calculated annually per person-year over the 10-year study period. Covariates include socio-demographic (age, gender, region, socioeconomic status, including insurance levels based on salary, low-income status, and median household income based on the individual's area of residence).

Statistical Analysis: The statistical analysis will utilize a comprehensive panel data approach to exploit the longitudinal features of the national claim datasets. Key demographic variables, NCDs, healthcare utilization, and cost data will be summarized through frequencies, percentages, and cross-tabulations. Advanced clustering techniques, specifically fuzzy cluster analysis, will identify significant clusters of related NCDs based on age, gender, and socioeconomic factors, enhancing the understanding of their interactions. Cost outcomes associated with different health states will be examined using generalized linear mixed models (GLMMs).[8] This method accommodates the distributional characteristics of cost data, enabling the modeling of fixed effects, such as demographic factors, alongside random effects that account for patient-specific variations. By adjusting for potential confounders, GLMMs will yield robust estimates of the impact of multimorbidity on healthcare costs. To address the complexity arising from numerous NCD condition combinations, penalized linear regression with a lasso penalty will be employed to mitigate overfitting. This approach shrinks the coefficients of less significant covariates, enhancing the model's predictive power while preserving interpretability. The synergistic effects of NCD clusters will be assessed through the analysis of dyads, triads, and tetrads of common NCDs, evaluating their jointed effects and interactions between conditions using both additive and multiplicative scales. The relative importance of individual NCDs in contributing to overall healthcare expenditures will be calculated using the Shapley value decomposition method[9] providing insights into their respective contributions. Finally, to estimate the total lifetime costs associated with multimorbidity, we will develop a resource utilization cost model. This model will aggregate costs incurred during the initial year of care and project future expenses based on observed trajectories of multimorbidity and patterns of healthcare utilization. We will also compare lifetime spending across different multimorbidity trajectories and socioeconomic groups.

## ORIGINALITY AND INNOVATION OF THE PROPOSAL AND THE IMPACT

This project is uniquely positioned to provide the most comprehensive analysis of multimorbidity costs in the global literature. While weighted multimorbidity adjusted cost indices have been implemented in only a few countries, this study will be the first of its kind in Taiwan and the region, potentially setting a new standard in cost-of-illness research for chronic diseases. By utilizing a large panel data analysis, we aim to yield robust evidence that surpasses previous studies.

The costing analysis subproject will be led by A/P John Tayu Lee, a world-renowned expert in the economic burden of NCDs. Dr. Lee has made significant contributions to health economics, with over 4,100 citations, an h-index of 34, and an i10-index of 56—remarkable accomplishments at this stage of his career. He has published 15 papers in high-impact journals, such as *Preventing Chronic Disease* and *Lancet Global Health*, specifically addressing the costs associated with comorbidity and multimorbidity in various countries.

The output of this subproject is vital for the overall success of our initiative. It will help bridge the evidence gap in Taiwan regarding the costs of comorbidity and multimorbidity, supporting future NCD research and informed decision-making in Taiwan and the region over the next decade.

## BUDGET

| Items/Project Year | First Year | Second Year | Third Year | Total/Subtotal for Each Item Budget |
|---|---|---|---|---|
| Personnel<br>人事費 | 碩博士級研究助理/研究員（全職或兼職數位）<br>670,000 | 碩博士級研究助理/研究員（全職或兼職數位）<br>950,000 | 碩博士級研究助理/研究員（全職或兼職數位）<br>880,000 | 2,500,000 |
| 使用衛福部資料科學中心 | 160,000 | 220,000 | 180,000 | 560,000 |
| Data 健保資料庫 | 350,000 | 0 | 0 | 350,000 |
| Consumable & miscellaneous expenses | 20,000 | 30,000 | 20,000 | 70,000 |
| International Conference | 0 | 0 | 120,000<br>(International Health Economics Conference) | 120,000 |
| Subtotal for Each Year | 1,200,000 | 1,200,000 | 1,200,000 | **3,600,000** |

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# 國立臺灣大學核心研究群研究計畫申請書

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|---|---|---|---|---|
| 子計畫三<br>Subproject 3 | 子計畫名稱 | 多重慢性疾病與衰弱對失智症及長期照護需求的影響評估：以C據點社區介入為基礎的政策評估 | 主持人<br>Co-PI | 陳雅美<br>Ya-Mei Chen |
| | Title of Project | Assessing the Impact of Multimorbidity and Frailty on Dementia and Long-Term Care Demands: Evaluating a Population-Based Community Care Policy Intervention. | | |

**Research Background and Gaps**

Taiwan, one of the world's fastest-aging nations, faces increasing long-term care (LTC) demands. In 2023, adults aged 65+ made up 18.4% of the population, projected to reach 42% by 2060 (行政院主計總處, 2021). Aging has led to higher disability and dementia rates. A survey found 15% of Taiwanese seniors had functional disabilities, expected to double within a decade (Lee & Ory, 2013). In addition, the Ministry of Health and Welfare reported dementia prevalence at 7.99%, with women disproportionately affected (9.36% vs. 6.35% for men). Both disability and dementia rates are the major causes for health care and long-term care needs (Rudnicka et al., 2020). Projections suggest that by 2035, LTC services will be needed for 1 million people, rising to 2 million by 2060, with 92.3% aged 65+ (Executive Yuan, 2013). There is a growing consensus worldwide that LTC services and support are essential to assist this population in achieving healthy aging (World Health Organization, 2019).

