Dementia in China: Past, Present, Future and Perspective on Intervention

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Thesis submitted for the degree of Doctor of Philosophy

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Declaration

I, Yixin Li, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background: According to a 2019 estimate, some 57 million people were living with dementia globally, and of these 15 million were living in China. Population ageing in China means this number will increase substantially in the coming decades. Projecting the future burden of dementia in China is essential for policymakers.

Aim: The aim of this thesis is to examine the recent time trends in dementia incidence in China, project the dementia prevalence to 2035 using a Markov model and to explore the potential impact of reduction in salt intake on dementia burden to 2035.

Method: A joint model was employed to study the time trend in dementia incidence in longitudinal cohort data. This incidence trend contributed input data for a novel state-transition Markov model to project the future burden of dementia in China and applied this model to explore the impacts of reduction in salt intake on dementia cases in China in the future.

Results: An annual 2.5% increase in dementia incidence was found from this study after accounting for competing risks of mortality and non-random losses to follow-up. For the burden of dementia in the future, the number of people with dementia is projected to be 22.1 million by 2025, 27.1 million by 2030 and 30.6 million by 2035. Prevalence of dementia is projected to be 10.0% in 2025, 10.5% in 2030 and 10.6% in 2035. An intervention scenario was examined using the Markov model. Compared with the persisting 2008 average salt intake level, assuming intake is reduced to 5 g/person per day by 2025 and remains stable to 2035, the intervention might result in 431,250 additional dementia cases by 2035 in China.

Conclusions: The dementia incidence was increasing in China between 2002 to 2014. The number of dementia cases is projected to increase substantially by 2035. And the reduction in salt intake might result in further cases by 2035.

Impact Statement

The work in this thesis has important implications inside and outside academia.

The burden of dementia has been growing and will continue to increase in future decades, driven by population ageing, and possibly an increasing dementia incidence rate. An epidemiological prediction model is developed to estimate the number of dementia cases in the future in China, and to be used as a tool to estimate the number of cases that may be prevented by salt intake reduction intervention in the Chinese population.

The benefits of this thesis inside academia can be divided into knowledge and methodology. In terms of knowledge, this thesis fills some academic research gaps. To be specific, this thesis provides the first study to estimate the trend in dementia incidence in a middle-income country. It explores the future burden of dementia, considering the calendar changes in dementia incidence, stroke incidence, stroke mortality as well as population structure-changing based on a state-transition Markov model. It also explores the potential impacts of reduction in salt intake on the future burden of dementia in China. In terms of methodology, the state-transition Markov model developed in this thesis also provides scholars with a possible tool to explore the potential impacts of possible preventive interventions on the burden of dementia in the future.

This thesis also has some important implications for policymakers and other stakeholders outside the academic sector. First, it is important to improve the awareness of dementia in China. The new evidence presented in this thesis confirms a worrying trend toward an increase in the incidence of dementia over the last 12 years. The potential for preventing dementia is of widespread interest. Specific and effective actions for reducing dementia risk factors across the life course are needed, such as reducing the prevalence of diabetes. It is never too early and never too late in the life course for dementia prevention.

Second, there is a clear and urgent need to improve healthcare coverage in China for people living with dementia now and in the future. This study shows that the number of dementia cases in China is projected to increase to more than 30 million by 2035. Through the projection model, this thesis suggests that the Chinese government and society need to extend the coverage of healthcare, access to care, treatment, and support for people with dementia.

Third, the reduction in salt intake and mid- and late-life blood pressure may reduce risk in those susceptible to dementia. However, this anti-hypertension intervention has effects on other health outcomes, with unexpected consequences for population health, for example, prolonging life expectancy in the older people could lead to increased dementia cases. Dementia is accompanied by cognitive and functional impairment, which has a profound effect on the patient’s quality of life, caregiver burden, and need for and cost of care. This study suggests that public health policy should not be isolated, particularly in vascular diseases. Interventions require overall planning and coordination as they involve many supporting policies and measures, such as increasing the number of social care givers.

Acknowledgements

Reflecting on my PhD research, it has been a real privilege to have been able to hitch a lift on the tidal wave of ageing epidemiology that gathered momentum in the 21st century. That immense impact of ageing inspired me and has since transformed my research life in unimaginable ways. The huge impact of ageing has plunged me into the sea of epidemiology study and converged wonderful researchers into this sea. One of the greatest fortunes of my PhD time has been studying with others, and I must acknowledge the help and kindness of many people I have worked with. I would like to express my appreciation to all the people who helped me.

First and foremost, I would like to thank my supervisors, Eric Brunner and Piotr Bandosz, for their encouragement, guidance and patience during my PhD study. Particularly, I want to express my appreciation to my primary supervisor, Eric Brunner. I am forever grateful for his immense knowledge, deep insights, and strong support for my PhD study. I want to thank him for supervising me throughout my PhD step by step, guiding me academically and spiritually, and always being there for me through the hard times. For my second supervisor, I want to express my thanks for his academic guidance, kindness and wealth of knowledge during my PhD study period. This work would not have been possible without my supervisors' support. Thanks go to Angela Cooper for proofreading this thesis.

Additionally, I want to extend my gratitude to all of my colleagues and friends that are part of the UCL family and beyond. Their emotional support and understanding helped me to persevere through the PhD journey.

Finally, I would like to thank my parents and dedicate this thesis to them. The support of my father and mother is the source of my strength to carry on.

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1 Introduction

This chapter introduces the context of this thesis, explains the rationale of the study, and outlines the structure of this thesis.

1.1 The context of this study

According to the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) (2019), over 57 million people were living with dementia in 2019.[1] It is estimated that the number of people with dementia in China in 2019 was 15 million, and this number is likely to increase substantially in the coming decades.[1] National annual economic costs of dementia for the Chinese economy in 2010 are estimated at United States dollar (USD) $47 billion, which increased more than 50-fold from that in 1990.[2]

China has a rapidly ageing population. The number of people over 65 years old has increased from 47 million in 1980 to 179 million in 2020, from 4.7% to 12.0% of the total population.[3] The ageing of the population is produced by two dynamics (1) falling mortality rates in older age groups and (2) increasing size of cohorts reaching age 65 years (see section 2.2.1 Population ageing). It is expected that population ageing is accompanied by an increasing number of people with dementia. Thus, an estimation of the recent time trends in dementia, a projection of the future burden of dementia in China and an exploration of the impacts of possible intervention are important public health issues in China.

An estimation of the future number of people with dementia using a method based on constant age and sex specific prevalence proportions will be unreliable if the occurrence of dementia is subject to change over time. A more accurate projection of the future dementia burden requires consideration of possible time trends in dementia incidence and changing mortality rates, as well as population ageing.

In addition, the epidemiology of stroke plays an important role in the projection of dementia prevalence. Specifically, the reduction in stroke mortality led to a prolongation of life expectancy[4], however, the decrease of vascular factors, such as behavioural and biomedical risk factors which are shared by cognitive and functional impairment, can also lead to a decrease in dementia incidence [5]. Without considering these epidemiological trends, estimating and projecting dementia prevalence would be inaccurate. Thus, to project future dementia prevalence precisely, these factors need to be considered.

These ageing and health issues can be studied in a stepwise process. First, an estimation of the recent time trends in dementia incidence, second, a projection of the future burden of dementia in China, and third, an exploration of the disease burden impacts of possible interventions intended to reduce the incidence of dementia in the Chinese context.

1.2 The rationale for this study

An estimation of the dementia incidence rate and its time trend is challenging and necessary for future trends in dementia burden. Some studies employed extrapolation to forecast the future prevalence of dementia, such as GBD projection, and do not account for the change in dementia incidence, which might lead to an inaccurate projection. To date, it appears there are no nationally representative studies of recent time trends in dementia incidence in China using longitudinal data and appropriate modelling techniques. Competing risks of mortality and non-random losses to follow-up may potentially bias the estimation. The analysis suggesting that dementia incidence has declined in recent years in the Framingham Heart Study[6] was later challenged for this reason[7].

Consideration of mortality and dropout, which may be associated with dementia risk, is a valuable development in modelling methods.[8] There are studies which explore time trends in dementia in China at city or provincial level using representative data sources but they did not consider the influence of non-random losses to follow-up or mortality.[9] Thus, an accurate estimation of the recent time trend in the incidence of dementia will fill the research gap and provide evidence to support forecasting studies.

Similarly, there is no study about projecting the future number of dementia cases in China, considering the time trends in dementia incidence, mortality as well as epidemiological characteristics of stroke. Several studies forecasting the number of dementia cases and economic burden of dementia in China are only based on constant point-in-time dementia prevalence proportion or without considering the time trends in dementia incidence or mortality.[2,10] Thus, the projection of the number of people with dementia in the future in China can fill the vacancy of a forecasting study and provide a modelling base for the next scenario study.

Research exploring the impacts of reduction in salt intake on dementia burden in China would be valuable for public health policy. Several existing studies exploring the impacts of reduction in salt intake on population health in China focused on cardiovascular disease rather than dementia.[11] A simulation of the impact of reduction in salt intake on the burden of dementia based on scenario analysis can throw some new light on the policy impacts on population health of the interventions to prevent dementia in China .

Therefore, it is important to estimate the recent time trends in dementia incidence in China, project the future number of dementia cases in China precisely and explore the impacts of interventions about reduction in salt intake on dementia burden in China. These issues have both research and policy implications.

1.3 Thesis structure

This PhD thesis contains nine chapters. Chapter 1 introduces the work, including the main context, rationale and structure. Chapter 2 reviews the epidemiological and technical background of the thesis. Chapter 3 sets out the aims and objectives. Chapter 4 introduces the main data source, the Chinese Longitudinal Healthy Longevity Study, employed in this study, and describes the variables of interest. The next three chapters address the specific objectives stepwise: Chapter 5 estimates the time trends in dementia incidence in China using the longitudinal data; Chapter 6 projects the future burden of dementia in China up to 2035 based on a state-transition Markov model; Chapter 7 explores the impact of the intervention of reduction in salt intake on dementia burden in China by scenario analysis. Chapter 8 summarises the key findings of this PhD thesis, interprets the research findings, reviews the strengths and limitations of this thesis, explains the implication of the findings and provides a perspective of future work. Chapter 9 concludes the PhD thesis.

2 Background

This chapter reviews the context of dementia with insights from the social and biological perspective. From the social perspective, the context of dementia in the world and China are reviewed. From the biological perspective, the risk factors of dementia and interventions to prevent dementia are outlined. Then this chapter reviews the previous epidemiological studies about the time trends in dementia incidence, the projection simulation studies and the impacts of reduction in salt intake on dementia cases. This chapter provides background information about the statistical methods in time trends analysis, modelling analysis and scenario analysis. This chapter also describes the challenges that this study needs to address in this PhD thesis.

2.1 The global challenge: dementia

Dementia is a progressive syndrome of global cognitive impairment, characterised by a progressive loss of cognitive and functional ability.[12] The subtypes of dementia include Alzheimer's disease, vascular, with Lewy bodies, and frontotemporal.

There are four universal epidemiological characteristics of dementia: Firstly, the number of people with dementia is large. It has been estimated the number of people with dementia globally in 2019 is more than 57 million, more than the whole population of England in 2022. [1,13] Secondly, the number of dementia cases in the world is growing rapidly and projected to triple in the next three decades (estimate, 152 million in 2050). [1] Every three seconds, one person in the world develops dementia. Thirdly, the biological characteristic of dementia – lack of cognitive and functional capacity – means that people with dementia need to be cared for by others. This leads to a large economic cost related to dementia. According to the World Alzheimer's Report, the economic cost of dementia had reached USD 818 million by 2016, more than USD $1 trillion by 2018, and will double by 2030.[14] Fourthly, there is as yet no cure for dementia. Despite decades of research, there is still no effective therapy for dementia.[15] These four epidemiological characteristics make dementia a huge challenge to the world.

In May 2017, the World Health Organization (WHO) adopted the Global Plan of Action on Public Health Responses to Dementia 2017-2025 in response to the growing challenge of the number of people with dementia and the economic burden of dementia.[16] This plan provides an overview of how countries around the world are tackling the challenge of dementia and sets out seven specific targets across 7 areas. The detailed content of the seven targets in the Global Plan is shown in Appendix 1.

2.2 Dementia in China

In addition to the universality of dementia, the epidemiology of dementia in China has its particularity under the Chinese socio-economic circumstances and the epidemiological context. The socio-economic circumstance of China has two characteristics in aspects of demographics and socioeconomics while the epidemiological context of dementia in China has two important indicators in terms of prevalence and health economics.

2.2.1 Population ageing

From the demographic perspective, China is a society with a rapidly ageing population. In recent years, life-expectancy is longer with the decline in mortality in China. From 2012, for the first time in Chinese history, most Chinese can expect to live longer than 75 years. By 2050, there will be almost 380 million people aged over 65 in China.[3] The pace of population ageing in China also is increasing dramatically. The number of people over 65 years old has increased from 47 million in 1980 to 179 million in 2020, from 4.7% to 12.0% of the total population.[3] The time left for China to deal with ageing related issues will be much shorter than in other high-income countries (China has been classified as a middle-income country by the World Bank). At the current rate, China will only have 27 years to experience the population ageing process of 115 years in France (number of years estimated for the proportion of people 65+ to rise from 7% to 14% for France and China: 1865-1980 and 2000-2027).[17] A longer life brings with it hopes and opportunities, but also challenges: Additional years provide opportunities to participate in activities and lives, but also with ageing, come the results from the impact of the accumulation of a variety of biological damage over time. The challenges brought from ageing, not only for the individual but also for the whole society: it influences the extent of individual and family opportunities and the ability to attend the activities in life, however, it also brings the stress of the public health system, especially for low-income or middle-income countries.

Table 2-1: Population and age structure in 1980, 2000 and 2020 in China

Year	Population (billion)	0-19 years (%)	65+ years (%)	Ratio of older: younger
1980	1.00	46.7	4.7	9.9
2000	1.29	32.8	6.8	4.8
2020	1.49	13.4	12.0	1.1

Data sources: United Nations, Department of Economic and Social Affairs, Population Division (2019). World Population Prospects 2019.[3]

2.2.2 Socioeconomic context

From the perspective of the socioeconomic context, the Chinese economy is still at a developing stage – at the national level, China is classified as a middle-income country by the World Bank[18]; at the individual level, the per capita income is still low. Per capita income in China is about a quarter of that in high-income countries, and about 336 million Chinese are living below the upper-middle-income poverty line of USD $5.50 a day in 2016.[19] Unlike other high-income countries, the Chinese population will become old before the country becomes developed and rich. The diseases and economic burden related to the old, such as dementia, pose important challenges to the public health system.

Under the population ageing and economic stress in China, the epidemiology of dementia in China has some special characteristics: first, in terms of the number of cases, China has the largest number of people with dementia in the world; second, in terms of economic cost, the economic cost of dementia in China increased fast during the past decade and is expected to continue to increase in the future; third, in terms of policy response, the dementia-related policy landscape is being transformed. These particularities of the epidemiology of dementia in China are introduced and explained as follows in these aspects.

2.2.3 Prevalence of dementia in China

According to the GBD Report 2019, 15 million people had dementia in China in 2019, accounting for one-fourth of global cases.[1] Another indicator which is also important to describe the burden of dementia is prevalence proportion.

Three studies have reported the nation-wide prevalence of dementia in China. Two studies were conducted in 2014, China Cognition and Ageing Study I (COAST I) [20] and China Mental Health Survey (CMHS) [21] which reported dementia prevalence in the population aged 65 and over and COAST II [22] conducted in 2018 which reported the dementia prevalence in the population aged 60 and over. COAST I, CMHS and COAST II are observational studies. Comparing these studies, CMHS covers the widest study area (covers 31 provinces, autonomous regions, and municipalities, samples from 157 counties or districts, follows the China Chronic Diseases and Risk Factors Surveillance organized by the Chinese Centre for Disease Control and Prevention, and used the same sampling frame), COAST II has the largest study population (N=46,011), and updated meta-analysis includes the many studies which could avoid the inaccuracy because of one-study bias.

All three studies declare that they can represent the whole of China. Although affected by the differences in study population, research area, and study period, the prevalence of dementia in China has slight differences in these four epidemiological studies, yet the results of these studies about dementia prevalence are generally similar: prevalence of dementia in China in the older people probably ranges from 5% to 6%, and from the COAST I and COAST II, the time trends in dementia prevalence can be inferred – the time trend in dementia prevalence was increasing. Table 2-2 shows the summary of studies on dementia prevalence nationwide in China.

Table 2-2: Estimates of nationwide dementia prevalence in China

Study	Author	Publish year	Study year	Number of participants	Age	Method	Cover area	Estimated prevalence (95% CI)
COAST I*	Jia JP et al.	2014	October 2008 to October 2009	13,806	65 and over	Cross-sectional study	Based on 5 representative cities, randomly selecting 10 urban districts and 12 rural counties	5.10% (4.7%-5.6%)
CMHS	Huang YQ et al.	2014	July 2013 to March 2015	32,552	65 and over	Cross-sectional study	31 provinces, autonomous regions, and municipalities	5.60% (3.5%-7.6%)
COAST II*	Jia LF et al.	2018	March 2015 to December 2018	46,011	60 and over	Cross-sectional study	12 provinces, autonomous regions, and municipalities	6·0% (5·8%–6·3%)

Abbreviation: COAST: China Cognition and Ageing Study; CMHS: China Mental Health Survey

*COAST I constitutes the baseline data of longitudinal COAST; because COSTA II only indicates the authors include all COAST group but did not show the association between COAST I and COSTA II and only include one wave data, COAST I and COAST II were cross-sectional, and they were separate. COSTA II studies larger population than COAST I and covers a wider area than COAST I.

Data sources: [20-23]

Another updated meta-analysis also reported dementia prevalence of people aged 60 and over in China is 5.30% (4.3%-6.3%). This updated meta-analysis combined the earlier review (up to Apr 2012) [24], World Alzheimer Report 2015 (Jan 2011–Mar 2015) [25] and an updated search (Mar 2015–Feb 2017). This updated meta-analysis includes 76 studies.

Dementia prevalence differs according to gender, geography and other factors. The updated meta-analysis shows that prevalence increases with age. The age-stratified dementia prevalence approximately doubles every five years of increment of age (estimated prevalence of 2.0% in 65-69 age group; 3.6% in 70-74 years group; 5.9% in 75-79 years group).[26] Moreover, the prevalence of dementia for females is higher than that for males (pooled prevalence of 3.7% in men vs. 5.6% in women), and the prevalence of dementia is higher in the western area of China compared with the central and southern areas (pooled prevalence 9.6% in west area; 3.8% in central area; 3.7% in south area).[23] COAST II showed a similar result about the geographic differences: dementia prevalence is higher in the western area than in the northern and southern areas (7.5% in west ; 6.3% in north; 4.7% in south).[22] These studies reveal that dementia might have regional inequality in China. Regional variation in early-life and mid-life exposures, such as the educational level, lifestyle and environment, may play a role in population health and the probability of developing dementia and provide a possible explanation for geographical inequality.[27,28] The ethnic minorities living in the west of China have different lifestyles and environments from the Han Chinese living in the northern and southern areas of China, which may lead to the differences in cognitive ability and functional ability of the older people in later life.[23]

2.2.4 The economic costs of dementia in China

There are nine studies estimating the economic cost of dementia or Alzheimer's disease in China (Table 2-3). The research subject of the five studies is all-cause dementia (Liu et al.[29], Xu et al.[2], Mould-Quevedo et al.[30], Zhang et al., and Huang et al.[31]), and the research subject of four studies is Alzheimer's disease, one major subtype of dementia, but without vascular dementia (Wang et al.[32], Yu et al.[33], Jia et al.[34] and Clay et al. [35]).

All nine studies provide information about the economic cost of dementia or Alzheimer's disease at individual level and national level. The studies differ in many aspects, including the component of economic cost, the study population, the unit of economic cost and the time period of the study.

Currently, there are no official national data on the cost of dementia in China and given the limitations of the different criteria and methods adopted in previous studies, directly comparing these studies on the economic cost is not appropriate. However, these studies can still throw some light on the economic burden of dementia in China. Researchers formulate a consensus that the economic costs of dementia have become a huge economic burden for the public health system in China.

In addition, the study conducted by Mould-Quevedo used the results (cost estimation) of this study to model the impact of medical services for patients with dementia (including the formal and informal sectors) on China's economy and found that the economic impact of dementia will exceed USD $1 trillion by 2050 (in 2011 prices). Furthermore, this study also suggests that caring for people with dementia can lead to a loss of labour, which has a huge impact on the economy (attribute 62% of the total economic impact).[30]

Five of the previous studies (Wang et al.[32], Xu et al.[2], Jia et al.[34], Huang et al. [31] and Clay et al. [35]) also provide projections of the economic cost of dementia or Alzheimer's disease for China in the future. The projection by Wang is much smaller than the projection of Xu and Jia in 2030 (CNY 76.6 billion, CNY 792.2 billion and CNY 507.0 billion), these differences in the projection might be because of inflation, the different scope of costs, different research subjects (Wang, Jia and Clay's study subject is Alzheimer's disease, and Xu's study subject is all-cause dementia). In addition, Clay's research reveals that changes in the number of dementia patients receiving treatment will have an impact on economic estimates for the future.[35] The higher treatment rate would lead larger economic cost burden of dementia (5% treatment rate: CNY 332.5 billion in 2030; 10% treatment rate: CNY 362.2 billion in 2030; 20% treatment rate: CNY 421.6 billion in 2030).[35]

The increase in costs arises from increases in numbers of people with dementia and in increases in per person. One study shows that these two elements each contribute around one half of the total increase.[36] In addition, per capita expenses may rise because (1) certain services have grown more expensive and (2) new services have been introduced, the coverage of existing services has been expanded, or existing service users are utilising the same services more intensely.[36] All these studies believed that the economic costs of dementia are huge for China and these costs will continue to increase in future decades.

Table 2-3: Estimates and projections of the economic cost of dementia in China

Author	Publish year	Study period	Study base area	Outcome	The projection of total economic cost of dementia in China in 2030
Wang et al.[32]‡	2008	Oct 2005 to Dec 2006	Shanghai	Annual economic cost of AD for individual (indirect cost and direct cost), annual economic cost of AD for the whole country	CNY ¥76.6 billion (GBP £8.7 billion) **
Mould-Quevedo et al.[30]	2010	Sep 2009 and Dec 2009	Seven regions†	Monthly costs, directly costs and indirectly costs of dementia	-
(Liu[29]*	2013	2003 to 2007	Beijing	Annual Medical cost, care cost, total cost of dementia	-
Yu et al.[33]	2015	Sep 2013 to Nov 2013	Beijing, Shanghai, Guangzhou	Monthly unit cost of healthcare resources	-
Xu et al.[2]‡	2017	Jan 2005 to Mar 2014	Shandong province	Annual costs of formal and informal care for individual, total cost of dementia for whole country	USD $114.2 billion (GBP £145.3 billion) **
Jia et al.[34]‡	2018	Oct 2015 to Mar 2016	Mainland China	Annual direct medical cost, direct nonmedical cost, and indirect cost of AD	CNY ¥507.0 billion (GBP £57.6 billion) **
Zhang et al.[37]	2019	2008 to 2013	Guangzhou	Annual direct medical cost of dementia (total hospitalization expenditures per inpatient)	-

Clay et al.[35] ‡	2019	2010 to 2050	Number of dementia cases was obtained from a previous meta-analysis	Costs have been adapted to reflect costs for treated and for untreated patients in China.	CNY ¥204.5 billion (GBP £23.3 billion) **
Huang et al. [31]‡	2022	Jan 2005 to Dec 2015	Six provinces (Hubei, Shanxi, Anhui Shanghai, Guangdong, Heilongjiang)	Annual economic cost of dementia for individual and whole country (direct medical costs, direct non-medical costs and indirect costs)	USD $100.4 billion (GBP £79.0 billion) **

Abbreviations: AD: Alzheimer's disease; CNY: Chinese Yuan; USD: United States Dollar; GBP: Great British Pound

*This study is the PhD thesis finished by Liu Zhaorui in 2013

**The economic cost of dementia was transferred to GBP manually, the converter: 1 GBP to CNY = 8.8;1 GBP to USD=1.27; 1USD to CNY=6.3

†The study conducted in 48 hospitals across seven regions of China (Northeast, Northern, Northwest, Southwest, Central, Eastern and Southern).

‡ These studies also provide projections for future economic burden of dementia in China.

Data sources: [2,29-32,34,37] [35]

2.2.5 The policy landscape related to dementia in China

China has become an ageing society since the 21st century. The number of the older people affected by dementia has increased rapidly since the 2010s, and now stands at an estimated 15.3 million. As the family care giving capacity has decreased because of the social changes after industrialization and urbanization, the one-child policy demands for social care have been increasing. China has worked hard to adapt to social change and to tackle the social problems which arise in its ageing society, such as promoting healthy ageing and the need for an increasing volume of long-term care, especially dementia care.

China approved a national dementia plan on 11th September 2020. This is the first national policy plan related to dementia in China. The Chinese national action plan sets out four specific goals, which form the underlying policy structural framework: reduction of risk, mitigation of cognitive decline, provision of family rest and encouragement of psycho-social service systems. In this action plan, the Chinese government proposed to raise public awareness of the prevention and treatment of dementia to 80% by 2022.

Specific National Action Plan tasks include supporting the development of cognitive screening and intervention pilots for the older people and building a comprehensive dementia screening, early diagnosis, and early intervention prevention and control system.

The National Health Commission has also issued a work plan for exploring special services for the prevention and treatment of dementia, which aims to implement the relevant requirements of the healthy China action (2019-2030) and National Action Plan and direct all provinces and regions to explore and implement comprehensive dementia prevention and treatment. This policy claims that the next 5 to 10 years will be a "window of opportunity" for China to construct and improve the ageing response system and develop a national Alzheimer's disease strategy. Therefore, the nation needs to encourage early diagnosis and treatment, hasten the research, production, and commercialisation of medications with distinct pathogenic processes.

In addition to the national dementia plan and the specific work plan, the Chinese government has also approved a series of national policy documents as supplements in the previous five to 10 years. Different goals of dementia prevention and treatment were determined in different periods. Appendix 2 shows the historical development of national policies related to dementia in China.

The Chinese government has identified dementia as a priority in Chinese public mental health and aims to establish a public health service system that can more accurately monitor the trend of dementia and provide care services for the older people with dementia. The public health policy in China is phased and planned for the treatment and service of dementia patients. In the past decade, the public health policy related to dementia in China has also undergone a transformation: from not attaching importance to dementia to attaching importance to dementia, from unprofessional to professional, from generalization to specificity, from one-side to comprehensive.

To conclude, the upward trends in the number of dementia cases continue to pose significant challenges for the public health system throughout the world and China is no exception. Due to the epidemiological characteristics of dementia, it may exert great pressure on Chinese dementia patients themselves, their families, the national public health service system and clinicians in the future. It is important to explore the recent time trend in dementia incidence accurately, project the future burden of dementia in China precisely and explore the impacts of interventions on modifiable risk factors such as salt intake on the dementia burden in China.

2.3 Overview of risk factors for dementia

A risk factor for dementia is the predictor of dementia. Researchers have found that some risk factors can affect people's probability of developing dementia. Some risk factors for dementia are avoidable, such as lifestyle, while others are uncontrollable, such as age and genes. Moreover, different risk factors have different effects at different stages of life.

Researchers have formulated a consensus on some risk factors for dementia. The Lancet Commission 2020 Report identified 12 potentially modifiable health and lifestyle factors which, if eliminated, could prevent dementia.[38] Although dementia typically develops in old age, the modifiable risk factors in midlife are correlated with low cognitive function in later life. These risk factors include 1 risk factor in early life (less education), 5 risk factors in midlife (hearing loss, traumatic brain injury, hypertension, alcohol abuse, and obesity) and 6 risk factors in later life (smoking, depression, social isolation, physical inactivity, air pollution and diabetes). These early-life, mid-life and later-life factors can affect the risk of developing dementia.

2.3.1 Hypertension, stroke and dementia

There is a strong association between hypertension, stroke and dementia. Some strong evidence shows that people with high blood pressure in midlife could significantly increase the risk of dementia.[39] Hypertension is an avoidable risk factor for dementia and also for stroke. People who have suffered a stroke are more likely to develop dementia than the people without a stroke.[40-43] A stroke is strongly linked with dementia, because vascular dementia is caused by problems with the blood supply to the brain.[44] Moreover, stroke and dementia shared some of the same risk factors.[5] Therefore, the prevalence of hypertension and stroke can affect the disease burden of dementia.

In recent years, great changes have taken place in the prevalence, control, treatment and death of hypertension and stroke in China. First, the age-standardised incidence of stroke in China has been declining over the past years. [45,46] Second, with the extension of early detection and diagnosis, improved treatments, and the implementation of multidisciplinary therapies, the mortality rate of stroke in China has gradually decreased in the past two decades.[45] These epidemiological changes will lead to complex effects. On the one hand, the declining age-standardised stroke incidence could lead to a decrease in the number of people with dementia, and on the other hand, the declining mortality from a stroke could contribute to an increment in the number of people with dementia.

2.4 Interventions to prevent dementia

Although the risk factors of dementia have been recognised, this does not mean that all dementias can be prevented by modifying these risk factors. Some studies exploring the effects of the intervention on dementia incidence are from the perspective of modifiable dementia risk factors.[47] These studies mainly involve the following aspects: anti-hypertensive drugs, other medications, Mediterranean diet, cognitive interventions, exercise and physical activity interventions, and social engagement.

Among these interventions, the anti-hypertensive drugs had a better performance compared with other interventions. To be specific, despite there being no statistically significant difference between the treatment and placebo groups (HR 0.86, 95% CI 0.67-1.09), when these results were combined in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, the combined risk ratio favoured treatment (HR=0.87, 95% CI 0.76-1.00, p=0.045).[48] Another meta-analysis showed that there is a smaller reduction in cognitive function ability in the treatment groups compared with that in the control groups (weighted mean difference 0·42, 95% CI 0·30–0·53).[49] These results are also constant with one randomized controlled trial which reduced the systolic blood pressure to less than 150mm Hg in people aged over 60 years by using nitrendipine, enalapril and hydrochlorothiazide.[50] The people in the intervention group are less likely to develop dementia compared with people who took the placebo. Thus, controlling blood pressure is important in preventing dementia. In terms of other medications, the results of the trial with non-steroidal anti-inflammatory drugs are negative.[51-53] One randomized controlled trial with a duration of 24 weeks aiming to explore the effects of oral hypoglycaemic, drug rosiglitazone,151 oestrogen hormone-replacement, therapy, statins,152 vitamins, and ginkgo biloba extract showed all negative results. Two trials aiming to explore the effects of statins also showed that statins cannot prevent the incidence of cognitive impairment and dementia. A recent review study of observational study and intervention studies showed that these studies did not contain enough evidence to support adequately the effects of progestin use, various oestrogen preparations or doses, or the duration of therapy.[54,55] In sum, these studies show that anti-hypertension drugs can reduce the risk of dementia and cognitive impairment incidents, however, other drugs cannot reduce the dementia risk (such as statins and aspirin).

In terms of diet, the effect of the Mediterranean diet on improving cognitive function is small. A meta-analysis including five RCTs with 1888 participants found the Mediterranean diet had a weak effect on global cognition (SMD 0·2, 95% CI 0·0–0·5) but no benefit of the Mediterranean diet for incident cognitive impairment or dementia.[56]

In terms of interventions on cognitive function, some epidemiological studies suggested that the single domain training (memory- verbal episodic memory, or reasoning-ability to solve problems that follow a serial pattern, or speed of processing-visual search and identification) or reasoning training have some possible benefits on cognitive ability. One study (with 2802 participants aged 65 to 94) showed that some older people gained functional benefits in a 10-year follow-up after receiving 10 group sessions focusing on attention, memory, or reasoning, and improvements occurred within the trained domains.[57] Another online study (with 6742 participants aged over 60) suggested that people who received reasoning training gained generalized benefits in both trained and untrained measures of executive function, on activities of daily living and verbal learning.[58] Some commercial brain training methods claimed that these tools can to some extent prevent the decline in cognitive ability, but these effects still cannot be proved.[59]

For exercise, the studies aiming to explore the effects of interventions on exercise did not show enough positive results. To be specific, one meta-analysis (with 25 randomized controlled trials of aerobic exercise, resistance training, or tai chi) suggested that only resistance training and tai chi had effects on preventing dementia.[60] However, another meta-analysis (with 29 randomized controlled trials, only 3 studies of people with cognitive impairment) suggested that people with mild cognitive impairment and receiving aerobic exercise had better performance in the memory compared with people without aerobic exercise.[61] Another randomized controlled trial (with 100 participants with mild cognitive impairment) suggested that the participants in the intervention group (resistance training) had better performance in the cognitive-related outcome (Alzheimer’s Disease Assessment Scale-cognition), compared with people in the control group (cognitive training).[62] The researchers inferred that the potential mechanisms for exercise to prevent dementia are through indirect pathways with modifiable risk factors (obesity, hypertension, hyper-cholesterolemia, cardiovascular disease) and through direct pathways with neurological factors (increased neurogenesis, cerebral blood flow, and BDNF concentrations).[63-65] Thus, the evidence that exercise can prevent dementia is not sufficient.

For social engagement, there is no sufficient evidence suggesting that social engagement can have an effect on preventing dementia or cognitive impairment. One randomized controlled trial showed that people in the intervention group had significant improvements. However, another randomized controlled trial study compared the effects of 3 interventions (cognitive training seminars, health promotion sessions and book clubs) on cognition ability in people with memory problems, and this study found that there is no difference between these groups.[66]

To sum up, the evidence from meta-analysis or trial studies showed that the interventions on anti-hypertension have some benefits on reducing the risk of developing dementia. Some available preliminary evidence showed that the modification of several risk factors of dementia may have a beneficial effect on cognitive ability, but the improvement effects are not significant.

One of the most common shortcomings in these intervention studies is that constrained by the low incidence of dementia, these dementia-related intervention studies always require a large trial sample size and long follow-up time. The multiple risk factors of dementia could explain why the majority of intervention trial studies are inconclusive, which contributes to the development of combination intervention strategies. There are four studies (FINGER study[67,68], PreDIVA study[69], MAPT trial[70] and HATICE[71]) that examined the impacts of multimodal strategies to prevent dementia. Three of these studies (PreDIVA study, MAPT trial, HATICE) found that the multimodal strategies had no significant effects on preventing dementia or keeping cognition ability. FINGER study found that participants in the intervention group had better performance in cognition ability compared with people in the control group, but the positive association was not found in memory ability. Table 2-4 shows detailed information about studies exploring the impacts of multimodal strategies on preventing dementia.

Table 2-4: Studies about exploring the impacts of multimodal strategies on preventing dementia

Name of study	Country	Study time length	Number of participants	Age of participants	Multimodal strategies	Results
FINGER study [67,68]	Finland	Over 2 years	more than 600	Aged over 60 years	Four strategies (diet, exercise, cognitive training, and vascular management)	Participants in the intervention group had better performance in cognition ability, but not in memory ability.
PreDIVA study [69]	Netherlands	6 years	3526	Aged 70-78	Reduced vascular risk factors (smoking habits, diet, physical activity, weight, and blood pressure, blood glucose and lipid concentrations)	There is no difference in dementia incidence between intervention group and usual care group (HR 0·92, 95% CI 0·71–1·19).
MAPT trial [70]	France and Monaco	Over 2 years	1525	Aged 70 and over	Examined omega 3 polyunsaturated fatty acids and a multidomain intervention (43 group sessions integrating physical activity, cognitive training, and nutritional advice and three preventive sessions)	There is no difference in combined cognitive scores between intervention group and control group.
HATICE [71]	Netherlands, Finland, and France	18 months	2724	Aged 65 and over	Coach-supported self-management or a control platform	There is no difference in the cognitive functioning in the intervention group and control group.

Abbreviations: FINGER study: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; PreDIVA study: Prevention of Dementia by Intensive Vascular Care; MAPT trial; HATICE: healthy ageing through internet counselling in the elderly; MMSE: Mini-Mental State Exam

Data sources: [67-71]

2.5 Interventions on reduction in salt intake

Numerous recommendations for study on the identification and testing of prophylactic techniques to decrease or halt the start of cognitive decline and lessen the rate of conversion to clinical dementia in those at high risk have been made. Observational studies reveal that dietary components may in some instances alter the pathophysiological processes leading to dementia. An excessive sodium (or salt) intake has been linked to unfavourable health effects on hypertension and stroke. Hypertension is a known risk factor for dementia. And high salt intake was associated with cognitive ability decline. These associations make the exploration of the impacts of the reduction in salt intake on dementia burden possible. This section introduces the background information and discusses the rationale for the intervention on the reduction in salt intake from the perspective of (1) salt intake in China, and (2) the effects of the reduction in salt intake on health.

2.5.1 Salt intake in China

Being recognised as the “king of all flavours”, salt has played an important role in the preparation and preservation of Chinese food for thousands of years. The salt intake of Chinese people is worryingly high, in fact, twice that recommended by WHO.

In recent years, many studies have reported salt intake in China. It is difficult to estimate the salt intake accurately, because of the difficulty in measuring the amount of salt added during the cooking. There are many measurements of salt intake in these studies (diet memory, food frequency questionnaire and 24-hour urinary sodium).[72] For different salt measurement methods, different measurements are used (salt intake, sodium consumption and urinary sodium excretion). Among these methods, the 24-hour urinary sodium excretion is considered as the "gold standard", which is the most reliable method to evaluate the salt intake compared to other methods.[73-75] A dietary survey tends to underestimate the salt intake.[76] One meta-analysis of 24-hour urinary sodium in China (includes 70 studies reporting sodium intake, published between 1950 to 01 February 2019) reported that the average urinary sodium excretion in China is approximately double the recommended maximum limits.[77] To be specific, in the 1980s, 1990s, 2000s and 2010s, the urinary sodium excretion in the whole of China reached 192.8, 191.2, 201.1 and 151.5 mmol/24h, respectively. Moreover, this study also reported that the urinary sodium excretion in northern China is higher than that in southern China (Northern China: 194.5, 95% CI 187.4-201.7; Southern China: 178.2, 95% CI 169.5-186.8 in 2010s).[77] Another large national observational study (measuring the salt intake by dietary survey method and validating the results by urinary sodium excretion) also reported a similar result, that the sodium consumption in China in 1991, 2000 and 2011 reached 6.8 g/per day, 5.9 g/per day and 4.3 g/per day, respectively. Both these studies based on urinary sodium excretion and a dietary survey reported that the salt intake in China in 2010 is approximately twice that recommended by the WHO.

There are policies about the reduction in salt intake from the international perspective and domestic perspective.

From the international perspective, the WHO recommended each person should only consume 5g/ per day of salt. The United Kingdom is the pioneer of national-level salt reduction initiatives, and the British government implemented the Consensus and Action on Salt and Health (CASH) in 1996 to encourage public sectors, food manufacturers and consumers to make salt reduction efforts.[78] CASH has initiated a National Salt Awareness Week in the United Kingdom since 2001 and implemented a national salt reduction campaign with a target of 3 g/per day by 2025.[79,80]

From the domestic perspective, China has taken some actions at both the national and provincial level to reduce the salt intake in Chinese people. Nationally, Healthy China Action 2019-2030 has initiated the National Salt Awareness Week in China since July 2019 and set the recommended salt intake at no more than 5 g/per day.[81] Each week including 15th September in one year is considered as National Salt Awareness Week, whose pronunciation is similar to "just for 5" in Chinese.[82] Regionally, the local government has also taken some actions to reduce salt intake in the population. Beijing and Shanghai distributed free salt restriction spoons to their residents in 2007 and 2008, respectively.[83,84] In 2009, the Beijing government also implemented the "Healthy Beijing-Action Plan advancing population health (2009–2018)".[85] To be specific, the policy plan set a target that the salt intake for each person should be no more than 10 g/per day and encouraged residents, restaurants and institutional canteens to consume low-sodium salt.[85] The Beijing government also proposed to provide subsidies for food manufactures to produce food with low-salt. The Beijing government also implemented a specific policy to encourage residents to consume low-sodium salt substitutes in supermarkets.[84] Specifically, the residents who purchased 400g of low-sodium salt from supermarkets would receive a bonus of 75 g of the same salt and a salt restriction spoon, which were paid by the local government.[84]

2.5.2 Effects of reduction in salt intake on health

Salt intake has a significant influence on physiology. The earliest record about the association between salt intake and blood pressure can be traced to 1904.[86] Recently, more evidence about the association between high salt intake and an increase of the risk of hypertension and stroke incidents was reported.