To cope with this demographic change, the World Health Organization (WHO) defined healthy ageing as "the process of developing and maintaining functional ability that enables well-being in older adults" (World Health Organization, 2015), emphasizing chronic illness control and the development of policies and care systems to achieve this goal. In response, Taiwan implemented the National 10-Year Long-Term Care Plan (TLTCP) 2.0 in 2017, prioritizing aging in place and community care. A key objective is to establish a community-based care model through the Tier ABC home- and community-based integrated care service system (吳淑瓊、莊坤洋, 2001; 衛生福利部, 2016). Among this network, 3,169 Tier C care stations (C據點) was also established to support frail older adults aiming to strengthen primary prevention, promote health, delay disability, and enhance the well-being and quality of life of older adults (吳淑瓊、莊坤洋, 2001; 衛生福利部, 2016).」 However, the effects of Teir care stations on frail older adults' effects may require further studies.

As the population ages, multimorbidity has become increasingly prevalent, contributing significantly to both physical and cognitive decline. Studies show that the accumulation of chronic conditions accelerates this decline (Aubert et al., 2022; Du et al., 2024; Lee et al., 2024), and certain clusters of conditions—such as hypertension, diabetes, and coronary heart disease—pose an even greater risk for dementia (Calvin et al., 2022). Frailty and depression, when combined with multimorbidity, further exacerbate functional and cognitive deterioration, reducing individuals' ability to perform daily tasks independently (Du et al., 2024; Jędrzejczyk et al., 2022).

Research and clinical practice are increasingly focused on targeting not only multimorbidity but also the combination of multimorbidity and frailty (Dent et al., 2019; Lee et al., 2022; Vetrano et al., 2019). Notably 72% of frail individuals have multimorbidity, but only 16% of individuals with multimorbidity are frail (Vetrano et al., 2019). The coexistence of these conditions is linked to increased mortality risks, but their combined impact on disability and dementia, particularly over time, requires further study. Additionally, lack of family support and poor mental health may worsen these conditions (Skou et al., 2022; Vetrano et al., 2019). In recent years, multidimensional frailty—encompassing physical, psychological, and social aspects—

has been a focus of integrated care for older adults (Gobbens et al., 2013), yet the extent to which these factors influence the burden of disability and dementia remains unclear and needs more exploration (Skou et al., 2022). Moreover, the current evidence supporting interventions, especially at population level interventions, for multimorbidity is insufficient, necessitating further research (Skou et al., 2022). Overall, these findings underscore the importance of longitudinal and integrated care approaches that address multimorbidity and multidimensional frailty across physical, psychological, and social domains.

**Specific Objectives of this Subproject**

The current sub-project proposes two objectives:

Objective 1: To assess the incremental impact of multimorbidity, particularly in combination with frailty, on the prevalence of dementia and the growing demand for long-term care services over time.

Objective 2: To evaluate whether the use of Tier C agency services is associated with a smaller increase in the risk of dementia and disability, particularly in individuals with multimorbidity and frailty.

The novelty of this subproject lies in its examination of the combined impact of multimorbidity and frailty on dementia and disability demand among Taiwan's aging population. Furthermore, it uniquely evaluates the effectiveness of a population-based policy intervention—Tier C care stations, community-based services aimed at reducing these risks. By employing machine learning (decision trees) and simulation models (PACSim), the study offers personalized insights and addresses a critical gap in understanding how multimorbidity and frailty contribute to dementia and long-term care demands, providing evidence to inform both policy and practice.

**Contribution of this Subproject to the Synergic Integration**

This subproject enhances the main study in three synergistic ways. First, by examining the combined impact of multimorbidity and frailty on dementia and disability, it deepens the understanding of how these multimorbidity's accelerate physical and cognitive decline, aligning with the main project's goal of assessing multimorbidity's health burden and cost. Second, it is the first to evaluate the role of Tier C agency services as a population-based policy intervention to reduce the impact of multimorbidity in frail older individuals, contributing to Taiwan's evidence base on community care models. Lastly, by addressing the interaction of physical, psychological, and social frailty, this subproject not only aligns with the main project but also offers new insights into integrated care approaches that improve health outcomes, furthering the main study's focus on the broader impact of multimorbidity. Additionally, the modeling approach will be conducted in collaboration with **Subproject 5**.

## METHODS AND APPROACH

**Study Design and Data Source**

This subproject will utilize a retrospective cohort design, supplemented by a survey study.