Evidence from observational studies and trial studies contributes to the association between salt intake and blood pressure. Several studies about the association between salt intake and blood pressure were from large observational studies. The large observational study, called INTERSALT, aiming to assess the relationship between 24-hour sodium excretion and blood pressure employed data from 52 population samples in 35 countries (10074 participants aged from 20 to 59). It demonstrated that even when four population samples with very low salt intake were excluded, with an increase of 100 mmol/day sodium excretion (about 6 g salt per day) it was estimated to elevate systolic blood pressure by 9 mm Hg over 30 years.[87] Other recently observational studies, such as EPIC-Norfolk and INTERMAP also reported similar results. In addition to the observational studies[88,89], some interventional studies also reported the association between salt intake and blood pressure. The reduction of salt intake leads to a fall in blood pressure in people with or without hypertension. One Cochrane systematic review and meta-analysis includes 34 randomized trial studies with a duration of at least four weeks reported that a modest reduction in salt intake for four or more weeks contributes to a significant fall in blood pressure in both hypertensive and normotensive individuals, irrespective of sex and ethnic group.[90] To be specific, a reduction of 4.4 g/day salt was associated with a fall of 4.18 mm Hg for systolic blood pressure. The reduction in blood pressure is also associated with the decrease of cardiovascular mortality and all-cause mortality.[90] The systematic review in 2016 including 123 randomized controlled trials showed that a reduction of 10 mmHg in systolic blood pressure was associated with 13% reduction in all-cause mortality.[91] Another systematic review in 2014 including 68 randomized controlled trials showed that a reduction of 10 mmHg in systolic blood pressure was associated with 16% reduction in cardiovascular-cause mortality and 10% reduction in all-cause mortality in hypertensives.[92] High blood pressure is a risk factor for cardiovascular diseases and mortality, thus, in addition to mortality, the decrease in blood pressure was also related to the decrease in the risk of diseases.[93] To be specific, a systematic review showed that a decrease in 10 mm Hg in systolic blood pressure was associated with a 36% and 16% reduction in stroke incidence for hypertensive individuals and normotensive individuals, respectively. To sum up, the reduction in salt intake not only lowers blood pressure and the incidence of hypertension, but it is also associated with a reduction in the incidence and mortality of cardiovascular diseases.

To summarise, a modest reduction in salt intake can improve vascular health. A reduction in salt intake lowers blood pressure, which finally reduces the rates of major cardiovascular disease and mortality from all causes. These benefits underscore the value of recommendations encouraging people to reduce salt intake and provide the possibility of exploring the impacts of reduction in salt intake on the number of dementia cases and prevalence of dementia in China through the modelling method.

2.6 Review of previous literature

This section reviews the previous literature on three research topics – time trends in dementia incidence, the projection simulation studies in the worldwide and the impacts of interventions about salt intake reduction on dementia cases.

2.6.1 Previous studies about time trends in dementia incidence

There are nine studies conducted in high-income countries which reported recent calendar trends in the dementia incidence rate. Table 2-5 shows the review of time trends in dementia in longitudinal studies. Several European and North American studies recently reported declining trends in dementia incidence. To be specific, one study showed that the incidence of dementia dropped by 2.7% annually in England and Wales (ELSA) [94], and another study showed an 1.7% annual drop rate in the United States (the Framingham Heart Study)[95]. However, one cohort study showed that the dementia incidence increased in Japan from 1998 to 2012 (the Hisayama Study).[96] Furthermore, in one recent study, after correcting for non-random losses to follow-up and competing risks of death, the declining trends in dementia incidence in the United States cannot be supported.[7] In general, in most high-income countries, the incidence rates of dementia were reported as declining or stabilizing.

Some studies based on registry data have also reported time trends in dementia incidence in some areas: Germany [97], Canada (Saskatchewan [98], Ontario [99]), Netherland [100], Sweden [101] and Denmark [102]. Except for Netherland and Sweden, studies conducted in other areas all reported stabilizing or declining trends in dementia incidence recently.

One factor that needs to be considered is that the majority of time-trend analysis in high-income countries employed traditional statistical methods (except ELSA estimation), such as the Cox proportional hazards models. The traditional method may have an inaccurate estimation of calendar trends in dementia incidence because there is no consideration of competing-risk deaths and non-random losses to follow-up. Satizabal reported a downward trend in dementia incidence in the United States in 2016 by using the data from Framingham Heart Study.[6] However, one study conducted by Binder et al.(2019) did not support the downward trend in dementia incidence, which was found in a previous study.[7] Binder employed a multi-state transition modelling method and the same dataset to re-examine the downward trend in dementia incidence which was found in the previous study. The results of Binder’s study cannot support the downward trend in dementia incidence and the researchers inferred that the different results in these two studies might be because of the previous study’s improper treatment of the non-random missingness such as competing risk of mortality. [7] Thus, an accurate estimation of calendar trends in dementia incidence needs to account for non-random missingness.

Table 2-5: Results of the systematic review.

Authors	**Publish Year**	**Location**	**The study Population**	**Methods**	**Relative change (per year %)**	**Period**
Schrijvers et al [103]	2012	Netherlands	the Rotterdam Study	Poisson regression model	-2.5%	1990-2000
Grasset et al [104]	2016	France	the Bordeaux Study	Multi-states illness-death models	-3.5%	1988-2000
Matthew et al [105]	2016	England	the Cognitive Function and Ageing Studies I and II	Full likelihood modelling and Poisson regression model	-1.9%	1989/1994-2008/2011
Ahmadi-Abhari et al [94]	2017	England and Wales	the English Longitudinal Study of Ageing	Cox proportional hazard model, competing risk model and joint model	-2.7%	2002-2013
Gao et al [106]	2016	USA	the Indianapolis-Ibadan Dementia Project	Logistic regression model	-5.5%	1992/2001-2009
Satizabal et al [95]	2016	USA	the Framingham Heart Study	Cox proportional hazard model	-1.7%	late 1970s to early 2010s
Derby et al [107]	2017	USA	the Einstein Aging Study	Poisson regression model	Not reported	1993-2015
Rajan et al [108]	2019	USA	the Chicago Health and Aging Project	Logistic regression model	No trend	1994-2012
Ohara et al [96]	2017	Japan	the Hisayama Study	Cox proportional hazard model and Fine-Gray model	+3.8%	1985-2012

Data sources: [95,96,103-108]

2.6.2 Previous studies about projection simulation for the future older people.

Some previous epidemiological studies have employed the simulation modelling method to project the future situations of the older people globally. However, few studies employed the simulation modelling method to project the future burden of diseases of the older people in China. The majority of projection studies in China, envisioning the future burden of diseases for the older people, employed the extrapolation method. This section reviews the previous literature on two topics: (1) projection studies developed simulation models to predict the future care needs of the older people globally (2) projection studies for future trends in dementia, stroke, hypertension, or mortality in China.

Projection simulation model about the future care needs of the older people globally

There are twelve studies about future care needs of old people using simulation models: 4 in the UK (CFAS, IMPACT-BAM for number of people with dementia and disabilities, PACSim) [109,94,110,111], 1 in the USA [112],1 in Japan [113],1 in Canada [114], 3 in Singapore [115,116,117],1 in New Zealand [118], and 1 in both the USA and Western Europe [119]. The future older people model (FEM), which was first proposed to project future costs and health status for the older people in the United States was applied to be used in Singapore and Japan later, and also used to project future costs of diseases for the older people in the USA and Western Europe. All these twelve studies show the exploration and expectation of the modelling studies associated with caring for old people. There are some differences between these studies in study location, model type and simulation time horizon. Table 2-6 shows the summary of studies about future care needs of old people using simulation models in the world.

Table 2-6: Summary of studies about future care needs of old people using simulation models in world

Authors	Publish Year	Location	The Study Population	Name of Model	Time Horizon
Goldman et al.[112]	2005	United States	Medicare Current Beneficiary Surveys	The Future Elderly Model (micro-simulation Model, American)	2000-2030
Jagger et al.[109]	2009	England	Cognitive Function and Aging Study	-	2006-2026
Michaud et al.[119]	2011	United States and Western Europe	Health and Retirement Study	The Future Elderly Model (American and Western Europeans)	2004-2050
Légaré et al.[114]	2014	Canada	National Population Health Survey, School Leavers Survey, Labour Force Survey, National Graduate Survey, Family Historical Survey, General Social Survey, census data, and Historical Statistics of Canada	LifePaths Microsimulation Model	2001-2051
Thompson et al.[115]	2014	Singapore	Social Isolation, Health and Lifestyles Survey	-	2020-2050
Ansah et al.[116]	2015	Singapore	Panel on Health and Ageing of Singaporean Elderly, Social Isolation, Health and Lifestyles Survey	Dynamic Multi-state Population Model (with or without accounting for education)	2000-2040
Chen et al.[113]	2016	Japan	Japanese Study of Aging and Retirement	The Future Elderly Model	2014-

				(microsimulation Model, Japanese)	2040
Ahmadi-Abhari et al.[94]	2017	England and Wales	English Longitudinal Study of Ageing	Impact Better Ageing Model (State-transition Markov model)	2007-2040
Guzman-Castillo et al.[111]	2017	England and Wales	English Longitudinal Study of Ageing	Impact Better Ageing Model (State-transition Markov model)	2007-2025
Lay - Yee et al.[118]	2017	New Zealand	New Zealand Disability Survey and Health Survey	BCASO (micro-simulation Model)	2001-2020
Kingston et al.[110]	2018	England	English Longitudinal Study of Ageing, Cognitive Function and Aging Study II	Population Ageing and Simulation	2015-2035
Chen et al.[117]	2019	Singapore	The Singapore Chinese Health Study	The Future Elderly Model (micro-simulation Model, Singapore)	2020-2050

Abbreviations: BCASO: Balance of Care in an Ageing Society

Data sources: [94,109-119]

Projection studies about future trends in dementia, stroke, hypertension, or mortality in China

There are seven studies containing the projection in the future trends in dementia, stroke, hypertension, or mortality in China. Among these seven studies, four studies containing outputs related to dementia or Alzheimer's diseases-Huang's study employed simple extrapolation [31], Han's study employed the discrete Markov model [120], Li's study employed Brookmeyer and Gray's model [10], and Jia's study employed the regression method [34]. The other three studies reported outputs containing mortality, hypertension and stroke. Although Han et al. employed a discrete Markov model (similar to the IMPACT-BAM model, which was developed to project dementia and disability burden in the England and Wales) containing the dementia output, the paper considered the life expectancy with disability as the outcome of the study and did not report the dementia-related results.[121-123]

All seven studies provided the projection for future trends in diseases in China. Although subjected to the data sources, diseases definition, model design, time horizon and study outcome, the projection results are not the same and difficult to compare directly, however, these studies could shed some light on the situations of the status of the older people in China in the future. The number of cases with dementia could reach 27.3 million (19.9 million to 35.2 million) in 2030, 39.7 million (29.7 million to 50.8 million) in 2040, 49.0 million (38.0 million to 61.7 million) in 2050.[10] Table 2-7 shows the summary of the systematic review. Appendix 3 shows the search terms of the systematic review.

Table 2-7: The results of systematic review.

Author	Methods	Outcomes	Time Horizon
Huang et al.[31]	Extrapolations	Economic burden of care for individuals with dementia	2010-2050
Han et al.[120]	Discrete-time Markov model	Cognitive impairment, functional impairment, (dementia), stroke and life expectancy	2010-2030
Li et al.[10]	Brookmeyer and Gray's modelling method	Number of cases with dementia and prevalence of dementia	2020-2050
Jia et al.[34]	Regression model	Economic cost of AD	2015-2050
Li et al.[121]	Daily T-mean mortality projections	Mortality	2020s, 2050s, and 2080s
Wang et al.[123]	Markov model	Hypertension	10 years (the 2011 cohort data were used for model validation)
Li et al.[122]	Leslie model and equilibrium model	Stroke and economic cost of stroke	2020-2040

Abbreviations: AD: Alzheimer's disease

*This study employed the model with dementia outcome, but the paper considered the life expectancy with disability as the main outcome, and did not report the results related to dementia

Data sources: [10,31,34,120-123]

GBD 2019 Dementia Forecasting Collaborators employed Bayesian meta-regression model[124], MR-BRT (Meta-Regression–Bayesian Regularised Trimmed)[125] and extrapolations method [126] to provide the projection of the number of dementia cases up to 2050 in the world, including China.[1] This study projected that the number of dementia cases in China will reach 45.5 million (95% Uncertainty Interval [UI] 32.3 million to 52.1 million) in 2050.

Little is known regarding the projection of the number of dementia cases and prevalence of dementia in China accounting for the prolongation of life expectancy and the complex effects of change in mortality and incidence of stroke as well as the time trends in dementia incidence, the subject of this PhD research.

2.6.3 Previous studies about the impact of salt reduction in epidemiological studies

In view of the benefits that lowering blood pressure gained from the reduction in salt intake, the impact of intervention about a reduction in salt intake in population health is expected to be explored. The modelling methods, which can combine many aspects of reduction in salt intake, make it possible to study the impacts of reduction in salt intake on population health. In epidemiology, the modelling method is always used to model the consequences of morbidity and mortality for the size, composition, and structure of the population. Epidemiologists focus on how transitions between possible health states (for instance, presence or absence of stroke) change the prevalence proportion of these health states and life expectancy.[127-129] Models can be extended to include underlying risk factors of incidence or mortality.

Recently, some studies exploring the health gains of reduction in salt intake on population health by modelling stand out. All these studies reported that the salt reduction intervention yielded large health gains in the population. For example, one study published in 2021 conducted in England employed the multistate life table modelling estimates that the gains of achieving the WHO target of 5 g/per day per person by 2030, would avert a further 8.8 thousand ischemic heart disease cases and 12.6 thousand strokes cases by 2050.[130]

There are some differences between these studies in the modelling method, health outcomes and study locations. First of all, from the perspective of the modelling method, the majority of studies employed the macro-simulation model, only one study used the approach that combines micro-simulation modelling and macro-simulation modelling.[131] The most commonly used modelling method in studies about estimating the impact of salt reduction on health gains is the state-transition Markov model. Seven studies using the state-transition Markov modelling method were undertaken in China, the United Kingdom, India, Brazil, Cameroon, New Zealand, and Austria. Among these seven studies, four studies use multi-state life table modelling. Multi-state life table modelling is a type of modelling method with a state-transition Markov property. Some researchers chose to use the PRIME multi-state life table model[132], which is a kind of model that belongs to the multi-state-transition model, which also follows the Markov process. PRIME (the Preventable Risk Integrated ModEl) is a free and easy-to-use scenario modelling tool that generates estimates of the number of people that can be saved by public health policies that change patterns in diet, physical activity, tobacco and alcohol for a given population.[133] The PRIME multi-state life table model can help researchers to estimate the impact of changes in non-communication disease risk factors on mortality and this model can also provide researchers with the possibility of using non-special software. The University of Oxford developed an Excel-based modelling tool based on the PRIME method to estimate the impact of changes in non-communicable disease risk factors on population health. These risk factors of this model tool include diet (energy, fruit, vegetables, fibre and salt intake), physical activity and BMI and alcohol and tobacco and the outcome of this model tool is the number of averted or delayed deaths. The only study that used the approach combining the micro-simulation modelling and macro-simulation modelling method (DYNAMO-HIA) was conducted in 9 countries in Europe. This modelling method was developed by Boshuizen and other researchers in 2012.[131] Boshuizen et al. combined micro-simulation of the exposure information with macro-simulation of the diseases and survival. Second, from the perspective of health outcomes, the health outcomes of these studies are different. The majority of studies set CVD cases and CVD deaths as the modelling study health outcome, but few studies considered QALY and DALY as the model outcome. Thirdly, in terms of study location, the modelling analysis was conducted in different countries. In the past, salt reduction modelling studies mainly focused on high-income countries (e.g., New Zealand and Australia), and recently more studies conducted in middle-income or low-income countries explored the impacts of salt reduction on population health (e.g., China, Vietnam and India). As noted, several studies employed modelling methods to study the impact of a reduction in salt intake on population health. The most commonly used modelling method is a state-transition Markov model, and the most common study outcome is related to cardiovascular diseases and the study locations of these studies involve both high-income countries and low-income countries. There is an absence of studies on dementia outcomes. Table 2-8 shows the summary of the systematic review of salt reduction modelling analysis.

In short, some existing modelling studies explored the health gains from the reduction in salt intake, but little is known about the impacts of interventions on salt reduction on the dementia burden in the future in China.

Table 2-8: Summary of previous studies about salt reduction modelling analysis.

Author	Location	Intervention	Type of model	Outcome
Wang et al.[134]	China	Estimate the effects of dietary salt reduction on CVD prevention.	CVD Policy Model-China (a state-transition Markov model)	CVD cases
Marklund et al.[11]	China	Estimate the impacts of replacing discretionary dietary salt with potassium enriched salt substitutes on morbidity and CVD death.	Comparative risk assessment models	CVD death and morbidity
Alonso et al.[130]	United Kingdom	Estimate the health and economic impact of reductions in salt intake in England during the period 2003 to 2018.	PRIMEtime-CE model (a multi-state life table model)	Health and economic outcomes
Basu et al.[135]	India	Estimate the effects of salt reduction on CVD prevention.	State-transition Markov model	CVD cases
EAF et al.[136]	Brazil	Estimate the effects of dietary salt reduction on CVD prevention.	PRIME model	CVD cases
LN A et al.[137]	Cameroon	Estimate impact of a modest reduction in salt intake on blood pressure, cardiovascular disease burden and premature mortality.	Multi-state life table model	Blood pressure, CVD and mortality
Hendriksen MA et al.[138]	Europe (9 countries)	Estimate the effects of salt reduction on IHD and stroke morbidity and total mortality.	DYNAMO-HIA	IHD and stroke morbidity and total

				mortality
Wilson et al.[139]	New Zealand	Estimate the effects of achieving dietary sodium reduction targets on large health gains and cost savings.	Markov model	QALYs
Cobiac et al.[140]	Australia	Evaluate population health benefits and cost-effectiveness of interventions for reducing salt in the diet.	Multi-state life table modelling	DALY

Abbreviations: CVD: Cardiovascular diseases; PRIME: Preventable Risk Integrated Model; DYNAMO-HIA: A Dynamic Modelling Tool for Generic Health Impact Assessments IHD: ischemic heart disease; QALYs: quality-adjusted life-years; DALY: disability-adjusted life years

Data sources: [11,130,134-140]

2.7 Review of statistical methods

This PhD study includes 3 parts: time-trend analysis, modelling analysis and scenario analysis. Joint modelling and state-transition modelling were employed in this study. To be specific, joint modelling was used to estimate the recent time trends in dementia in China (Study 1); state-transition modelling was developed to project the future burden of dementia in China (Study 2) and explore the impact of intervention of reduction in salt intake on the dementia burden in China (Study 3). Table 2-9 showed the summary of statistical methods employed in this thesis.

Table 2-9: Summary of statistical methods used in this thesis.