Objective 1—Secondary Data Analysis

Data Source and Sample: We will utilize Taiwan's National Health Insurance Program (NHIP) claims dataset, the Taiwan Longitudinal Study on Aging (TLSA), long-term care data, and the Teir C service utilization platform. The NHIP, a single-payer program launched in March 1995 in Taiwan, enrolls approximately 99% of Taiwan's 23 million population. When individuals fall ill, data on their use of health services is recorded within the NHIP. The Taiwan Longitudinal Study on Aging (TLSA) was initiated in 1989 by the Taiwan Provincial Institute of Family Planning in collaboration with the University of Michigan, supported by Taiwan's government and the U.S. National Institute on Aging. It focuses on individuals aged 50 and

older, having completed 9 waves of data collection, with the most recent wave collected in 2019. TLSA includes 4 generational cohorts and maintains a nearly 90% completion rate (please Figure 1) (國民健康署, 1989-2015; 衛生福利部統計處, n.d.). For this subproject, we will include only the third and fourth generational cohorts, covering the period from 2003-2019, as NHIP data has been available only since 1995.

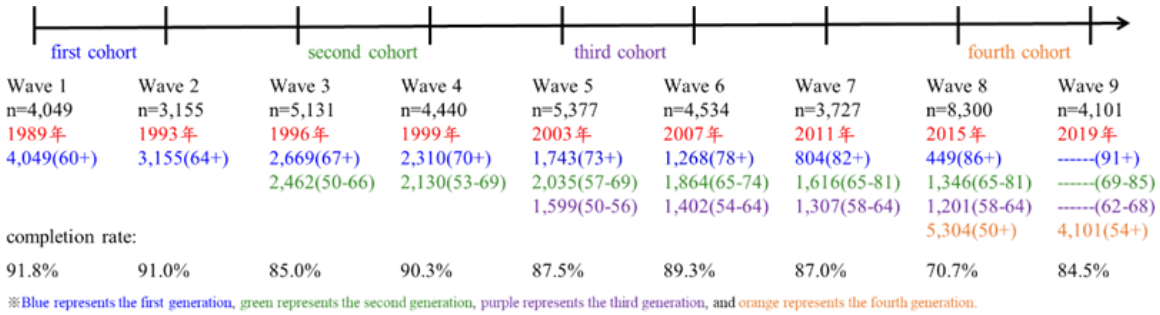


**Figure 1.** TLSA Time Chart.

Objective 2—Second Data Analysis and Community-based Survey:
Data Source and Sample: We will collaborate with local governments and utilize their Tier C care station service utilization platform, an online system that collects detailed information on assessments and service usage, including free exercise programs and congregate meals (國民健康署, 1989-2015; 衛生福利部統計處, n.d.). In addition to secondary data analysis, for those who have stopped using services, we will conduct a community-based survey to gather further insights. Starting in the second year, we will collaborate with local governments to survey the disability and dementia status of 800 individuals who had used Tier C care stations for more than 20 weeks in any year between 2017 and 2024 but subsequently discontinued services. This approach will provide comprehensive data on how Tier C care stations influence the effects of multimorbidity and frailty on disability and dementia outcomes.

**Measurements and Analysis Plan**
Analytic Approach: Multimorbidity, defined using the same criteria as in the main study, will be extracted from the NHIP dataset. Data on disability, dementia, and frailty will be obtained from the TLSA dataset. **Based on the quantitative assessments from Subprojects 1 and 2, for Objective 1**, the impact of multimorbidity on the risk of disability and dementia, as well as the interaction between frailty and these factors, will be analyzed using survival analysis and logistic regression models. Additionally, the interaction between multimorbidity and frailty on disability and dementia risk will be examined. For **Objective 2**, all key variables, including multimorbidity, frailty, disability, and dementia, will be sourced from either the Tier C care station service utilization platform or a community-based survey. For Objective 2, a similar simulation will be conducted among Tier C station users. Comparing the findings from Objectives 1 and 2 will assess whether Tier C policy interventions—such as free exercise programs and congregate meals—reduce the impact of multimorbidity on the risk of disability and dementia. These findings will provide both practical and scientific evidence to inform policy and practice regarding the prevention and management of multimorbidity among frail older adults.
Modeling Approach: The Population Ageing and Care Simulation (PACSim) model, developed by a British research team (Kingston et al., 2018), will be applied to simulate the interactions of these factors. This modeling approach will enhance our projections by providing more refined estimates of current and future long-term care needs and demands for individuals with multimorbidity, based on quantitative assessments. **This modeling approach will be**

**conducted in collaboration with Subproject 5**.

Decision Tree Approach: Next, decision trees will be used to assess the influence of multimorbidity, frailty, and individual characteristics—such as health behaviors—on the development of disability and dementia among Taiwan's older population, as well as those who have used Tier C care station services. We will apply the widely utilized Decision Tree Learning algorithm from machine learning (Witten et al., 2011) to uncover essential patterns for classification. This approach allows for a more personalized experience, as it tailors predictions based on individual characteristics and unique combinations of factors, offering greater relevance for each person's specific health profile. While decision trees offer clear visual insights into the decision-making process, they may not capture all nuances for every individual case. To improve predictive accuracy, we will also employ random decision forests (Podgorelec et al., 2002). Both decision trees and decision forests have been applied in health care research, including diagnosis, treatment, and public health studies (Wolfenden et al., 2020). Our research team has previously applied decision trees to identify the combinations of LTC services that led to fewer unmet care needs among older adults using TLTCP 2.0 services.

## 5. Research Budget (Please list the sum)： Funds include personnel expenses, consumable & miscellaneous expenses, travel expenses, and equipment expenses.

| Project Year<br>Budget Categories (NT$) | First year from 01/25 to 12/25 (MM/YY) | Second year from 01/26 to 12/26 (MM/YY) | Third year from 01/27 to 12/27 (MM/YY) | Total for the entire term of the Consortium Project |
|---|---|---|---|---|
| Personnel expenses | Master's Level Research Assistant *1: 637,868 | Master's Level Research Assistant *1: 651,015 | Master's Level Research Assistant *1: 668,717 | 3,236,100 |
| | Part-time Assistant*1: 96,000 | Part-time Assistant*1: 96,000 | Part-time Assistant*1: 96,000 | |
| Operating expenses | NHIRD: 95,400 | | | |
| | Equipment Usage Fee: 117,600 | Equipment Usage Fee: 100,800 | Equipment Usage Fee: 67,200 | |
| | IRB: 19,500 | | | |
| | | Case Survey Fees (Telephone Interviewer Costs): 160,000 | Case Survey Fees (Telephone Interviewer Costs): 160,000 | |
| | | Submission Fee: 30,000 | Submission Fee: 30,000 | |
| Consumable and miscellaneous expenses | 10,000 | 10,000 | 10,000 | |
| travel expenses | GSA Conference Registration Fee: 60,000 | GSA Conference Registration Fee: 60,000 | GSA Conference Registration Fee: 60,000 | |
| 合計 Subtotal(s) for Each Year | 1,036,368 | 1,107,815 | 1,091,917 | |

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# 國立臺灣大學核心研究群研究計畫申請書

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| 子計畫四<br>Subproject 4 | 子計畫名稱 | 精神-身體多重慢性疾病的負擔、影響及相關因素 | 主持人<br>Co-PI | 張書森<br>Shu-Sen Chang |
| | Title of Project | The burden, impact, and associated factors of mental-physical multimorbidity | | |

**1. Specific Objectives of this Subproject**

**Specific objectives**: The overarching goal of this subproject is to investigate the burden, impact, and associated factors of mental-physical multimorbidity and potential interventions. Specific objectives include -

Objective 1: To quantify the population health impact of mental-physical multimorbidity in Taiwan across geography (at the township level) and time.
Objective 2: To evaluate the health system costs of mental-physical multimorbidity.
Objective 3: To project the future population health and health system costs burden of mental-physical multimorbidity in Taiwan
Objective 4: To investigate the mortality outcomes and associated factors (e.g., socioeconomic, factors, comorbid physical illness, and care quality and continuity) of mental-physical multimorbidity.

**Significance**: Mental-physical multimorbidity is a major public health issue due to its impact on healthcare utilization, costs, and patient outcomes. Individuals with mental-physical multimorbidity face significantly higher healthcare use and financial burdens [1]. This condition also leads to poorer quality of life and greater disability, especially in older adults with depression and cognitive impairment [2]. Managing these complex needs requires a shift from single-disease models to integrated care approaches that prioritize coordination and person-centered care [3].

**Knowledge gaps**: The knowledge gap on mental-physical multimorbidity is significant. Limited past research suggests that mental-physical multimorbidity is more common in socioeconomically deprived populations [4], but this has been rarely examined outside the Western settings. The economic burden is also substantial, with higher healthcare costs and out-of-pocket expenditures [1], but this has never been examined in Taiwan. Furthermore, with rapid population aging in Taiwan and other countries, multimorbidity is expected to rise significantly [4]. Mental-physical multimorbidity is expected to lead to increased healthcare utilization, greater economic strain, and poorer health outcomes [5], while relevant research in Taiwan is lacking.

**International competitiveness**: This subproject stands out internationally due to its use of national datasets and comprehensive assessment of the burden, impact, costs, geographic variations, trends, and associated factors of mental-physical multimorbidity. Unlike many studies that rely on smaller, regional samples or short-term analyses, this project leverages robust national data. The focus on geographic variations offers a unique perspective on how local environments, healthcare access, and regional policies contribute to health outcomes, a topic often underexplored in global research. The comprehensive assessment of economic costs further sets this research apart, addressing the financial burden of multimorbidity on individuals and healthcare systems, an area of growing international concern. Given the scope and depth of this project, the results are expected to be published in leading international journals, where they will contribute significantly to the global body of knowledge on multimorbidity and health inequalities.