Study number	**Objective**	**Study type**	**Statistical methods**	**R package**
Study 1	Estimate the recent calendar trends in dementia incidence rate in China.	Time-trend analysis	Joint model	JM[8]
Study 2	Project future trends in dementia burden in China based on the association between hypertension, stroke, dementia, and death.	Modelling analysis	State-transition model	Markovchain[141]
Study 3	Explore the impact of salt intake reduction on dementia burden in China in the future based on the state-transition Markov model.	Scenario analysis	State-transition model	Markovchain[141]

Data sources: Table adapted from the references provided.

2.7.1 Time-trend analysis

The work begins with time-trend analysis. Time-trend analysis is a type of longitudinal epidemiological study and can provide a view of a disease incidence and mortality. Time-trend analyses in disease incidence and mortality are often used to assist in public health needs assessments, service planning, and policy development. The Cox model, competing risk regression model and joint model are three main types of statistical method that are commonly used in epidemiological study to explore the time trends in disease incidence and mortality. Table 2-10 shows the summary of three main types of statistical methods for time trends analysis.

Table 2-10: Summary of the main types of statistical methods for time trends analysis

Example	Representative researcher	Year	Characteristics	Software
Cox proportional hazards regression model	Cox[142]	1972	Without the consideration of non-random missingness	Stata, R
Competing risk regression model	Fine and Grey[143]	1999	With the consideration of the competing events that prevent the event of interest from occurring	Stata, R
Joint model	Rizopoulos[8]	2018	With the consideration of the non-random missingness, include the non-random losses to follow-up and competing risk of deaths	R

Data sources: [8,142,143]

The Cox proportional hazards regression model is one of the most popular regression techniques for the time-to-event data. The Cox model is common to determine which variables can affect the hazard function accounting for the influence of survival time. Though the Cox model is popular in survival analysis, one of the challenges specific to the Cox model is problems of non-random missingness which may be due to loss of follow-up, dropout, study termination or detection limits which are often overlooked. For example, non-randomly censored covariates arise in the setting of Acquired Immune Deficiency Syndrome (AIDS) analyses. An important question in the field of AIDS is how best to quantify associations between potential risk factors and death from AIDS. Often, competing risks occur, such as people who die from non-AIDS causes cannot experience the event of interest, are non-randomly censored. In these cases, for a sensible and appropriate data analysis, statistical methods need to account for informative censoring. This allows us to account for the non-random missingness and gain the accurate value of statistical analysis.

The competing risk regression model is based on the proportional sub-hazards model which was proposed by Fine and Gray in 1999 and widely applied in later years.[143] The competing risk regression models can account for the competing risk events that prevent the event of interest from occurring, such as non-AIDS caused deaths mentioned above in the AIDS death analysis. The joint model is a statistical technique when researchers want to predict the time to an event with variables that are measured longitudinally and are related to the event.

The joint model can combine the two types of model-survival analysis model (such as the Cox proportional hazards model) and the multilevel regression model together. The joint model allows us to account for the non-random missingness, including the competing events and non-random losses to follow-up, and power the study appropriately.[8,144] For instance, joint models provide a more accurate parameter estimation in an HIV analysis.[145] To sum up, compared with Cox proportional hazards models, joint models can account for the informative dropouts and competing risks of death and provide a more accurate estimation of parameters in analysis.

In this study, joint models were employed to estimate the recent calendar trends in the dementia incidence rate in China. R package JM was used to fit the joint model.[8] Detailed information about time-trend analysis will be displayed in the following corresponding chapter.

2.7.2 Modelling analysis

In the stage following the time-trend analysis, the modelling analysis was conducted – one state-transition Markov model was developed. Modelling analysis is a tool widely used in public health to project future situations and explore the possible impacts of public health intervention at the population level or individual level. “Simulation model” is an umbrella term for two distinct models: macro-simulation and micro-simulation in the epidemiology study. In this study, a state-transition Markov model belonging to the macro-simulation model was employed to project future trends in the dementia burden in China. R package Markovchain was used to develop a multi-state Markov model. Detailed information about modelling analysis is displayed in the following corresponding section.

The following section includes two parts (1) the review of the methods to project the future burden of dementia, and (2) the context of overall modelling methods, including the detailed information about the one specific class of the model – the state-transition model, and uncertainty analysis in modelling methods.

The methods to project the future burden of dementia

This section summarises the statistical methods in projection studies about forecasting the future burden of dementia and reviews the advantages and disadvantages of these methods.

Overview of methods to project the future burden of dementia in epidemiological studies

Generally, there are three distinct methods used to project the future burden of dementia: extrapolations, state-transition cohort model (macro-simulation) and state-transition individual-level model (micro-simulation). Extrapolations estimate the future number of cases of dementia by simply multiplying the expected number of cases within specific age and sex strata from an existing population projection by an estimate of the current prevalence proportion of dementia within the same strata.[126] Macro-simulations estimate the future number of dementia cases by developing a multi-state Markov model based on the baseline prevalence proportion and transition probabilities between health states. Micro-simulations estimate the number of dementia cases by developing dynamic modelling of ageing and health estimation drawn with regard to the effects of the changing of risk factors and the impact of policy changes. Table 2-11 shows the main advantages and disadvantages of the extrapolations, macro-simulations and micro-simulations.

Advantages and disadvantages of the extrapolations, macro-simulations, and micro-simulations

Table 2-11: Main advantages and disadvantages of the extrapolations, macro-simulations, and micro-simulations.

Characteristics	**Extrapolations**	**Macro-simulations (state-transition Markov model)**	**Micro-simulations (state-transition individual level model)**
Extend of complexity	Simple	Not overly complex	Complex
Consider for time change in mortality		√	√
Consider for time change in dementia incidence	√	√	√
Allows identification of distributional characteristics of systems			√

Data sources: [146]

The selection of modelling method in projection analysis needs to account for the complexity of the developing model, requirements of time change in mortality and incidence and availability of data sources.

To conclude, little is known regarding the projection of the number of dementia cases and the prevalence of dementia in China. Accounting for the prolongation of life expectancy and the complex effects of change in mortality and incidence of stroke as well as the recent calendar trends in dementia incidence rate form the subject of this research. Modelling method has been applied to project the future burden of disease in the world and specifically China. Extrapolations, state-transition Markov model and state-transition individual level model are three main types of methods to conduct projection analysis. The state-transition Markov model is a characteristic account for the time trends in incidence and mortality, the transition between health states, the ability to simulate more real life and the appropriate extent of complexity, which are widely used to project the future burden of dementia.

Overview of modelling methods

Modelling has become an important tool for health technology assessment. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) modelling task force, which was founded in 2000 and works as the Professional Society for Health Economics and Outcomes Research, published a series of papers to propose recommendations for the best practice in modelling methods.[147] According to the ISPOR modelling task force's guidelines for good practice in modelling, there are three main types of modelling that are commonly used in epidemiological and health economic studies: state-transition model, discrete event model and dynamic transmission model.[147] All these three types of models can be used as tools to assess health technology and explore epidemiological problems. The difference in study problems determines the choice of type of model. For state-transition models, there are two main types: state-transition cohort model (Markov model) and state-transition individual-level model (Micro-simulation model), and these two types of models are often used to solve problems involving health, disease or treatment processes as a set of health states.[148] For the discrete event simulation model, this type of model is often employed to address the problem involving constrained or limited health resources.[149] For the dynamic transmission model, the majority of this type of model was performed by employing system dynamics, in which the transition between compartments is represented by various equations and was often used for acute infectious diseases.[150]

Recently, there has been good progress in epidemiological and health economic modelling methods. Table 2-12 shows the differences in the state-transition model, discrete event model and dynamic transmission model.

Table 2-12: The differences in the state-transition model, discrete event model and dynamic transmission model.

Model type	**State-transition model**	**Discrete event model**	**Dynamic transmission model**
Mainly Sub-type	● State-transition cohort model (Markov model) ● State-transition individual-level model (micro-simulation model)	● Micro-simulation model	● System dynamics
Characteristics	For the state-transition cohort model: ● Time-dependent parameters ● Time-to-event is important ● Repeated events ● A manageable number of states for the state-transition individual-level model: ● Individual-level behavioural entity ● Distributions	● Queuing problems ● No fixed time cycles ● Time to event	● Modelling spread of disease over time ● Often used for acute infectious diseases
Good practices	● UKPDS [151] ● IMPACT-BAM model [94]	● Animation Emergency Room [152]	● SIR model (Susceptible-Infected-Recovered Model) [153] ● Cohort Transmission model [154] ● Agent-Based Transmission model

Abbreviation: UKPDS: The United Kingdom Prospective Diabetes Study; IMPACT-BAM: Impact Better Ageing Model; SIR: Susceptible-Infected-Recovered Model

Data sources: [94,148-154]

State-transition model

State-transition modelling is an intuitive, flexible and transparent computer-based decision analysis modelling method. There are two main types of the state-transition model – the Markov cohort simulation model and the individual-level micro-simulation model. State-transition modelling conceptualizes a decision problem according to a set of health states and the transition between these states. State-transition modelling is one of the most extensive modelling technologies in epidemiological projection analysis, clinical decision analysis, health technology evaluation and health economic evaluation.

The differences in the state-transition cohort model and the individual level model are in the ease of model development, ease of model debugging, ease of communication to non-experts, Markov assumption (memoryless), decision-analytic software available, ease of modelling many different populations, danger of explosion in the number of states, distribution of outcomes, and report of individual history and computation time.[148] Siebert summarised and analysed the differences in the state-transition cohort model and state-transition individual-level model in 2012. Table 2-13 shows the differences in state-transition cohort model and state-transition individual-level model.

Table 2-13: The differences in state-transition cohort model and state-transition individual-level model.

Type of model	State-transition cohort model	State-transition individual-level model
Simplicity of model development	High	Low
Simplicity of model debugging	High	Low
Simplicity of understanding and explanation to non-experts	High	Low
Markov assumption	Yes	No
Modelling software available	Yes	Yes (requires more advanced skills)
Simplicity of modelling many different population	Low	High
Danger of explosion in number of states	Yes	No
Distribution of outcomes	Possible	Yes
Information of individual patient history	No	Yes
Computation time	Low	High

Data sources: [148]

It is appropriate and reasonable to choose a state-transition cohort model when the study problem can be framed in terms of states and the population of interest is a cohort. The elements and input parameters of a state-transition cohort model are states, transitions, initial state value, transition probabilities, cycle length, state values and logical exams performed at the start of each cycle to determine the transitions and stop criteria.

Due to modelling having become a standardised and systematic process, modelling in epidemiological, public health or the health economic studies process has formed consensus specification steps in epidemiological, public health or health economic studies. Professor M.G Myriam Hunink published Decision Making in Health and Medicine (2nd Edition) and proposed her recommendation process to develop a general model-PROACTIVE in 2014.[155] Hunink framed the modelling process into three parts: PRO-identifying the study problem and objectives; ACT-considering the alternatives, consequences, and trade-offs and IVE-finish the integration and exploration. For one of the specific types of model-state-transition cohort models, the normal process of developing a state-transition cohort model includes parts of identifying the problem, starting cohort, defining states, transition effects, heterogeneity, time horizon, cycle length and model symmetry. State-transition Markov models are a special kind of state-transition models. Markov models are one of the simplest and most wildly used methods for modelling recursive events. The Markov model represents a type of model with stochastic processes of great interest for the wide spectrum of practical applications.

The Markov model is a kind of model with a stochastic process with wide application prospects. Specifically, the discrete-time Markov model allows the transition probability between different states to be modelled by a matrix. Numerous mathematic theory books and references have explained the stochastic processes and Markov chain, see Chiang in 1968[156], Bremaud in 1999[152], Dobrow in 2016[157] and online literatures include Konstantopoulos in 2009[158], Snell in 1999[159] and Bard in 2000[160]. Table 2-14 shows the key mathematical concepts of stochastic process and Markov model.

Table 2-14: The key mathematical concepts of stochastic process and Markov model.

Concept	Explanation or equation
Stochastic process	The process involves depending on time-related uncertainty
Stochastic model	The model involves the stochastic process, also can be called probabilistic model
Markov property	The behaviour of the process after any cycle does not depend on the history before the cycle. This property is also called memoryless property.
Markov chain	$P_r(X_n = X_{n+1} \| X_1 = x_1, X_2 = x_2, \dots, X_n = x_n)$ $= P_r(X_{n+1} = x_{n+1} \| X_n = x_n)$ X_1, X_2,…, X_n denote a series of random variables.
Transition probability	The probability moves from one state to another state: $p_{ij} = P_r(X_1 = s_j \| X_1 = s_i)$ s_j denotes state j, s_i denotes state i, p_{ij} denotes the transition probability to move from state i to state j.
Transition matrix	The probability distribution of transitions from one state to another. For example, if the number of states equals 4, the transition matrix is as follows: $P = \begin{bmatrix} p_{11} & p_{12} & p_{13} & p_{14} \\ p_{21} & p_{22} & p_{23} & p_{24} \\ p_{31} & p_{32} & p_{33} & p_{34} \\ p_{41} & p_{42} & p_{43} & p_{44} \end{bmatrix}$ P denotes the transition matrix.

There are three main applications of the state-transition Markov model.

The main applications of Markov models are in the area of decision analysis, prognostic modelling and the epidemiological projection area. In terms of decision analysis, the Markov models are often used for comparing alternatives in clinical studies or health economic studies.[148] In terms of prognostic modelling, the Markov models are often used to predict the event probabilities for a single patient in clinical epidemiological studies. For epidemiological projection, the Markov models are widely used to forecast the prevalence, mortality or costs for a population in epidemiological, health economics or health policy studies. The application by Markov modelling is often projected for the events with relevance for health care or public health planning and the need to address the heterogeneity in different populations. The application of a Markov model is determined by study problems.

There are several good practices for the state-transition cohort model in epidemiological and health policy studies. One example model called the United Kingdom Prospective Diabetes Study Outcomes Model (UKPDS Outcomes Model) was developed by Clarke in 2004 to estimate the long-term impact of health interventions of people with type-2 diabetes.[151] To be specific, UKPDS Outcomes Model was employed to explore the different indicators status (life expectancy, quality adjusted life expectancy), when risk factors (blood glucose level, blood pressure, lipid levels and smoking) changed. Another example is called the IMPACT-BAM model developed by Ahmadi-Abhari and Brunner in 2017 to envision the future trends of diseases and explore the public health interventions of people in the United Kingdom.[94] Specifically, IMPACT-BAM was developed to forecast the prevalence of dementia and disability in the older people in the United Kingdom in the future, estimate the life expectancy for all the population and life expectancy for people with disability and explore the impact of smoking on cardiovascular diseases in the future.

Software for state-transition models

Some software can be used to develop decision-analytic models: TreeAge™, Decision Maker ™, AnyLogic ™, Arena, Berkely Madonna, C++, R and Excel. There are several available R packages that have been developed for the state-transition cohort model. For example, Hesim (Health Economic Simulation modelling) R package developed and maintained by Devin Incerti and other researchers provided a method for statistical analysis in economic modelling. The Hesim package can be used for developing three types of models: cohort state-transition discrete time Markov models (can be time homogeneous or time-inhomogeneous); N-state partitioned survival models; and state-transition individual continuous time models.[161] Another example is the Markovchain R package developed and maintained by Giorgio Alfredo Spedicato and other researchers which provided methods for discrete time Markov models (time homogeneous, time-inhomogeneous), continuous Markov models. There are two differences between these two R packages.[141] The first difference between these two R packages is that models are implemented as R6 classes in Hesim R package and as S4 classes in Markovchain R package. The second difference is that the Hesim package can be directly employed to simulate disease progression, quality-adjusted life-year and costs after modelling, whereas the Markovchain R package can only be used for modelling (simulating diseases progression) but needs to calculate related outcomes (such as quality-adjusted life-year and costs) manually. Moreover, there are several other R packages for other kinds of models based on the Markov Chain: msm, mcmR, hmm and mstate. Table 2-15 shows the summary of the R packages related to the Markov Chain.

Table 2-15: The summary of the R packages about Markov Chain.

R package	Author or programmer	Year	Target application model type
Hesim	Devin Incerti et al. [161]	2021	Markov models
Markovchain	Giorgio Alfredo Spedicato et al. [141]	2017	Markov models
msm	Jackson [162]	2011	Multi-state models for panel data
mcmR	Geyer and Johnson [163]	2013	Monte Carlo Markov Chain
hmm	Himmelann and .lini.com [164]	2010	Hidden Markov models
mstate	de Wreede, Fiocco, and Putter [165]	2011	Multi-state models based on Markov chains

Data sources: [141,161-165]

The Markov model can be one of the chosen models if the research problem can be conceptualized and represented by a manageable number of health states, which contains the nature and all the features related to the epidemiological problem on the ground of the characteristics of Markov model-transparency, efficiency, ease of debugging, and the ability to analyse the value of specific information.

Uncertainty analysis

The scope of application of uncertainty analysis partly relies on the decisions that the modelling seeks to support. The purpose of uncertainty analysis is to assess the certainty and robustness of the study outcomes and investigate the value of collecting additional information.[166] There are three types of uncertainty analysis: stochastic uncertainty, parameter uncertainty and model structure uncertainty.[167]

Stochastic uncertainty analysis refers to first-order uncertainty and is related to the possible events that may happen in the future. The parameter certainty refers to second-order uncertainty and is often used to solve the measurement of the error-limited sample-size with fixed or variable underlying true value. The parameter uncertainty analysis often requires researchers to choose the distributions, which could represent uncertainty in the parameters rather than the variability in the interested population. To be specific, for the parameters that could be estimated from the observed data, the chosen distribution of parameters could reflect uncertainty. It is necessary to incorporate the expert’s opinion as supplementary documents and consider for generalizability. It is required to consider the logical bounds of the interested parameter values. The parameter uncertainty analysis is often conducted by deterministic sensitivity analysis and probabilistic sensitivity analysis. In a deterministic sensitivity analysis, the input parameters were changed manually to estimate the sensitivity of the model’s outcomes. In probabilistic sensitivity analysis, input parameters (available) are changed simultaneously, with various sets of parameters being sampled from a priority distribution. Generally, it is appropriate to report both deterministic sensitivity analysis results and probabilistic sensitivity analysis results.[155] The model structure uncertainty refers to the uncertainty related to model inherent assumptions. Table 2-16 shows the concept and academic terms used in stochastic uncertainty, parameter uncertainty and model structure uncertainty.

Table 2-16: The concept and academic terms used in stochastic uncertainty, parameter uncertainty and model structure uncertainty.

	Concept	**Terms sometimes used**
Stochastic uncertainty	Random variability in model outcomes between identical patients	First-order uncertainty; Monte Carlo errors
Parameter uncertainty	The uncertainty in ascertaining interested parameter in the model	Second-order uncertainty
Model structure uncertainty	The model assumptions inherent in the model	Model uncertainty

Data sources: [167]

The deterministic sensitivity analysis includes two types of form: univariable analysis and multivariate analysis.[155] Univariable analysis, also called one-way analysis, as one of the simplest types of deterministic sensitivity analysis which examines the uncertainty by inputting one parameter changed manually (in a plausible range) while holding all other variables in the model constant at the base estimation value. Multivariate analysis is used to explore the combined effect of changed parameters by inputting two or more varied parameters (compared with the base estimation value of parameters) simultaneously. To overcome the difficulty of changed various parameters, the sensitivity analysis could be presented as the form of scenario analyses.

The probabilistic sensitivity analysis is a form of preferred method for examining the uncertainty driving from parameter imprecision in models.[168] In probabilistic sensitivity analysis, the probability distributions are applied to employ plausible ranges for important parameters rather than the varied point estimation of each parameter in models. Then samples are randomly created from these distributions through a large number of simulations (such as in the Monte Carlo simulation approach). The probabilistic sensitivity analysis allows all parameter-related uncertainty to be simultaneously reflected in the outputs of models.

One factor that needs to be noticed by researchers is that except for the number of iterations in Monte Carlo simulation which need to be reported, the distributions chosen for probabilistic and associated terms also need to be displayed in the final report.[167] Table 2-17 shows the differences in deterministic sensitivity analysis and probabilistic sensitivity analysis

Table 2-17: The summary of deterministic sensitivity analysis and probabilistic sensitivity analysis.

Type of sensitivity analysis	**Deterministic sensitivity analysis**	**Probabilistic sensitivity analysis**
Main sub-type analysis	Univariable analysis (one-way analysis); multivariate analysis	Monte Carlo simulation
Purpose	Testing how parameters effect on the model outputs or identify which parameters are important drivers of models.	Exploring uncertainty driving from parameter variables imprecision in models
Strengths	● Allow researchers to identify the parameters that are important for the model ● Easy to operate in statistical software	● Allow researchers to explore the uncertainty related to all parameters which are simultaneously reflected in the outputs of the models.
Shortcomings	● Cannot explore the uncertainty related to all parameters	● Complex to operate in statistical software ● Require long computation time
Preferred	-	Yes

Data sources: [155]

The most commonly used for uncertainty analyses are stochastic sensitivity analysis and parameter sensitivity analysis. It is useful to figure out the differences in application between these two types of sensitivity analysis. The stochastic simulation in the individual-level models, such as discrete event simulation models and state-transition micro-simulation models, which are developed around states at the individual patient level, requires the simulation of a number of virtual people. For these individual-level models, it is essential to eliminate the stochastic sensitivity when conducting the assessing of the parameter sensitivity analysis. For the cohort models, such as the Markov model, it is normally addressing the parameter uncertainty analysis rather than the stochastic uncertainty analysis.

There are four steps in the process of probabilistic sensitivity analysis. Firstly, researchers or programmers need to identify the data sources of the parameter's uncertainty. Second, researchers or programmers characterize the uncertain parameters as probability distributions. Thirdly, researchers or programmers need to define the correlations (individual-level data, regression methods). Fourthly, researchers or programmers need to propagate uncertainty through models employing the Monte Carlo simulation method.

The Monte Carlo simulation, also called second-order simulation, sometimes is employed as a sampling method to conduct probabilistic sensitivity analysis. The Monte Carlo simulation is commonly used as a class of computational algorithms in order to simulate the health behaviours of systems. The Monte Carlo simulation could be distinguished from other simulation methods by being stochastic.

Selecting appropriate and plausible distributions is important for probabilistic sensitivity analysis. There are four important properties in selecting distributions for probabilistic sensitivity analysis. Firstly, a universe of possible distributions is available in practice. Second, the choice of the probability distribution is often criticized as arbitrary. Thirdly, researchers and programmers often chose a given distribution that is relatively small. Fourthly, the parametric choices are often carried out in the statistical analysis.

O'Hagan et al. summarised the experts' opinion on probabilities interpreted as expressions of their uncertainty judgments in 2006.[169] Table 2-18 shows the commonly used probabilities distribution in the probabilistic sensitivity analysis.

Table 2-18: The summary of probabilities distribution in probabilistic sensitivity analysis.

Parameters	**Distribution**	**Detail information**
Probabilities	Beta distribution	Between zero and one
Costs	Log-normal distribution; Gamma distribution	Range from 0 to +∞
Utilities	Beta distribution; Gamma distribution	-∞ to1
Relative risks	Log-normal distribution	Ratios additive (risk ratio, hazards ratio, and odds ration) on the log scale

Data sources: [169]

There are five main strengths of the modelling methods. Firstly, the characteristics of the modelling method are systematic, explicit and quantitative, which increases the accuracy, transparency and credibility of the modelling results. Secondly, the application of modelling methods is wide. To be specific, the modelling methods can be applied in clinical studies, epidemiological studies or health economic studies. Thirdly, the availability of sensitivity analysis allows the researchers and programmers to examine the changes of assumptions. Fourth, the possibility of model validation allows the researchers to validate the results against internal and external data. Fifthly, for renewability, the modelling methods allow researchers to update the model to gain new matching results when new data are available. Because of these strengths in the aspects of characteristic, application, sensitivity analysis, validation and renewability and the modelling methods, the modelling method has become a more and more widely used method for researchers to explore clinical, epidemiological and health economics problems.

However, there are also some limitations of the modelling methods. Firstly, modelling is not an empirical approach and secondly, models may be too simplistic that cannot reflect all realistic situations. Thirdly, sometimes, if the state of art is employed, models require the researchers to conduct extensive work to gain the results. Fourthly, modelling requires the researchers to translate the results to the public. These limitations require the researchers to consider when developing the model to explore the study problem.

To conclude, modelling is a commonly used method in clinical studies, epidemiological studies and health economic studies. The state-transition models, discrete event models, dynamic simulation models are the three main types of models in modelling methods. The state-transition models include the state-transition cohort model and the state-transition individual model. The study problem determined the type of model to choose. The application of the state-transition model includes decision analysis, prognostic modelling and epidemiological projection area. Modelling methods have formed a standardised and systematic process, including concepting the model, developing the model, sensitivity analysis and model validation. The three types of uncertainty-stochastic uncertainty, parameter uncertainty and model structure uncertainty are often addressed in sensitivity analysis. Depending on whether variable parameters are input manually or sampled from distribution, the parameter sensitivity analysis can be divided into deterministic sensitivity analysis and probabilistic sensitivity analysis. The Monte Carlo simulation is a commonly used statistical method to conduct probabilistic sensitivity analysis. The strengths and limitations of modelling methods need to be considered when developing models.

2.7.3 Scenario analysis

Finally, there is a scenario analysis, a type of analysis process of projecting the expected outputs under the different situations related to changes in the values of parameters in a specific time period. Scenario analysis can be used to explore the impacts of the intervention on disease burden at the population level in different scenarios.

For epidemiological study, scenario analysis is employed to explore the impacts of public health intervention and evaluate alternatives on population health. Scenario analysis is also called scenario planning, and is a method for projecting future problems, evaluating alternatives and reflecting on the consequences of alternative futures.[170] It was widely used in economics and ecology in the early years.[171,172] Scenario analysis starts by considering current instabilities within a specific circumstance and potentially influential external drivers for change.[173] These internal instabilities and external drivers for change are then used to develop different scenario plots through a process of discussions and creative thinkings.[173] Scenario analysis is not about forecasting the future, rather, anticipating alternative futures that may come to pass.[174] The benefit of scenario analysis is that due to scenario analysis, the anticipating process occurs in a specific context, that can encourage researchers to propose different assumptions, which might significantly affect the direction of future projection. Recently, scenario analysis has become an important method in public health and epidemiology. For example, this approach has been widely applied for treating global health challenges, such as AIDS in Africa[175] and the health care delivery area[176-178], and recently, it has also been employed to anticipate the future of global research.[179] Scenario analysis can speculate on the future based on different possible assumptions.

Though there is no answer to the question of how many scenarios are optimal in a scenario analysis, 3 to 5 scenario plots are considered appropriate and reasonable by most of the researchers.[180,181] The scenario analysis process works well especially under the conditions with high uncertainty, which characterize many epidemiology issues today.[182] Hence, this process can provide a description of the future and alternative futures.

There are also some limitations of scenario analysis that need to be considered in the epidemiological scenario analysis. The first limitation of scenario analysis is that sometimes researchers overestimate the exactness of scenarios because scenario analysis is not predicting the future as each analysis step always entails evaluations of abstract and complex facts.[170] Secondly, scenario analysis sometimes requires high computing ability and is difficult for the public without a professional background to understand. Thirdly, the construction of scenarios is determined by the researcher's imagination, information and ability to participate.[178,179] To conclude, scenario analysis involves both qualitative analysis (researchers' discussion and opinions) and quantitative analysis (calculation or modelling programming).[183-185] Scenario analysis recently has been applied into the study of population ageing, mental health and dementia-related issues. Scenario analysis is a valuable tool in epidemiology and public health, which can provide recommendations for policymakers.

Conclusion

To conclude, this study used quantitative analysis to estimate the recent time trends in the dementia incidence rate, project the future burden of dementia in China and explore the impacts of potential interventions on the number of dementia cases in China. These study types involve time-trends analysis, modelling study and scenario analysis. The specific statistical methods involve a joint model and a state-transition Markov model. The detailed information about statistical analysis was shown in the following corresponding chapter.

2.8 The challenges needing to be addressed in the study

There are several challenges in projecting future trends in dementia prevalence in China.

- Case definition of dementia in longitudinal data

Although there are several common international clinical diagnostic criteria (DSM-IV, DSM-V, NINDS-AIREN, NINCDS-ADRDA) and epidemiological case definitions of dementia (ELSA for England and Wales, Framingham study for the United States), the appropriate case definition of dementia for the Chinese longitudinal study still needs to be decided carefully. The optimal case definition of dementia needs to align with clinical diagnostic criteria and refer to case definitions in other epidemiological studies, taking into account the testing methods of cognitive and functional ability and cut points of testing to be consistent with the requirements of sensitivity and specificity. The testing methods of assessing cognitive and functional ability (the basic activity of daily living and instrumental activity of daily living) and cut points of testing need to be taken into account. Thus, it is inappropriate to directly use a definition used in previous studies without censor and modification. This study is needed to establish neuropsychological norms to define cognitive impairment and functional impairment for a case definition of dementia.

- Estimation of the calendar trends in dementia incidence rate

The projection of the number of dementia cases in China only based on simple extrapolation is not accurate. The accurate projection needs to be considered for the dynamic changes in the time trends in incidence. It appears no study has employed national representative data and an appropriate modelling method to study for the calendar trends in dementia incidence rate in China. Thus, an accurate estimate of the recent calendar year trends in dementia incidence is important for future projection.

● Non-random dropouts and competing risk of mortality

In the cohort studies assessing the changes in cognitive ability, the tests of cognitive ability need to be repeated. This raises the possibility that selective dropouts of people who are frail and less able with leaving participants who are relatively 'healthy'.[186] The non-random dropouts and competing risk of mortality in the longitudinal study of old people need to be considered.

● The epidemiological trends that need to be considered to project the future burden of dementia in China

The projection of dementia prevalence is only based on a constant number which may not be accurate, because it can only reflect the population ageing process. The accurate projection of dementia prevalence in China needs to be considered for the epidemiological trends: not only the dementia incidence but also the stroke incidence as well as stroke mortality play a significant role in the projection of dementia prevalence. On the one hand, the upward time trends in dementia incidence could lead to an increase in dementia prevalence in the subsequent years. On the other hand, the decreasing trends in stroke incidence and decreasing stroke mortality could also lead to an increment in dementia prevalence. Without considering these epidemiological trends would cause an underestimation in projecting dementia prevalence. Thus, it is a challenge to address these disease determinates in epidemiological trends to project the future burden of dementia in China.

●The impact of alternative public health interventions on dementia burden in China in the future

Prevention of dementia onset is a priority with the potential to reduce not only the risks of cognitive and functional impairment of individuals but also the associated social and economic burden to the whole society. To explore the impacts of possible interventions on reducing the dementia burden in China, several alternative public health strategies need to be considered such as scenarios, and to present alternative options for outcomes resulting in varying projections and corresponding implications.

●The uncertainty in projecting the future burden of dementia in China and exploring the impacts of interventions on dementia.

Modelling is the primary method available to project the future prevalence of dementia and explore the impacts of interventions on dementia. Models predict the burden of dementia The outputs of models are based on model structure, time trends in disease incidence and mortality, and a host of parameters whose values describe the health state process being simulated. Even if the assumptions and input parameters of models reflect the situations believed to be true, there are still some inaccurate ones in the modelling process. Thus, the uncertainty of modelling analysis needs to be considered in this analysis.

2.9 Conclusion

To conclude, dementia is a major public health challenge for countries around the world and China. In terms of the basic epidemiological characteristic of dementia in China, the prevalence of dementia in China in the older people probably ranges from 5% to 6%, and this figure might increase in the future. The economic burden of dementia in China is also very large. The Chinese government has implemented some policies and adopted some actions to support people with dementia and their families. In terms of risk factors of dementia, scientists have formulated a consensus about risk factors of dementia, and these factors involve biological, behavioural and socioeconomic aspects. Several studies showed that anti-hypertension can reduce the risk of dementia and preliminary results of studies showed that modification of some risk factors has a beneficial effect on cognition function. To accurately project the future prevalence of dementia several challenges, such as case definitions of dementia and practice effects in the longitudinal study, the prevalence of risk factors and epidemiological trends need to be addressed in the study.

3 Overall aims and objectives of the thesis

3.1 Overall aims

The overall aim of this thesis is to examine the recent time trends in dementia incidence in China, project the dementia prevalence to 2035 using a Markov model and to explore the potential impact of reduction in salt intake on dementia burden to 2035 in China.

3.2 Specific objectives

Objective 1: Estimate the recent time trends in dementia incidence in China

Hypothesis: It was hypothesised that the age-adjusted dementia incidence rate in China increased between 2002 to 2014.

a) To estimate the recent time trend in the dementia incidence rate in China in the period 2002-2014 using longitudinal data with repeat measures of cognitive impairment and functional impairment.

b) To explore the role of biological and socioeconomic risk factors as determinants of the time trend in dementia incidence in China.

Objective 2: Project future trends in dementia burden in the Chinese population based on the associations between hypertension, stroke, dementia, and death, according to age, sex and calendar year.

Hypothesis: It was hypothesised that the future number of dementia cases in China can be predicted by the Markov model developed in this thesis with the time trends in the health states and population structure.

a) To estimate the prevalence proportion and number of people with dementia by age and sex in China annually up to 2035 using a state-transition Markov model that represents and synthesises the observed transitions between the health states of interest, and project observed trends into the future.

b) To estimate the age-standardised prevalence of dementia in China annually up to 2035 using a state-transition Markov model, standardised to the population structure in 2015.

c) To explore the uncertainty in these predictions at Objective 2(a) and (b) using Monte Carlo simulation with the state-transition Markov model.

Objective 3: Explore the impact of salt intake reduction on dementia burden in China in the future based on the state-transition Markov model.

Hypothesis: It was hypothesised that compared with the persisting 2008 average population salt intake, declining trends in salt intake will result in higher burden of dementia cases in China in the future, as a consequence of reduced competing mortality risks.

a) To explore the prevalence proportion and number of people with dementia in China up to 2035 under the salt intake reduction using a state-transition Markov model.

b) To compare the prevalence proportion and number of people with dementia in China in 2035 under the public health intervention on salt intake reduction, 5g/per day (recommended salt intake by World Health Organization-WHO), 3g/per day (recommended salt intake by Consensus and Action on Salt and Health-CASH), and 8.5g/per day (the midpoint between WHO recommended salt intake value and current salt intake value).

c) To project the number of people with dementia in China to 2035 under the public health intervention on salt intake reduction, based on the assumption that the change in systolic blood pressure does not affect mortality and compare the results with primary results.

d) To explore the uncertainty in these predictions at Objective 3 (a) and (b) using Monte Carlo simulation with the state-transition Markov model.

3.3 Hypotheses

The three main objectives were accompanied by three hypotheses:

a) It was hypothesised that the age-adjusted dementia incidence rate in China increased between 2002 to 2014.

b) It was hypothesised that the future number of dementia cases in China can be predicted by the Markov model developed in this thesis with the time trends in the health states and population structure.

c) It was hypothesised that compared with the persisting 2008 average population salt intake, declining trends in salt intake will result in *higher burden of dementia cases in China in the future, as a consequence of reduced competing mortality risks.*

4 Methodology

This chapter introduces the Chinese Longitudinal Healthy Longevity Study employed in this thesis. The definition of dementia is described, along with other covariates included in the analyses.

4.1 The study design

The Chinese Longitudinal Healthy Longevity Study (CLHLS) is a longitudinal study providing the information about health status and quality of life of Chinese old people.[187] The general goal of CLHLS is to have a better understanding of the determinants of healthy longevity of human beings. CLHLS encourage the use of innovative statistical methods to analyse the longitudinal survey data. The purpose of CLHLS is to explore the roles that risk factors (social risk factors, behavioural risk factors, biological risk factors and environmental risk factors) play in healthy longevity. The three characteristics-large sample size, focus on the healthy longevity and risk factors, demographic analyse strategy—have made CLHLS become an innovative database and research project.

CLHLS provided detailed data about health conditions and quality of life of 56,949 people aged over 40 years in 23 provinces, municipalities and autonomous regions of China in the period 1998 to 2018. In order to maintain representativeness, refreshment participants were recruited to study regularly. CLHLS represents 85% of the Chinese population and provides eight waves of data: 1998, 2000, 2002, 2005, 2008, 2011, 2014 and 2018. Appendix 4 showed the flow-diagram of total participants in

CLHLS between 1998 to 2018.

4.2 Variables of interests

4.2.1 Case definition of dementia

Dementia is a progressive syndrome of global cognitive impairment, which encompasses a group of neurodegenerative disorders. These are characterised by a progressive loss of cognitive function and ability to perform activities of daily living that can be accompanied by neuropsychiatric symptoms and challenging behaviours of varying type and severity.[12] The underlying pathology is usually degenerative and represents a decline from a previously higher level of cognitive functioning. The subtypes of dementia include Alzheimer’s disease, vascular, with Lewy bodies, and frontotemporal.

Clinical definitions of dementia

The clinical diagnostic criteria were compared for the specific requirements of cognitive ability and functional ability. The differences between these clinical diagnostic criteria are: DSM-IV and DSM-V refer to all-cause dementia, NINDS-AIREN refers to vascular dementia, and NINCDS-ADRDA refers to Alzheimer’s disease. The cornerstone of the clinical diagnostic criteria for dementia is deficits in two or more cognitive domains which result in a loss of ability for daily living.

Table 4-1: Clinical diagnostic criteria for dementia showing specific requirements of cognitive ability and functional ability

	DSM-IV	DSM-V	NINDS-AIREN	NINCDS-ADRDA
Cognitive criteria	Presence of both a memory disorder and impairment in at least one additional cognitive domain	Substantial impairment to be present in one or (usually) more cognitive domains.	Cognitive decline from previously higher level of functioning and manifested by impairment of memory and of 2+ cognitive domains	Cognitive or behavioural impairment involves a minimum of two of the domains
Functional criteria	Both memory disorder and impairment in cognitive domain interfere with social function or activities of daily living (ADL).	Impairment sufficient to interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental ADL, such as paying bills or managing medications.	Deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.	Interfere with the ability to function at work or at usual activities

Abbreviations: DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Version IV; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, Version V; NINDS-AIREN: National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.

Data sources: [12,188-190]

Epidemiological definitions of dementia

The definitions of dementia in cohort studies were reviewed. Even though the specific methods of measuring cognitive impairment and functional impairment are different, cohort studies formulate the basic consensus on the definition of dementia: based on DSM-IV or DSM IIIR and require (1) cognitive impairment (2) functional impairment or other clinical tests. Table 4-2 showed the review of definitions of dementia in cohort studies.

Table 4-2: A review of definitions of dementia in cohort studies

	Dementia cases definition		Based criteria	Detailed information
	Cognitive measure	**Functional measure**		
IMPACT-BAM (UK) [94]	√	√	DSM-IV, NINDS-AIREN, NINCDS-ADRDA	IQCODE and ADL assessment
CFAS (UK) [109]	√	√	DSM-IIIR, DSM IV	GMS-AGECAT
Framingham (US)	√	√	DSM-IV, NINDS-AIREN, NINCDS-ADRDA	MMSE, Neurological Exam and CDR
Rotterdam (European study) [103]	√		DSM-IIIR	MMSE, GMS, CAMDEX, neurologist test, 112europsychologist test and MRI
COAST II [22]*	√	√	DSM-IV, NINDS-AIREN, NINCDS-ADRDA, NIA-AA	MMSE, MoCa test, WHO-UCLA AVLT; FAQ; Hachinski Ischemic Score; CDR; MRI or CT
10/66 Dementia Project† [191-193]	√	√	DSM-IV	There are two methods for diagnosing dementia. The primary dementia outcome is defined as individuals scoring above a cut point of the anticipated probability of DSM-IV Dementia syndrome based on the logistic regression equation created in the 10/66 international pilot study, utilising coefficients from the GMS, CSI-D, and 10-word list learning tasks. The second technique comprises the direct use of research diagnostic criteria for DSM IV and the following subtypes of dementia: NINCDS-ADRDA Alzheimer's disease criteria, NINDS-AIREN vascular dementia criteria, and Lewy Body Dementia.