## 2. Contribution of this Subproject to the Synergic Integration

Undertaking the research questions related to the burden, impact, and associated factors of mental-physical multimorbidity in this subproject has a synergistic effect on the main project by integrating key elements from Subprojects 1, 2, and 5 and extending their relevance to a critically underserved area of public health, i.e., multimorbidity. While Subprojects 1-3 provide the essential frameworks—such as methodological approaches, data analysis techniques, and foundational insights—this subproject applies those advancements specifically to mental-physical multimorbidity. Data from national health records and long-term follow-up assessments, developed and refined in earlier subprojects, can be repurposed to assess the specific life expectancy gap in populations with mental illness and co-occurring physical conditions. The findings from this targeted research will have profound implications for shaping public policies and improving clinical guidelines, providing a bridge between theoretical research and practical, real-world applications.

## 3. Methods and Approach

**1. Study sample:** The study will utilize Taiwan's National Health Insurance (NHI) database spanning from January 1, 2002, to December 31, 2019, to extract a national cohort of patients who have been discharged from inpatient psychiatric care. We will identify newly psychiatric discharge cohort members as patients who were discharged from psychiatric wards during the study period. We will exclude patients under the age of 15 and those who had been ever discharged from inpatient psychiatric care in the previous three years. Two comparison groups will be identified. First, each discharged case will be matched to two sex-and-age-matched comparison individuals who had visited psychiatric outpatient clinics at least two times prior to the index date, which will be defined as the date of discharge of the matched discharged case. Second, each discharged case will be matched to 10 sex-and-age-matched comparison individuals who had not been discharged from the inpatient psychiatric services in the three years or visited psychiatric outpatient clinics (at least two times) before their index dates.

**2. Mortality outcome:** Both the discharged and comparison cohorts will be followed from the index dates until the dates of their death or the end of the study period (i.e., December 31st 2023), whichever came first. The national cause-of-death data files will be linked to the discharge and comparison cohorts by anonymous identification numbers. The cause-of-death mortality data files will provide information on the date of birth, date of death, locale of death, address of death, and the underlying cause of death, coded according to the International Classification of Disease (ICD).

**3. Covariates:**

Physical comorbidities: Information related to physical health and injury will be extracted from the NHI database, including comorbid physical diagnoses, medicine for diabetes and smoking cessation (e.g., metformin, bupropion and varenicline), and history of admission for external causes (e.g., traffic accident, injury and self-harm).

Socioeconomic factors: Variables representing socioeconomic status will also be extracted from the NHI database, including insurance levels based on salary, low-income status, and median household income based on the individual's area of residence.

Medical care variables: These will include indicators of the quality of care, such as the frequency of blood sugar and HbA1c checks in diabetes care, continuity of medical treatments and outpatient follow-up.

Health care costs: Claim data for medical assessments, examinations, procedures, and treatments will be extracted from the NHI database.

**4. Statistical analysis:** The methodologies established in subproject 1 will be employed to

quantify the population burden of mental-physical multimorbidity across various socioeconomic groups, geographic locations (at the township level), and over time. The techniques developed in subproject 2 will assess the health system costs associated with mental-physical multimorbidity. Meanwhile, the strategies from subproject 5 will be utilized to forecast future population health outcomes and the financial burden on health systems resulting from mental-physical multimorbidity. Cox regression models, as used in our previous research [6], will be used to investigate the differences in psychiatric discharged patients, psychiatric outpatients, and comparison individuals regarding mental-physical multimorbidity, all-cause and cause-specific mortality risk, and associated socioeconomic and healthcare factors (care quality and continuity).

**5. Co-I's past achievements:** Professor Shu-Sen Chang, the Co-PI, previously published a series of studies showing the associations of suicide, the most tragic outcome of mental illness, with various physical risk factors or illnesses. Prof Chang and his colleagues showed the association between suicide and obesity [7], underweight [8], cardiometabolic factors [7-9], end-stage renal diseases [10], HIV [11], and inflammatory markers [12]. In a recent study, he and colleagues examined the pattern of all-cause and cause-specific mortality over time in 158,065 Taiwanese patients recently discharged from inpatient psychiatric care and found circulatory and respiratory diseases as the leading causes of death (Figure 1), indicating the pressing need for integrated physical and mental health care to reduce excess mortality among psychiatric patients. These research outputs demonstrate that Prof. Chang has a distinguished publication record in studying the effects of comorbid mental and physical disorders. His extensive expertise and experience position him well to successfully carry out the proposed research on the burden and consequences of mental-physical multimorbidity.

Figure 1. Circulatory and respiratory diseases as the leading causes of death from the second-year post-discharge in psychiatric inpatients [6].

**Table 2.** Number (*n*), percentage (%), and rates (per 100 000 person-years) of mortality during different follow-up periods in the discharged cohort

| | 0–3 months | | | 4–6 months | | | 7–12 months | | | 13–36 months | | | 37–60 months | | | > 60 months | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cause of death | *n* | (%) | Rate | *n* | (%) | Rate | *n* | (%) | Rate | *n* | (%) | Rate | *n* | (%) | Rate | *n* | (%) | Rate |
| All causes | 1843 | (100) | 4734 | 1369 | (100) | 3677 | 2363 | (100) | 3286 | 6876 | (100) | 2778 | 4464 | (100) | 2823 | 5042 | (100) | 2253 |
| Unnatural causes | 634 | (34) | 1629 | 418 | (31) | 1123 | 568 | (24) | 790 | 1473 | (21) | 595 | 797 | (18) | 504 | 923 | (18) | 413 |
| Suicide | 508 | (28) | 1305 | 328 | (24) | 881 | 417 | (18) | 580 | 999 | (15) | 404 | 551 | (12) | 349 | 594 | (12) | 266 |
| Homicide | <3 | - | - | 5 | (0) | 13 | 5 | (0) | 7 | 10 | (0) | 4 | 9 | (0) | 6 | 14 | (0) | 6 |
| Injury | 125 | (7) | 321 | 85 | (6) | 228 | 145 | (6) | 202 | 462 | (7) | 187 | 234 | (5) | 148 | 309 | (6) | 138 |
| Natural causes | 1209 | (66) | 3106 | 951 | (69) | 2554 | 1795 | (76) | 2496 | 5403 | (79) | 2183 | 3667 | (82) | 2319 | 4119 | (82) | 1841 |
| Infection | 56 | (3) | 144 | 36 | (3) | 97 | 79 | (3) | 110 | 228 | (3) | 92 | 143 | (3) | 90 | 190 | (4) | 85 |
| Neoplasm | 151 | (8) | 388 | 120 | (9) | 322 | 202 | (9) | 281 | 786 | (11) | 318 | 583 | (13) | 369 | 724 | (14) | 324 |
| Metabolic and endocrine | 101 | (5) | 259 | 74 | (5) | 199 | 124 | (5) | 172 | 338 | (5) | 137 | 240 | (5) | 152 | 308 | (6) | 138 |
| Nervous system | 28 | (2) | 72 | 14 | (1) | 38 | 41 | (2) | 57 | 130 | (2) | 53 | 94 | (2) | 60 | 119 | (2) | 53 |
| Circulatory system | 256 | (14) | 658 | 198 | (14) | 532 | 413 | (17) | 574 | 1102 | (16) | 445 | 801 | (18) | 507 | 867 | (17) | 387 |
| Respiratory system | 249 | (14) | 640 | 199 | (15) | 535 | 362 | (15) | 503 | 1075 | (16) | 434 | 710 | (16) | 449 | 760 | (15) | 340 |
| Digestive system | 122 | (7) | 313 | 106 | (8) | 285 | 232 | (10) | 323 | 746 | (11) | 301 | 473 | (11) | 299 | 491 | (10) | 219 |
| Genitourinary system | 64 | (3) | 164 | 47 | (3) | 126 | 99 | (4) | 138 | 269 | (4) | 109 | 164 | (4) | 104 | 183 | (4) | 82 |

## 4. Originality and Innovation of the Proposal and the Impact on the Community

This subproject presents a novel approach by focusing on the critical issue of mental-physical multimorbidity, a topic that has predominantly been examined through descriptive studies in the past. Unlike prior research, which often lacks depth and comprehensive analysis, this subproject aims to employ a rigorous, up-to-date methodology for assessing disease burden. By utilizing detailed national databases, the subproject will offer a more nuanced understanding of the complexities surrounding mental-physical multimorbidity. The scarcity of similar research highlights the innovative nature of this undertaking, which seeks to fill significant gaps in existing literature. Through this comprehensive approach, the subproject

not only aims to shed light on the intricate relationship between mental and physical health conditions but also aspires to inform policy decisions and clinical practices. By generating robust data and insights, this research has the potential to pave the way for future investigations into the management and treatment of mental-physical multimorbidity, ultimately contributing to improved health outcomes for affected populations.

## 5. Research Budget (Please list the sum)： Funds include personnel expenses, consumable & miscellaneous expenses, travel expenses, and equipment expenses.

| Project Year | First year from 01/2025 to 12/2025 | Second year from 01/2026 to 12/2026 | Third year from 01/2027 to 12/2027 | Total for the entire term of the Consortium Project |
|---|---|---|---|---|
| Budget Categories (NT$) | | | | |
| personnel expenses | 700,000 | 700,000 | 700,000 | 2,100,000 |
| consumable & miscellaneous expenses | 280,000 | 280,000 | 280,000 | 840,000 |
| travel expenses | 120,000 | 120,000 | 120,000 | 360,000 |
| equipment expenses | 100,000 | 100,000 | 100,000 | 300,000 |
| Subtotal(s) for Each Year | 1,200,000 | 1,200,000 | 1,200,000 | 3,600,000 |

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# 國立臺灣大學核心研究群研究計畫申請書

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|---|---|---|---|---|
| 子計畫五<br>Subproject 5 | 子計畫名稱 | 台灣多重慢性疾病的微觀模擬：預測與政策 | 主持人<br>Co-PI | 黃從仁<br>Tsung-Ren Huang |
| | Title of Project | Microsimulation of Multimorbidity in Taiwan for Projections and Policies | | |

**1. Specific Objectives of this Subproject**

**Specific objectives:** Multimorbidity, the presence of two or more chronic conditions, is a major public health challenge due to its significant impact on healthcare utilization, costs, and patient outcomes (Skou et al., 2022). Individuals with multimorbidity often face dramatically higher healthcare use and financial burdens, as well as poorer quality of life and functional status (Garín et al., 2015) (Lai et al., 2020) (Wise, 2018). This growing burden poses serious challenges to healthcare systems, as the complexities of managing multiple concurrent conditions can lead to suboptimal care, medication interactions, and increased risk of adverse outcomes.