Abbreviations: IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; GMS-AGECAT: Geriatric Mental State Automated Geriatric Examination Assisted Taxonomy; MMSE: Mini-Mental State Examination; CDR: Clinical Dementia Rating; CAMDEX: Cambridge Examination for Mental Disorders of the Elderly; ADL: activities of daily living;

MRI: magnetic resonance imaging; CT: computed tomography; MoCa test: Montreal Cognitive Assessment for global cognition; WHO-UCLA AVLT: WHO University of California-Los Angeles Auditory Verbal Learning Test; FAQ: Functional Activities Questionnaire; IMPACT-BAM: IMPACT-Better Ageing Model; CFAS: The first UK Cognitive Function and Ageing Study; COAST: China Cognition and Aging Study; DSM-IIIR: Diagnostic and Statistical Manual of Mental Disorders, revision of the Version III; NIA-AA: National Institute on Aging and the Alzheimer's Association. (DSM-IV, NINDS-AIREN, NINCDS-ADRDA see Table 4-1)

***** COAST II, China Cognition and Aging Study, is a cross-sectional study in China, could provide reference for the dementia case definition.

†10/66 study is a two-phase survey (first-phase baseline survey: 2003-2007; second-phase incident survey: 2007-2010) which was conducted on all residents aged 65 and over in seven middle income countries (China, India, Mexico, Peru, Cuba, Dominica, Venezuela).

Data sources: Table is adapted from the references provided.

MMSE as an instrument for identifying dementia

The Folstein Mini-Mental State Examination (MMSE) is a cognitive function assessment with a total score 30 that assesses attention and orientation, memory, registration, recall, calculation, language and visuospatial ability.[194] The review of MMSE for the detection of dementia in people aged 65 and over, conducted by Creavin in 2016, used sensitivity (true positive detection rate) and specificity (true negative detection rate) to determine the detection accuracy of MMSE score at different cut points for dementia.[195] The higher the sensitivity, the better the ability to identify people with dementia, and the higher the specificity, the better the ability to identify people without dementia. Higher sensitivity and specificity define higher accuracy. There is a trade-off between sensitivity and specificity, because increasing the threshold score leads to the increase in sensitivity but the decline in specificity. The review based on 28 community setting studies and 6 primary care setting studies found pooled accuracy at a cut point of 24 was sensitivity 0.85 (95% confidence interval [CI] 0.74-0.92), specificity 0.90 (95% CI 0.82-0.95), which means 15% of dementia cases are misclassified as non-cases, but 10% of non-cases would be misclassified as cases. The dementia detection accuracy of MMSE supported that MMSE contributes to a definition of dementia cases in low prevalence settings, but should not be used in isolation to confirm or exclude disease (see limitations section below).[195]

The MMSE was translated into Chinese from English in 1975 and applied in clinical practice and epidemiological studies to screen for dementia. The CMMSE was administered at every wave of CLHLS and used to identify cognitive impairment. CMMSE is a modified version of the English MMSE, without questions related to reading and writing skills.[196] CMMSE has six dimensions (24 questions): orientation (5 questions), registration (3 questions), the number of foods that can be reported in one minute (1 question), attention and calculation (5 questions), recall ability (3 questions) and language (7 questions). The score range of CMMSE is 0-30 with higher scores indicating better cognitive function.

The conventional cut point in Western countries is 23/24.[197] However, education attainment level, culture and ethnic differences in China make these unstratified cut points inappropriate to screen for dementia. Li and Jia conducted a large-scale, cross-sectional study in Chinese community residents (N=9629) aged over 65 years and used the Clinical Dementia Rating score[198] (a 5-point scale used to assess six domains of cognitive and functional performance applicable to dementia) and based the diagnosis of DSM-IV, to provide a standard reference norm for the clinical value for the Chinese version of MMSE and cut point.[199] The educational-based cut point for MMSE in this study with good accuracy is recommended to be used as a part of the dementia definition criteria (no formal education: 0.87 sensitivity and 0.81 specificity; primary school 0.94 sensitivity and 0.93 specificity; secondary school or above: 0.94 sensitivity and 0.94 specificity). Table 4-3 shows the different cut points for MMSE.

Table 4-3: Cut-off points for the Chinese version of MMSE

Author	**Publication year**	**Cut points**	**Note***
Anthony et al.[200]	1982	<24 (No education-specific values)	Same as English version
Gao et al.[201]	2017	<18 (No education-specific values)	Some studies used this cut-off point to study cognitive impairment
Katzman and Zhang et al.[202]	1988	No formal education <=17, primary school <=20, secondary school or above< =24	Commonly used cut-off point
Li et al.[199]	2018	No formal education <17, primary school <20, secondary school or above <24	There is large-scale national clinical evidence support

Data sources: Table adapted from the references provided.
*The CLHLS used the revised version of MMSE to assess cognitive ability, which could reduce the influence of education

Limitations of MMSE for identifying dementia

Although MMSE could provide a brief test to assess the severity of cognitive impairment, MMSE has some limitations. The first limitation is that the sensitivity of the MMSE for mild cognitive impairment is low, though the sensitivity of moderate to severe cognitive impairment is high.[197] MMSE has high accuracy in the detection of moderate or severe cognitive impairment, though it showed the ceiling effect (low sensitivity, but high specificity) on the detection of mild cognitive impairment. The second limitation is that the items in MMSE mainly test verbal ability, and it lacks adequate items to test for visuospatial and/or constructional praxis.[203-206] Items used for assessing language ability tend to be over-simplistic and not sensitive for mild impairment.[203,206-209] MMSE is quite effective in identifying dementia, but if the interviewee's MMSE score is higher than the threshold (the result is negative), the MMSE tool should not be relied on solely to define dementia. Because of these characteristics of MMSE, MMSE should not solely be used as a diagnostic tool to identify dementia.

Dementia goes beyond cognitive impairment, also encompassing functional disability. With disease worsening, physical, cognitive and clinical problems accumulate, and the pattern of loss follows a distinct progression. The first areas requiring external support in functional status are the instrumental activities of daily living and, over time, there is a need for support in performing basic activities of daily living.[210]

Functional impairment is a characteristic of all-cause dementia, and in all clinical definitions (Table 4-1). An ADL questionnaire as well as MMSE are therefore likely to improve the specificity and sensitivity of an epidemiological case definition, and have been recommended previously.[211] Functional impairment is also characterized by the loss of ability to perform activities of daily living (ADL), including basic activities of daily living, BADL refers to maintaining self-skills, such as feeding and bathing and instrumental activities of daily living and IADL refers to complex higher order skills, such as taking public transportation.[212] Assessment of BADL contributes to discriminating the advanced stage of Alzheimer's disease, while assessment of IADL contributes to discriminating the early stage of Alzheimer's disease compared to cognitively normal people.[213] Thus, functional measurements are recommended as part of dementia case findings.

Non-MMSE cognitive testing

Beyond MMSE, there are some other cognitive tests that could be used as part of dementia case definitions in cohort studies. The commonly used cognitive testing methods include Mini-Cog[214,215], the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[216], Montreal Cognitive Assessment (MoCA test)[217], Eight-item Informant Interview to Differentiate Aging and Dementia (AD-8)[218] and General Practitioner Assessment of Cognition (GPCOG)[219]. IQCODE, GPCOG and Mini-Cog require informant information which could trace the changes in participants' memory and language ability. According to a cognitive assessment toolkit (a guide released by Alzheimer's Association to detect cognitive impairment quickly and efficiently during the Medicare Annual Wellness Visit), Mini-Cog is more suitable for distinguishing dementia from non-dementia, while IQCODE, MoCA, AD-8 and GPCOG are more suitable for distinguishing cognitive impairment from non-cognitive impairment, but not suitable for dementia case definitions.[220] Components of a full dementia case definition can vary depending on the presentation and include tests to rule in or out the various causes of cognitive impairment and assess its severity.[220] Besides cognitive tests, the full dementia case definition could also contain functional assessment (BADL and IADL), depression assessment and a review for medications that may affect cognition ability. Structural brain imaging, including magnetic resonance imaging or computed tomography, also play a role as supplementary aids in dementia case definition in cohort studies and dementia case diagnosis in clinical trials. Table 4-4 shows the total score, components, advantages and disadvantages of cognitive tests.

Table 4-4: The total score, components, advantages and disadvantages of non-MMSE cognitive tests.

The cognitive test	Total score	Components of cognitive test	Advantages	Disadvantages
Mini-Cog[214,215]	0-5	Memory, visuospatial, and executive function	• Development and validation for primary care • Multiple language accessibility • Little or no education or racial bias	• Using different word lists may influence the failure rate
AD-8[218]	0-8	Memory, orientation, judgment, and function.	• The administration time is short • Free from education bias	• Limited use in studies because published data are relatively new
GPCOG[219]	0-15	Orientation, memory, language, visuospatial, executive function, and other daily living functions	• Developed and validated for primary care • Initially useful informant component • Complaints are based on informants • Little or no educational bias • Multiple languages accessibility	• There is an indeterminate range of patient component scores that need to be scored by informants in order to be rated as pass or fail. • Low specificity of the informant component alone • Lack of data on any language or cultural bias

MoCA[217]	0-30	Memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation	• Designed to detect for mild cognitive impairment • Multiple languages accessibility • Tests seven separate cognitive domains	• Lacks data on general practice settings • Involves education bias • Limited use in studies because published data is relatively new
IQCODE (short form)[216]	16-80	Orientation, memory, language, and other daily living functions	• Validated for long time • Based on informant assessment • Little or no education bias • Available in different languages	• Not suitable to detect mild cognitive impairment

Abbreviations: AD-8: Eight-item Informant Interview to Differentiate Aging and Dementia; GPCOG: General Practitioner Assessment of Cognition; MoCA: Montreal Cognitive Assessment; IQCODE: The Informant Questionnaire on Cognitive Decline in the Elderly

Data sources: Table adapted from the references provided.

The appropriate method to define cases of dementia in CLHLS

The selection of methods for defining dementia in an epidemiological study needs to take account of clinical diagnostic criteria, and the cognitive and functional measures available, in the epidemiological context.

Cognitive impairment and functional impairment are both critical to the definition of dementia in epidemiological studies. Thus, based on DSM-V, NINDES-AIREN and NINCDS-ADRADA for the diagnostic criteria of dementia, the criterion that co-existed of cognitive impairment and functional impairment was adapted to define cases of dementia in CLHLS.

CLHLS is a cohort study with repeated measures of cognitive ability (revised version of MMSE) and functional ability (Katz index and IADL index). Although there is a weakness that the MMSE has low sensitivity of mild cognitive impairment, the research subject is dementia and MMSE still can be used as a method to assess cognitive ability for dementia. The revised Chinese version MMSE and cut points (no formal education <17, primary school <20, secondary school or above <24) were used to define cognitive impairment. The BADL index (Katz index) and IADL (IADL index) were used to define the functional impairment.

Conclusion

According to the clinical diagnostic criteria of dementia and the epidemiological definition of dementia, both cognitive ability and functional ability are important components of the diagnosis and definition of dementia in the clinical and epidemiological context. Although MMSE has shortcomings in that it is limited to assess cognitive ability to define mild cognitive impairment, MMSE could still be used as an instrument to assess cognitive ability to define dementia. Other non-MMSE cognitive testing methods could also be used as an instrument to assess the cognitive ability of dementia in the epidemiological study. The cognitive assessment (revised version MMSE) and functional assessment (Katz index and IADL index) were used as appropriate methods to define dementia in CLHLS.

4.2.2 Other variables

There are several other variables of interest in this study. These variables are related to biological, behavioural, and socioeconomic aspects.

- Biological variables: age, gender, hypertension, stroke, diabetes, hear loss
- Behavioural variables: smoking, drinking, exercise, socially isolated
- Socioeconomic variables: regional differences (urban and rural area), education

The biological factors (hypertension, stroke, diabetes and hear loss), behavioural factors (smoking, drinking, exercise, socially isolated) and socioeconomic factors (regional differences, education) were considered as risk factors in this thesis. The selection of risk factors followed the Lancet Commission 2020 Report. The Lancet Commission 2020 Report identified 12 potentially modifiable health and lifestyle factors which, if eliminated, could reduce the risk to develop dementia.[38] These risk factors include 1 risk factor in early life (less education), 5 risk factors in midlife (hearing loss, traumatic brain injury, hypertension, alcohol abuse, and obesity) and 6 risk factors in later life (smoking, depression, social isolation, physical inactivity, air pollution and diabetes). We identified and analysed the available variables in the CLHLS. Risk factors that are unavailable in CLHLS (such as traumatic brain injury, depression, air pollution and obesity) are excluded from this analysis. Stroke is also identified as a risk factor for dementia [221], despite the Lancet Commission 2020 Report excluded it as a dementia risk factor because it was a part of the definition of the vascular dementia. The prevalence of dementia was different in rural areas and urban areas in China [222]. Thus, stroke and socioeconomic status (regional differences) were included in the statistical analysis.

The covariates used in this thesis include educational attainment, disease status and health behaviours. The participants or proxy informants were asked about current disease status, health behaviours and socioeconomic status, including stroke, diabetes, hypertension, smoking history, drinking, exercise, hear loss status, socially isolated, education attainment, region area (urban or rural area). The corresponding variables were defined at each study phase. Participant or proxy informants with a self-reported doctor diagnosis of stroke were defined as with stroke. Participant or proxy informants with a self-reported doctor diagnosis of hypertension or participants with systolic blood pressure of 140 and over (systolic blood pressure>=140), or diastolic blood pressure of 90 and over (diastolic blood pressure>=90) were defined as hypertension. Participant or proxy informants with a self-reported doctor diagnosis of diabetes were defined as with diabetes. The interviewers were asked whether the respondent could hear the interview questions. Respondents who needed hearing assistance and those who could not hear the interview questions were defined as hearing loss. Participant or proxy informants who self-reported with an exercise habit currently were considered as with exercise. Participant or proxy informants who self-reported with smoking habits currently or with smoking habits records before, were defined during the study with a smoking history. Participant or proxy informants who self-reported with drinking habits currently were defined with drinking. Four items were used to assess whether people experienced socially isolated or not: “To whom do you usually talk most frequently in daily life?”, “To whom do you talk first when you need to say something about your thoughts?”, “Who do you ask first for help when you have problems/difficulties?”, “When you are sick, who usually takes care of you?” One or more items reported as “nobody” were defined as socially isolated. Participants were self-reported whether they were born in a rural or urban region.

5 Study 1: Estimated time trends in dementia incidence in China

In this chapter, the time trends in dementia incidence after correcting for mortality and non-random losses to follow-up in China were estimated, and how many of the risk factors affected the time trends in dementia incidence were explored.

5.1 Background

According to the estimation of GBD Study 2019, over 57 million people were living with dementia in 2019.[13] China accounts for approximately a quarter of dementia cases.[223] The national annual economic costs of dementia to the Chinese economy in 2010 are estimated at USD $47 billion, which increased more than 50-fold from that in 1990.[2] China's rapid ageing process is occurring at an earlier stage of economic development than other countries, posing great demands on society, particularly health and care services.[94] An accurate estimation of the temporal trend in the incidence of dementia in China is critical in order to tackle future challenges and formulate public health policies.

An estimation of the time trend in the dementia incidence rate, based only on observed cases, may not be accurate. In a longitudinal study setting, an estimated incidence based on observed cases can be biased by selective attrition. Not-at-random missingness may be due to death, or to loss to follow-up.[224,225] Dementia reduces life expectancy and death may occur before the disease is identified at follow-up.[226] This is a competing risk problem.[227] Additionally, respondents may dropout for reasons such as moving house, and permanent or temporary withdrawal from the study. To estimate the time trends in dementia incidence accurately, the potential influence of selective attrition should be considered using appropriate modelling methods.[228]

China is a significant country in which to estimate the dementia incidence trend, to date unknown. China is home to around 25% of the global population of people living with dementia, or around 15 million patients. The total population was 1.4 billion in 2019, and the number of older people was 176 million (12.9% ≥65 years). The rate of population ageing is high, and it is estimated that by 2050, one in four people aged 65 and over (26.9%), and the number of people living with dementia will have significantly increased. Therefore, it is crucial to estimate the recent time trend in incidence in China accurately in order to help face the challenge of increasing care needs for dementia in the future.

China is an upper–middle-income country. The evidence that is available, however, indicates that high-income countries have downward time trends in dementia incidence.[94] It is currently unclear, in view of its less-developed status, whether the time trend is also downward in China. The dementia incidence trend and the effect of risk and protective factors on the incidence rate are estimated in this study.

5.2 Aim

The objective of this study is to estimate the time trends of dementia incidence in China. The specifics of this study are written as follows:

- To estimate the time trends in dementia incidence in China between 2002 to 2014

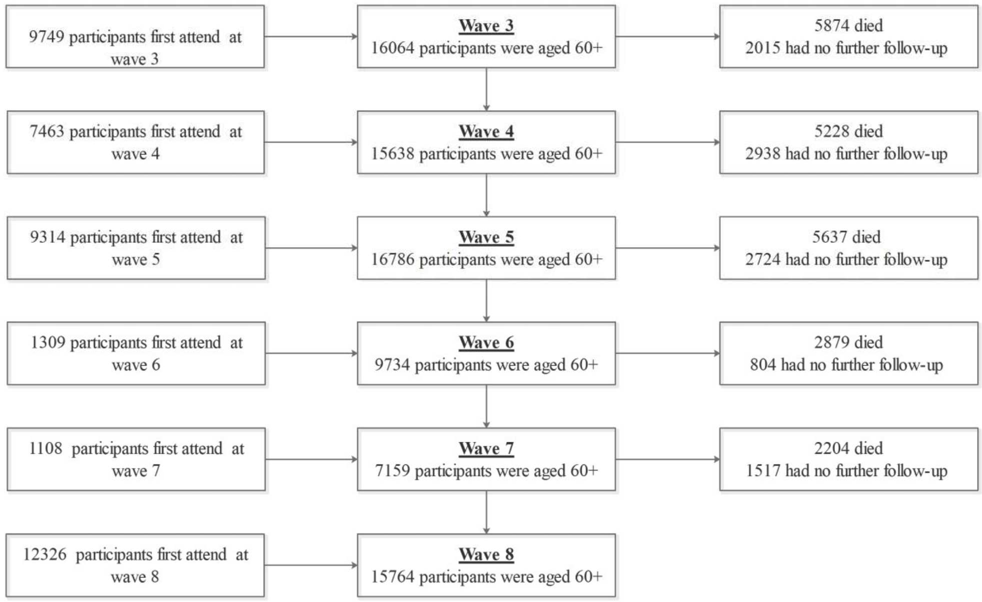
- To explore to what extent the risk factors can affect the time trends of dementia incidence in China

5.3 Methods

5.3.1 Study population

Data came from the CLHLS wave 3 (2002) to wave 8 (2018).[229] CLHLS wave 3 to wave 8 provided information about health status and quality of life of 47,584 people aged over 60 years in 23 provinces, municipalities and autonomous regions of China. In order to maintain representativeness, refreshment participants were recruited to study periodically. CLHLS represents 85% of the Chinese population and provides eight waves of data: 1998, 2000, 2002, 2005, 2008, 2011, 2014 and 2018. The data from wave 8 was used to assess cognitive function in wave 7.

Figure 5-1: The flow-diagram of participants recruited to Chinese Longitudinal Healthy Longevity Study (2002-2018)



5.3.2 Definition of dementia

The CMMSE was administered at every wave of CLHLS and used to identify cognitive impairment. CMMSE is a modified version of the English MMSE, without questions related to reading and writing skills.[196] CMMSE has six dimensions (24 questions): orientation (5 questions), registration (3 questions), the number of foods that can be reported in one minute (1 question), attention and calculation (5 questions), recall ability (3 questions) and language (7 questions). The score range of CMMSE is 0-30 with higher scores indicating better cognitive function.[230] Education is strongly associated with CMMSE score [231], and education-based cut-points have been developed to define cognitive impairment in the older people.[232] Participants or their proxy informants reported their years of education at interview. Participants were divided into three groups: no formal education, primary education (1-6 years schooling), secondary and higher education (more than 6 years schooling). The CMMSE cut points defining cognitive function were: no education <17; primary <20, and more than six years of education <24.[233] In order to exclude cases of transient cognitive impairment at the time of the survey e.g. mental disorder, participants who improved by 1.5 SD or more on the CMMSE score at the subsequent survey wave were considered free of cognitive impairment.