The overarching goal of this subproject is to develop a microsimulation model tailored to the Taiwanese population to forecast the future burden of multimorbidity. Here, microsimulations of agent-based models rather than time series models are used for forecasting because they can better capture the dynamic and heterogeneous nature of population health transitions. Moreover, these agent-based models allow us to ask what-if questions and implement interventions in silico to inform the making of national health policies. The specific objectives include:

Objective 1: Calibrating our model by the historical data about the incidence and prevalence of multimorbidity across age groups and socioeconomic strata in Taiwan.
Objective 2: Forecasting the future trajectories of multimorbidity and related health outcomes up to 2050.
Objective 3: Evaluating the potential impacts of various policy interventions on the future burden of multimorbidity.

**Research gaps:** As the population in Taiwan rapidly ages, multimorbidity, the presence of two or more chronic conditions, is expected to rise significantly (Fu et al., 2014)(Hu et al., 2019). This growing burden of multimorbidity will lead to increased healthcare utilization, greater economic strain on the healthcare system, and poorer health outcomes for individuals affected. However, relevant research on the prevalence, impact, and effective management of multimorbidity in the Taiwanese context is currently lacking. Addressing this research gap is crucial to inform policies and strategies that can effectively address the challenges posed by the growing burden of multimorbidity in Taiwan's aging population.

**International competitiveness**: This subproject distinguishes itself internationally through its utilization of comprehensive national datasets and its in-depth assessment of the burden, impact, costs, geographic variations, trends, and associated factors of multimorbidity. Unlike many studies that rely on smaller, regional samples or short-term analyses, this subproject integrates multiple national datasets to provide a unique perspective on how medical history, local environments, and lifestyle factors contribute to health outcomes, a topic that is often underexplored. Moreover, the methodological approach and the comprehensive national datasets utilized in this research can serve as a valuable reference for other Asian countries facing similar demographic and epidemiological transitions.

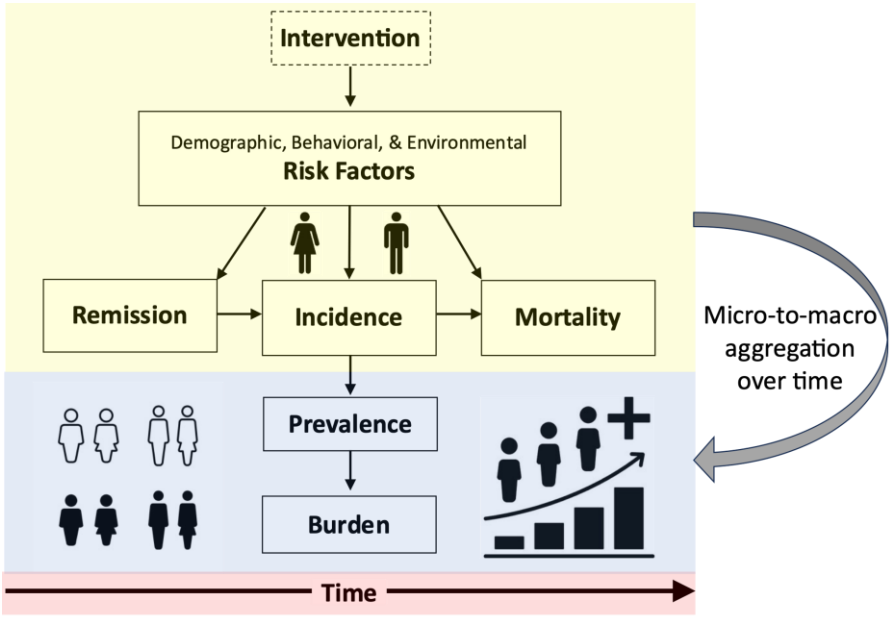
**2. Contribution of this Subproject to the Synergic Integration**

This subproject will be integrated with and contribute to other subprojects within the broader

research initiative. Specifically, this subproject will work closely with Subproject 2 to incorporate the comprehensive burden of multimorbidity, including direct healthcare costs, indirect costs such as lost productivity, and the overall impact on the economic burden of disease. Additionally, this subproject will collaborate with Subproject 3 to leverage the projected prevalence and severity of multimorbidity in order to estimate the future demand for long-term care services and resources. Furthermore, this subproject will work in tandem with Subproject 4 to investigate the intricate interplay between physical and mental conditions and their combined impact on health outcomes.

With the integration of these complementary subprojects, this research initiative will provide a comprehensive, evidence-based foundation to guide the development of policies and interventions that can effectively address the challenges posed by the growing burden of multimorbidity in Taiwan's rapidly aging population.

## 3. Methods and Approach




The core methodology adapts existing frameworks—such as the IMPACT$_{NCD}$ model (Watt et al., 2022) and the PACSim model (Head et al., 2024)—to Taiwan's specific demographic, health, and socioeconomic context. The steps include:

1. **Data Integration**: We will utilize comprehensive longitudinal data from Taiwan's national health insurance records, linking them with the latest census data and population-level health surveys. This will allow us to capture detailed individual-level characteristics, including age, sex, socioeconomic status, health behaviors, and medical history. The incidence, prevalence, and mortality estimation from Subproject 1 will also be utilized to inform the model.
2. **Modeling Disease Dynamics:** The microsimulation model will simulate the onset, progression, and complex interactions of various chronic conditions over time using state-transition probabilities estimated from real data. We will carefully model individual-level risk factors such as obesity, hypertension, physical inactivity, and other relevant lifestyle and environmental factors, integrating them with the trajectories of multimorbidity development.

3. **Projection of Future Burden:** Using this robust, individual-based simulation model, we will project the incidence and prevalence of multimorbidity and its associated healthcare demand from 2024 to 2050. Special attention will be given to accurately capturing the impacts of Taiwan's rapidly aging population and how the burden of disease clusters evolves across different geographic regions, socioeconomic groups, and urban-rural divides.
4. **Policy Simulation:** The microsimulation model will be utilized to simulate the potential impacts of various policy interventions, such as preventive healthcare measures, targeted chronic disease management strategies, and innovative care delivery models. This will help identify the most cost-effective and impactful approaches to addressing the growing challenges posed by multimorbidity in Taiwan's healthcare system.

The Co-PI, Tsung-Ren Huang (Associate Professor in Department of Psychology at National Taiwan University; Visiting Scholar in Department of Psychology at Stanford University) is a leading expert in computational modeling of human behavior. His interdisciplinary studies have been published in high-profile journals, such as *American Psychologist* (IF=**12.3**; JCI rank=3/218=**1%** in Psychology-Multidisciplinary) and *IEEE Transactions on Affective Computing* (IF=**9.6**; JIF rank=14/197=**7%** in Computer Science, Artificial Intelligence). In 2024, he co-earned two Future Tech Awards (未來科技獎) from National Science and Technology Council (NSTC) in Taiwan. The PI of Subproject 1, Hsien-Ho Lin, will also join the efforts of forecasting. Dr. Lin has extensive experiences in disease modeling in noncommunicable and communicable diseases using compartmental models and agent-based models. Their modeling work has been published in the *Lancet Diabetes and Endocrinology* (IF=**44.0**; JCI rank=1/186=**0.5%** in Endocrinology & Metabolism) (Pan et al., 2015), the *Lancet Global Health* (IF=**19.9**; JCI rank=6/403=**1%** in Public, Environmental & Occupational Health) (Langley et al., 2014), and *JAMA Internal Medicine* (IF=**22.5**; JCI rank=7/325=**2%** in Medicine, General & Internal) (Ng et al., 2021).

## 4. Originality and Innovation of the Proposal and the Impact on the Community

In terms of innovation, this research is the first of its kind in Taiwan, applying microsimulation methods to project the burden of multimorbidity and inform policy development. This Taiwan-specific model considers environments (e.g., air quality) and behavior (e.g., lifestyles) in addition to demographic variables and medical history of physical and mental conditions. This allows for a more nuanced and holistic understanding of the drivers of multimorbidity in Taiwan's unique context.

In terms of impact on the community, the findings from this research will be instrumental in guiding the design, implementation, and evaluation of public health policies and healthcare strategies that aim to effectively address the growing burden of multimorbidity in Taiwan's aging population. The insights gained will support the development of targeted interventions, resource allocation, and the restructuring of care delivery models to better meet the complex needs of individuals affected by multimorbidity.

In summary, this subproject represents a pioneering effort to employ advanced microsimulation modeling techniques to project the future burden of multimorbidity in Taiwan while also investigating the underlying drivers and evaluating the potential impact of policy interventions.

## 5. Research Budget (Please list the sum)： Funds include personnel expenses, consumable & miscellaneous expenses, travel expenses, and equipment expenses.

| Project Year | First year from 01/2025 to 12/2025 | Second year from 01/2026 to 12/2026 | Third year from 01/2027 to 12/2027 | Total for the entire term of the Consortium Project |
|---|---|---|---|---|
| Budget Categories (NT$) | | | | |
| personnel expenses | 600,000 | 600,000 | 600,000 | 1,800,000 |
| consumable & miscellaneous expenses | 100,000 | 100,000 | 100,000 | 300,000 |
| travel expenses | 0 | 0 | 0 | 0 |
| equipment expenses | 500,000 | 500,000 | 500,000 | 1,500,000 |
| Subtotal(s) for Each Year | 1,200,000 | 1,200,000 | 1,200,000 | 3,600,000 |

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