Participants or their proxy informants were asked about the ability to conduct BADL and IADL independently. The Katz Index and IADL Index were used to assess BADL and IADL, respectively. The six BADL items in Katz Index were: ability to bathe (get in and out of tub alone if the participant uses a tub as usual means of bathing), dress (without help), toilet (use toilet, clean self, and arrange clothes without help), transfer (get in and out of bed and chair without help), continence (ability to control urination and bowel movement completely) and feed independently. The eight instrumental activities of daily living items were: ability to visit neighbours, shop, cook, wash clothes, walk continuously for one kilometre, lift a weight of 5 kg (such as a heavy bag of groceries), crouch and stand up three times, and take public transportation. One or more ADL reported as difficult was defined as functional impairment.

We defined dementia as co-existence of cognitive impairment and functional impairment. See case definition of dementia material (Section 4.2.1 Case definitions of dementia) for additional information.

5.3.3 Covariates

The covariates used in this analysis include educational attainment, disease status and health behaviours. The participants or proxy informants were asked about current disease status, health behaviours and socioeconomic status, including stroke, diabetes, hypertension, smoking history, drinking, exercise, hear loss status, socially isolated, education attainment, region area (urban or rural area). Corresponding variables were defined at each study phase. Participant or proxy informants with a self-reported doctor diagnosis of stroke were defined as with stroke. Participant or proxy informants with a self-reported doctor diagnosis of hypertension or participants with systolic blood pressure of 140 and over (systolic blood pressure >=140), or diastolic blood pressure of 90 and over (diastolic blood pressure >=90) were defined as hypertension. Participant or proxy informants with a self-reported doctor diagnosis of diabetes were defined as with diabetes. The interviewers were asked whether the respondent could hear the interview questions. Respondents who needed hearing assistance and those who could not hear the interview questions were defined as hearing loss. Participant or proxy informants who self-reported with an exercise habit currently were considered as with exercise. Participant or proxy informants who self-reported with smoking habits currently or with smoking habits records before, were defined during the study with smoking history. Participant or proxy informants who self-reported with drinking habits currently were defined with drinking. Four items were used to assess whether people were socially isolated or not: “To whom do you usually talk most frequently in daily life?”, “To whom do you talk first when you need to say something of your thoughts?”, “Who do you ask first for help when you have problems/difficulties?”, “When you are sick, who usually takes care of you?” One or more item reported as “nobody” were defined with socially isolated. Participants self-reported the place of birth in an urban area or a rural area.

5.3.4. Deaths

A questionnaire about deceased participants was addressed to a family member or a close friend. The respondent answered questions including date of death.

5.3.5 Statistical analysis

To estimate the time trend in dementia incidence, a Cox proportional hazards model was fitted, with adjustment for age and sex, and a term for calendar year. The incident date was defined as the midpoint between the wave when dementia was identified and the previous round of investigation. To estimate the time trend in dementia incidence accounting with the competing risks of deaths, the competing risks regression model with dementia incidence as the outcome and death as a competing risk was fitted, adjusting for age, age square, sex and calendar year. To account for the competing risks of deaths and non-random losses to follow-up, a joint model was fitted, with two parts: a longitudinal model of CMMSE score and a survival model for dementia incidence [8]. A random intercept at individual level was allowed. Other covariates were years since entry, calendar year, sex and age at entry. From the joint model, the individual probability of remaining alive among those lost to follow-up was predicted, then the individual probability was transferred to the odds of incidence dementia. To estimate the time trend in dementia incidence, a linear regression model was fitted with log odds of incident dementia as outcome, with covariates of age, sex age squared and calendar year.

The equation of base joint models can be written as follows:

The sub-longitudinal model is given by:

$$Y_{ij} = \beta_0 + \beta_{age} age_{ij} + \beta_{sex} sex_{ij} + \beta_{calendar} calendar_{ij} + \beta_{years} years_{ij} + U_j + e_{ij}$$

Where Y_{ij} denotes the cognitive function score for the participants i at time j, β_0 denotes the mean cognitive function score for individuals in the reference group, β_{age} denotes average slope for the association between age and cognitive function score, β_{sex} denotes average slope for the association between sex and cognitive function score, $\beta_{calendar}$ denotes average slope for the association between calendar year and cognitive function score, β_{years} denotes average slope for the association between year since entry and cognitive function score, U_j denotes group-specific variation around the mean intercept, e_{ij} denotes the residuals.

The sub-survival model is given by:

$$h(t, X) = h_0(t) * \exp\,(\beta_{age} * age + \beta_{sex} * sex + \beta_{calendar} * calendar + \beta_{agesquared} * agesquared)$$

Where $h_0(t)$ denotes the baseline hazard, β_{age} denotes the regression coefficients associated with the hazard and age, β_{sex} denotes the regression coefficients associated with the hazard and sex, $\beta_{calendar}$ denotes the regression coefficients associated with the hazard and calendar year, $\beta_{agesquared}$ denotes the regression coefficients associated with the hazard and age squared.

To explore the effects of the change in potential risk factors on the calendar trends in dementia incidence, covariates (educational attainment, stroke, smoking, drinking, exercise, hypertension, diabetes, hear loss, socially isolated, region differences) were added into the joint model and multivariable linear regression model, and the percentage attenuation was calculated. The data were prepared and analysed using Stata/MP-15.1 (StataCorp, revision Sep 2018), and R statistical software. Rizopoulos' JM R package was used for the joint model.[8]

5.4 Results

5.4.1 Sample description

There were 14,825 men (41.8% of participants) in the study. A majority had no formal education (63.7%, 22,548 participants). Table 5-1 shows basic characteristics of the CLHLS participants at each wave. A total of 12,328 participants were ascertained to have dementia between 2002 and 2014 of whom 70.7% were female. Of the 12,328 participants with dementia, 7882 (76.3%) had no formal education.

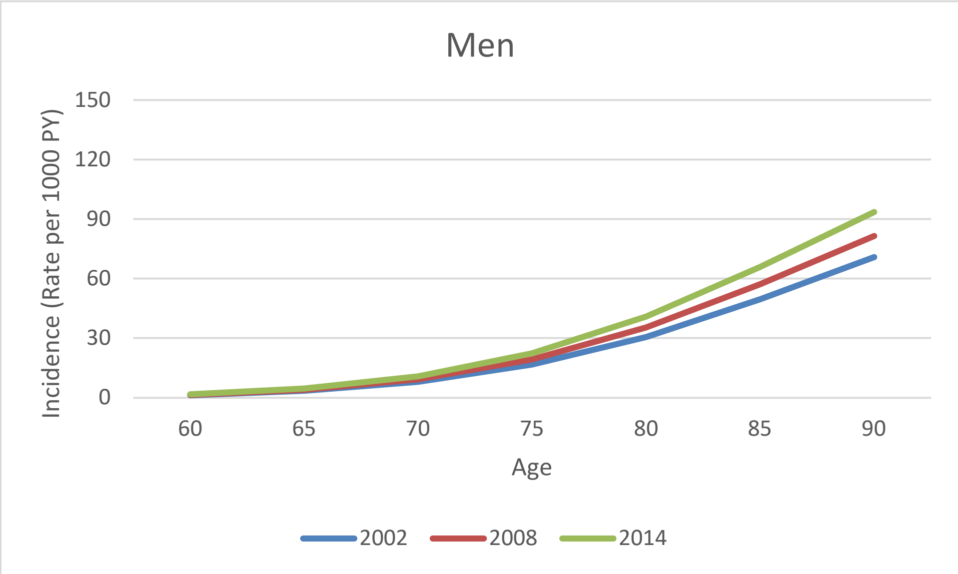
Table 5-1: Characteristics of Chinese Longitudinal Healthy Longevity Study participants at each wave.

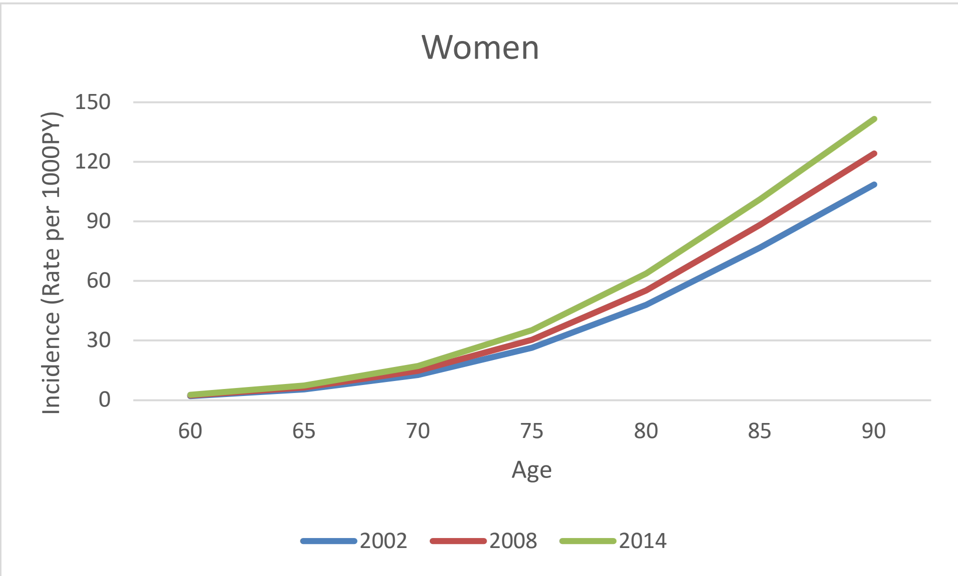
	Wave 3 (2002) N=16,064	**Wave 4 (2005) N=15,638**	**Wave 5 (2008) N=16,786**	**Wave 6 (2011) N=9734**	**Wave 7 (2014) N=7159**
Sex (male)	6845 (42.6%)	6704 (42.9%)	7133 (42.5%)	4387 (45.1%)	3301(46.1%)
Age	86.33 (11.7)	86.16 (11.7)	87.15 (11.6)	85.9 (11.3)	85.4(10.6)
Education level					
Without education	9880(61.5%)	9525(60.9%)	10510(62.6%)	5637(58.2%)	3962(55.9%)
Primary education	4511(28.1%)	4448(28.4%)	4593(27.4%)	2968(30.6%)	2277(32.1%)
Secondary or higher education	1568(9.8%)	1603(10.3%)	1633(9.7%)	1088(11.2%)	847(12.0%)
Smoking history	5545 (34.5%)	5651(36.1%)	5628(33.5%)	3548 (36.5%)	2760 (38.6%)
Current drinkers	5275 (32.8%)	5428 (34.7%)	5419 (32.3%)	3501 (36.0%)	2747(38.4%)
Exercise	5056 (31.5%)	4783 (30.6%)	4604 (27.4%)	3179 (33.2%)	1835(25.6%)
Hypertension	5947(55.7%)	7385(47.3%)	7846(46.7%)	5403(55.5%)	4166(58.2%)
Diabetes	337(2.1%)	393(2.5%))	409(2.4%)	379(3.9%)	370(5.2%)
Hearing loss	5089(31.7%)	4909(31.4%)	5951(35.1%)	2912(29.8)	2026(28.2%)
Stroke	767(4.8%)	783(5.0%)	958 (5.7%)	750(7.7%)	574(8.0%)
Socially isolated	2007(12.5%)	1291 (8.3%)	1743 (10.4%)	799(8.2%)	422(5.9%)
Region (urban area)	2498(15.6%)	2426(15.5%)	2170(12.9%)	1027(10.6%)	684(9.6%)

5.4.2 Calendar trend in incident dementia

The calendar year trend in age-sex specific dementia incidence was obtained without correcting for the competing risks of mortality and non-random loss to follow-up, from a Cox model. After adjusting for sex and age, dementia incidence increased 3.6% per year in relative terms (hazard ratio [HR]=1.036, 95% CI 1.008-1.064). The magnitude of the calendar year trend in age-sex adjusted dementia incidence, considering risk of mortality, was obtained from a competing risks model. With this model, the age-sex adjusted dementia incidence increased 2.6% per year (HR=1.026, 95% CI 1.024-1.026). The calendar trend in dementia incidence accounting for competing risk of mortality and non-random losses to follow-up was obtained from a joint model and linear regression model. With this model, age- and sex-adjusted dementia incidence increased 2.5% per year (odds ratio [OR]=1.025, 95% CI 1.024-1.026). Women had higher odds of dementia compared with men (OR=1.468, 95% CI 1.461-1.476). Table 5-2 shows the time trends of dementia incidence in China. Figure 5-2 A and B show the time trends in dementia incidence among men and women, respectively.

Figure 5-2: The time trends in dementia incidence among men and women, respectively.





5.4.3 Dementia incidence according to age and sex

After correcting for competing risks of mortality and non-random loss to follow-up, dementia incidence at age 70, 80, 90, 100 among men in 2002 was 7.96, 30.51, 70.94, 102.95 (1000 person years [PY]) respectively, while among women it was 12.65, 47.85, 108.69, 154.76 (1000 PY) respectively. Dementia incidence in 2012 at age 70, 80, 90, 100 among men was 10.74, 40.83, 93.62, 134.26 (1000 PY) respectively, while among women it was 17.04, 63.65, 141.60, 198.50 (1000 PY) respectively. Table 5-2 shows the age-sex specific dementia incidence in China corrected for mortality and non-random losses to follow-up

Table 5-2: The age-sex specific dementia incidence in China corrected for mortality and non-random losses to follow-up.

	2002 (Rate for 1000PY)		2008 (Rate for 1000PY)		2014 (Rate for 1000PY)	
	Men	Women	Men	Women	Men	Women
70	7.96	12.65	9.24	14.68	10.74	17.04
80	30.51	47.85	35.30	55.22	40.83	63.65
90	70.94	108.69	81.56	124.21	93.62	141.60
100	102.85	154.76	117.65	175.56	134.26	198.50

Abbreviations: PY, person years

5.4.4 Effect of changes in risk factors on time trends in dementia incidence

Using the model accounting for competing risk of mortality and non-random loss to follow-up, the effects of potential explanatory factors (education attainment, hypertension, stroke, diabetes, hear loss, smoking, drinking, exercise, socially isolated, regional differences) for the calendar trends were examined.

After adjusting for the age, sex, age squared, calendar year and potential risk factors, dementia incidence increased 2.0% per year. Changes in available protective and risk factors accounted for about 20% of the time effect in dementia incidence. Table 5-3 shows the effect of risk factors on calendar trends in dementia incidence in China.

Table 5-3: Attenuating effects of adjustment for time-varying risk factors on calendar trends in dementia, CLHLS, 2002-2014.

	Annual changes in dementia incidence	
	OR (95% CI)	Relative Annual Change (%) (95% CI)
Calendar Trend (per year)* adjusted for	1.025 (1.024-1.026)	+2.5% (2.4%-2.6%)
Education	1.027 (1.026-1.029)	+2.7% (2.6%-2.9%)
Stroke (cerebrovascular disease)	1.014 (1.012-1.015)	+1.4% (1.2%-1.5%)
Hypertension	1.032 (1.031-1.034)	+3.2% (3.1%-3.4%)
Diabetes	1.029 (1.028-1.030)	+2.9% (2.8 %-3.0%)
Drink	1.029 (1.028-1.030)	+2.9% (2.8%-3.0%)
Smoke history	1.025 (1.023-1.026)	+2.5% (2.3%-2.6%)
Current exercise	1.030 (1.028-1.031)	+3.0% (2.8 %-3.1%)
Hearing loss	1.021 (1.019-1.022)	+2.1% (1.9%-2.2%)
Socially isolated	1.018 (1.017-1.019)	+1.8% (1.7%-1.6%)
Region (urban area)	1.022 (1.020-1.023)	+2.2% (2.0%-2.3%)
Multivariable Adjusted	1.020 (1.017-1.022)	+2.0% (1.7%-2.2%)

Abbreviations: OR, odds ratio; CI, confidence interval

*Base model is adjusted for age, sex, age squared and calendar year

5.4.5 Sensitivity analysis

In order to address uncertainties in the dementia incidence trend estimates, sensitivity analysis was conducted. The sensitivity analysis used two different cut points for the CMMSE: <18 and <24, as criteria for cognitive impairment in the analysis. Using 24 cut point as the criterion of cognitive impairment, the dementia incidence increased 3.8% by each year after considering the competing risk of deaths and non-random loss to follow-up (HR=1.038, 95% CI 1.0121-1.065). Using 18 cut point as the criterion of cognitive impairment, the dementia incidence increased 3.0% by each year after considering the competing risk of deaths (HR=1.030, 95% CI 1.003-1.057).

5.5 Discussion

As far as is known, this is the first study to estimate the trend in dementia incidence in a middle-income country. This longitudinal study employed joint modelling with time-to-event data to explore the time trends in dementia incidence for 12 years in China (2002-2014). According to our estimate adjusted for survival bias, the age and sex adjusted incidence rate of dementia among the older people in China increased by 2.5% per year over 12 years to 2014.

Recently, several European and North American studies reported declining trends in dementia incidence. Table 2-5 shows the review of time trends in dementia in longitudinal studies. One study showed that the incidence of dementia dropped by 2.7% annually (the English

Longitudinal Study of Ageing).[94] However, one cohort study showed that the dementia incidence increased in Japan from 1998-2012 (the Hisayama Study).[96] In general, in most high-income countries, the incidence of dementia is declining or stabilizing.

Some studies based on registry data have also reported time trends in dementia incidence in some areas: Germany [97], Canada (Saskatchewan[98], Ontario [99]), Netherland [100], Sweden [101] and Denmark [102]. Except for Netherland and Sweden, studies conducted in other areas all reported stabilizing or declining trends in dementia incidence recently.

Although the population and number of dementia patients in China is large, there are no national longitudinal studies to date on trends in dementia incidence. A small area study conducted in Xicheng District, Beijing, showed an increased trend in dementia incidence from 1997 to 2007 [9], however, this study is not representative of the whole country. Another study used data from Global Burden of Diseases 2019 reported that the increasing time trends in dementia incidence in China (1990-2019) , which is consistent with this study.[234] Another study used an age-period-cohort model found that prevalence of self-reported ADL impairment, tested physical performance and cognitive impairment increased between 1998 and 2014, consistent with this study.[235] The researchers thought this might be because of the prolonging of life expectancy in recent years. In this study, it was found that the age-sex standardised prevalence of dementia was also increasing over the 12 years. It was considered that the increasing trends in the number of dementia cases were not just because of the increase in life expectancy, but also due to the increase in dementia incidence.

China is going through an epidemiological transition.[236] A systematic review of the prevalence of dementia in the East Asian incidence of dementia will increase in the future decades which will also indicate East Asian countries enter the B Stage of "longer expectancy but unhealthy aging".[237] However, this hypothesis is not supported by the evidence. The increasing trends in dementia incidence found in this study are different from the conclusion found in the United Kingdom, France, Netherlands and the United States. The findings of this study are that the dementia incidence among the older people in China is increasing, which seems to reflect that China has entered the B stage of "longer expectancy but unhealthy aging".

When the possible reasons for the increase in the incidence rate are interpreted, one hypothesis related to increasing time trends in diabetes incidence and unhealthy lifestyle emerges.

Firstly, non-communicable diseases may explain the increasing trends in dementia incidence. Although China has undergone the stage of many deaths due to hunger, diarrhoea and war, China still faces the threat of non-communicable diseases. According to previous studies, stroke, obesity, mid-life hypertension and diabetes are risk factors for dementia.[238] In recent years, the prevalence of obesity, hypertension, and diabetes has increased in China [239-241] . This study believes that noncommunicable diseases may contribute to the increase of dementia incidence in China.

Secondly, the unhealthy lifestyle may partly explain the increase in dementia incidence. These unhealthy life factors include drinking, smoking and unhealthy dietary habits. China is one of the countries with the fastest growth in alcohol consumption, and in recent years, the proportion of people who smoke heavily is also increasing.[242,243] In addition, China has experienced a nutritional transition: from traditional plant-based diets to a westernized diet which consists of highly-processed foods with added animal products.[244] The mid-life risk factors are associated with dementia incidence in later life. [5] Therefore, the unhealthy lifestyle in China may partly cause the increase in the incidence of dementia.

5.5.1 Strengths of the study

To our knowledge, this study is the first study to estimate the recent time trend in dementia incidence in a middle-income country. This study has some strengths in the perspective of studying samples, statistical methods and research design.

Firstly, from the perspective of the study sample population, this study employed data from CLHLS (covers 23 provinces or area in China for 12 years). A sufficiently large study sample covering all levels of educational attainment provides a representative sample of the dementia incidence in Chinese older people people. A sufficiently long tracking time (2002-2014) also allows better exploration of the recent time trends in the dementia incidence in China.

Secondly, from the perspective of statistical methods, this study employed the joint models which can allow accounting for the competing risk of death and non-random losses to follow-up in the time-to-event data. Compared with traditional available statistical modelling (Cox regression model), the joint model through tracking changes in intrinsic biomarkers and linking the longitudinal model and survival analysis model can avoid any selection bias of missingness in the cohort data.

Thirdly, from the perspective of research design, this study chose longitudinal data to explore the time trends in the dementia incidence rate rather than cross-sectional data to explore the epidemiological problems with dementia in any given year. Several previous studies employed cross-sectional data to estimate epidemiological characteristics of dementia in one specific year, which might lead to the misclassification of dementia (without accounting for the transient cognitive impairment in one time of research). In this study, cohort study data tracked over 12 years and appropriate case definitions were both used to estimate the time trends in incidence rate in China.

5.5.2 Limitations of the study

Despite the strengths of this study, there are some limitations which also need to be mentioned. The first limitation of this study was about the study population sample. Initially, although CLHLS covers a large sample of China (23 provinces in China), it still does not possess data from other areas (Guizhou, Yunnan, Xizang, Gansu, Qinghai, Ningxia, Xinjiang, Inner Mongolia, Hong Kong, Taiwan, and Macau). Because the trends in dementia incidence may be dissimilar between the east-west area and urban-rural region, the fact that the sample data do not cover all the Chinese regions may influence the representativeness of the data.

The second potential limitation is caused by the recall bias and covariate definition change over time. The health status (chronic disease) and lifestyle factors of CLHLS were collected by self-reporting. This process of covariate definitions may lead to recall bias and changes of diagnosis criteria over time.

5.6 Conclusion

In conclusion, an annual 2.5% increase in dementia incidence was found from this study after correcting for competing risks of mortality and non-random losses to follow-up between 2002 to 2014. Changes in risk factors account for about 20% of the time effect in dementia incidence.

6 Study 2: Projected future burden of dementia in China: Based on Life-cycle Ageing Model (LAM)

In this chapter, the Markov model - Life-cycle Ageing Model (LAM) - which concentrates on hypertension, stroke, dementia, and mortality in the population was developed in order to project the future number of dementia cases and future prevalence proportion of dementia in China. The varying calendar effects on dementia incidence were applied in the LAM to test how much of the changes in the hypothesis on time trends in dementia incidence can affect future trends in dementia prevalence. A probabilistic sensitivity analysis was conducted to test the robustness of the model, and a validation analysis was conducted to demonstrate that the modelling method is appropriate for the projection of the future burden of dementia in China.

6.1 Background

Dementia is a global challenge that will persist for the foreseeable future. According to the GBD Study 2019, over 57 million people were living with dementia in 2019.[1] China is home to around 25% of the global population of people living with dementia, or around 15 million patients.[1] The national annual economic costs of dementia for the Chinese economy in 2010 are estimated at USD $47 billion, which increased more than 50-fold from that in 1990.[2] Providing reliable forecasting of the prevalence of dementia in the future is crucial for clinicians and policymakers to meet future challenges.

The estimation of the number of people with dementia based on a constant point-in-time prevalence proportion might be not reliable, because this could only reflect population ageing. A more accurate projection of the future dementia burden requires consideration of possible time trends in dementia incidence and changing mortality rates, as well as population ageing.

In addition, the epidemiology of stroke plays an important role in the projection for dementia prevalence. Specifically, the reduction in stroke mortality led to a prolongation of life expectancy[4], however, the decrease of vascular factors - like behavioural and biomedical risk factors which are shared by cognitive and functional impairment–can also lead to a decrease in dementia incidence [5]. Without considering these epidemiological trends, estimating and projecting dementia prevalence would be inaccurate. Thus, to project future dementia prevalence precisely, these factors need to be considered.

To project the prevalence of dementia in China, a novel state-transition Markov model called the Life-cycle Ageing model (LAM) was developed. The LAM is a probabilistic Markov model which enables the prediction of future calendar trends in dementia prevalence through health states of hypertension, stroke and dementia to death.

Little is known regarding the projection of the number of dementia cases and prevalence of dementia in China accounting for the prolongation of life expectancy and the complex effects of change in mortality and incidence of stroke as well as the time trends in dementia incidence, the subject of this research.

6.2 Aims

The overall aim of the study was to project future trends in the burden of dementia in the Chinese population based on the associations between hypertension, stroke, dementia, and death, according to age, sex and calendar year. The specific aims are as follows:

- To estimate the prevalence proportion and number of people with dementia by age and sex in China annually up to 2035 using a state-transition Markov model that represents and synthesises the observed transitions between the health states of interest, and project observed trends into the future.

- To estimate the age-standardised prevalence of dementia in China annually up to 2035 using a state-transition Markov model, standardised to the population structure in 2015.

- To explore the uncertainty in these predictions using Monte Carlo simulation with the state-transition Markov model.

The research questions are as follows:

(1) What will the number of people with dementia be in China up to 2035 using a state-transition Markov model?

(2) What will the crude prevalence of dementia be in China up to 2035?

(3) What will the age-standardised prevalence of dementia be in China up to 2035 using a state-transition Markov model (standardised to population

structure in 2015)?

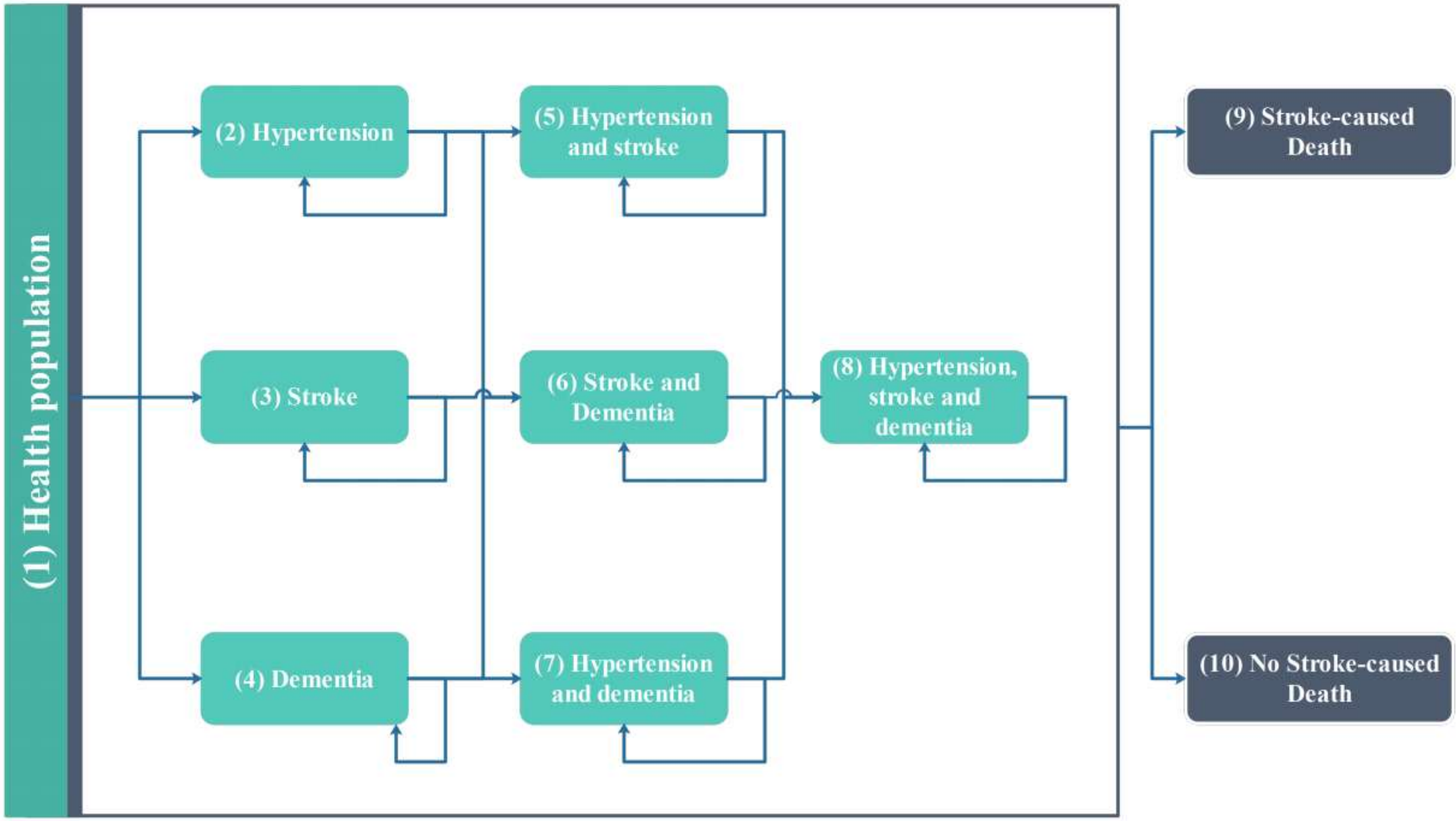
(4) How much will the uncertainty of the number of people with dementia be in the future in the LAM model?

The state-transition Markov model – Life-cycle Ageing Model (LAM) – which concentrates on hypertension, stroke, dementia, and mortality in the population was built. Here, the LAM was constructed to project the future burden of dementia in China.

6.3 Methods

The state-transition Markov model was constructed of hypertension, stroke, dementia, and death based on data from a sample of Chinese population. The Figure 6-1 shows the structure of LAM.

Figure 6-1: The structure of LAM



6.3.1 Case definition

Dementia was defined with the co-existence of cognitive impairment and functional impairment. The CMMSE was administered at every wave of CLHLS and used to identify cognitive impairment. CMMSE is a modified version of the English MMSE, without questions related to reading and writing skills. Education is strongly associated with the CMMSE score [231], and education-based cut points have been developed to define cognitive impairment in the older people.[232] Participants or their proxy informants reported years of education at interview. Participants were divided into three groups: no formal education, primary education (1-6 years schooling), secondary and higher education (more than 6 years schooling). The CMMSE cut points defining cognitive function were: no education <17; primary <20, and more than six years of education <24. In order to exclude cases of transient cognitive impairment at the time of the survey e.g. mental disorder. Participants who improved by 1.5 SD or more on the CMMSE score at the subsequent survey wave were considered free of cognitive impairment.

Participants or their proxy informants were asked about their ability to conduct BADL and IADL independently. The Katz Index and IADL Index were used to assess BADL and IADL, respectively. One or more ADL reported as difficult was defined as functional impairment.

See case definitions of dementia material (Section 4.2.1 Case definitions of dementia and Section 5.3.2 Definition of dementia) for additional information. The definition of other covariates could be found in other variables material (Section 4.2.2 Other variables).

Participant or proxy informants with a self-reported doctor diagnosis of stroke were defined as with stroke. Participant or proxy informants with a self-reported doctor diagnosis of hypertension or participants with systolic blood pressure of 140 and over (systolic blood pressure>=140), or diastolic blood pressure of 90 and over (diastolic blood pressure >=90) were defined as hypertension.

A questionnaire about deceased participants was addressed to a family member or a close friend. The respondent answered questions including date of death.

6.3.2 Statistical analysis

Overview of LAM model

To project the dementia prevalence to 2035, a life-cycle ageing model - LAM model, a state-transition Markov model was constructed. An LAM model is a probabilistic discrete time Markov model. The constructed state-transition Markov model of dementia, hypertension, stroke, stroke-cause mortality and all-cause mortality was based on data from a sample of the Chinese population. LAM models the transitions and progress of the Chinese population aged 35 and over through health situation states of diseases and deaths.

The Markov model was populated with age-sex-specific prevalence estimates, and the transition probabilities were applied in each annual iteration to predict the number of deaths and prevalence proportion of various LAM health states for the following year. The LAM projects the future prevalence proportion of dementia, stroke, hypertension, stroke-cause mortality and all-cause mortality.

Input data in LAM include the Chinese population structure, the age-sex initial prevalence at start year, and age-sex transition probabilities at each year between health states. The number of Chinese people for each age and sex at year 2008 (the beginning year of the LAM model iterations) was obtained from the China Statistical Yearbook of the National Bureau of Statistics (NBS) in China.[245] The age-sex specific prevalence for each health state was pooled from CLHLS, and was attributed to the midpoint of the data collection timeframe (2008). The curve fitting tool in MATLAB was employed to obtain data for the specific year of age, beginning at age 35 years.

The age-sex specific transition probabilities in LAM for 2008 were calculated by fitting logistic regression models on CLHLS, with the targeting state as outcome and terms for age, sex and a variable defining starting state. The transitions between two sequential waves in CLHLS were pooled so that the individual contributed as many observations as corresponded to the number of three-year intervals. The logistic regression models were applied to estimate the transition probabilities in LAM rather than Cox proportional hazard models, because the interval between the data collected wave is relatively stable and the odds ratio can be transferred to one-year transition probabilities. The equation applied to transfer the three-year transition probabilities (TTP) to one-year transition probabilities (OTP) was as follows.

$$OTP = 1 - e^{((\ln(1-TTP))/3}$$

The transition probabilities to stroke death and non-stroke death were calculated by combining CLHLS and GBD 2019.

The time trend in dementia incidence was observed from the previous study (study one). It was assumed that the incidence of dementia would increase initially (as observed in CLHLS and also in other studies in China) and then decline (as observed in high-income countries). To make the numeric value transition smoothly, the curve was fitted with a piecewise function. The time trends in stroke incidence and stroke mortality from 2002 to 2014 were obtained from GBD 2019. Appendix 11 shows the detailed information about calendar effects on transition probabilities.

Statistical software R was employed to develop the state-transition Markov model, and STATA-15 was employed to conduct data cleaning and data management. R package Markovchain, written and maintained by Giorgio Alfredo Spedicato et al,. was used to develop LAM.[141]

Appendix 7 shows the process of developing LAM. Appendix 8 shows the data sources and input parameters in LAM. Appendix 9 shows description of health states in LAM. Appendix 10 shows description of transition probabilities in LAM. Appendix 12 shows the matrix calculations of LAM. Appendix 13 shows the calculation of transition probabilities. Appendix 14 shows the assumptions in the LAM.

Sensitivity analysis

To explore the uncertainty in this study, a deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted. To explore how much the specific parameters affect the outputs of the LAM model, the deterministic sensitivity analysis was conducted by inputting the varied parameter (time effect on dementia incidence) manually. To calculate the uncertainty interval, the probabilistic sensitivity analysis was conducted. The selected probability distribution arose from a plausible range from observed data. Then the Monte Carlo simulation method was used as the sampling method in this step. The detailed information is shown in the following section (Section 6.5 Sensitivity analysis).

Validation

To validate the model, the outputs of LAM model were compared with internal and external resources. The detailed information is shown in the following section (Section 6.6 Validation).

6.4 Results

6.4.1 Projected number of dementia cases in China by 2035

According to the analysis of forecasting the future burden of dementia in China up to 2035, the number of cases with dementia is projected to increase significantly in 2035. The number of cases with dementia is projected to increase from 6,549,234 in 2010, to 17,075,733 in 2020, to 27,094,979 in 2030, and to 30,563,654 in 2035. The number of people with dementia is predicted to be five times higher in 2035 than in 2010. The increase in the number of people living with dementia mainly occurs in the 65-75 age group population, which might be due to the baby boom in 1960s in China.

6.4.2 Projected prevalence of dementia in China by 2035

The crude prevalence in people aged 65 and over in China is set to increase from 4.81% in 2010, 8.53% in 2020, 10.46% in 2030, and to 10.56% in 2035.

The age-standardised prevalence (standardised to population structure in 2015) in people aged 65 and over for all the population is forecast to increase from 4.79% in 2010, 8.68% in 2020,10.43% in 2030, and to 10.46% in 2035. The age-standardised prevalence in people aged 65 and over for men is forecast to increase from 3.84% in 2010, 6.62% in 2020, and 7.64% in 2035. The age-standardised prevalence in people aged 65 and over for women is forecast to increase from 5.69% in 2010, 10.44% in 2020, and 12.63% in 2035. Both prevalence of dementia in men and women are forecast to increase to 2035, and the prevalence of dementia increase would be faster in women than men.

Figure 6-2 shows the number of people with dementia up to 2035. Appendix 15 shows the projected number of cases with dementia in all the population with a 95% uncertainty interval. The methods, assumptions, and results about calculating the uncertainty interval (probabilistic sensitivity analysis) are in the following section 6.5 sensitivity analysis.

The projected number of dementia cases to 2035 was shown in Table 6-2. Figure 6-3 shows the age-standardised prevalence of dementia.

Appendix 16 shows the projected specific number of dementia cases to 2035 in China for the total, males and females.

Figure 6-2: The projected number of people with dementia in LAM

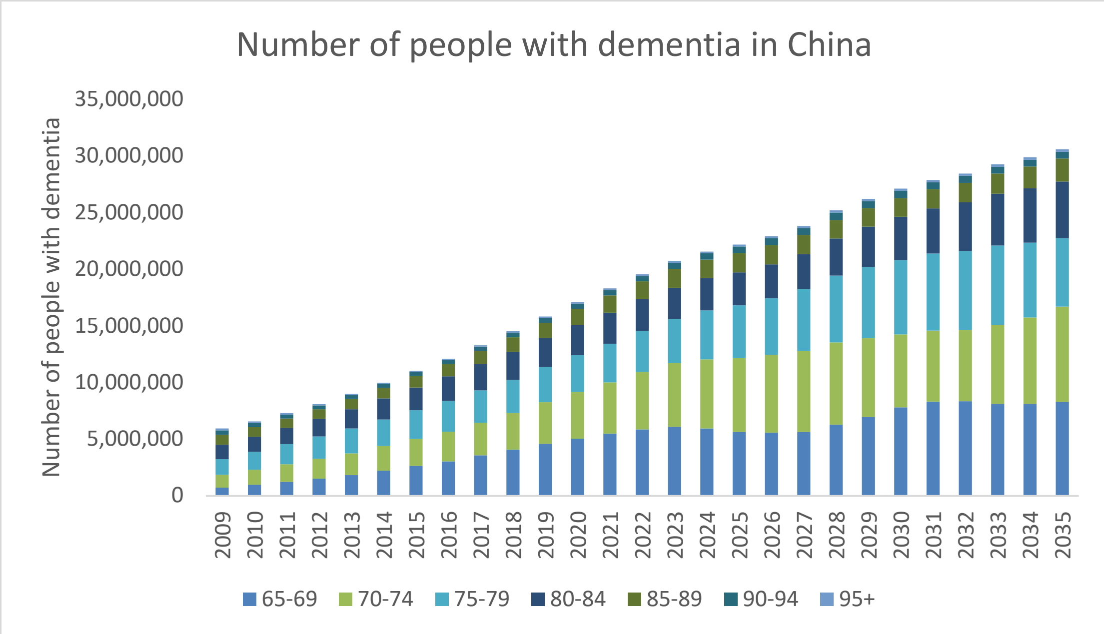


Figure 6-3: The age-standardised prevalence of dementia in China

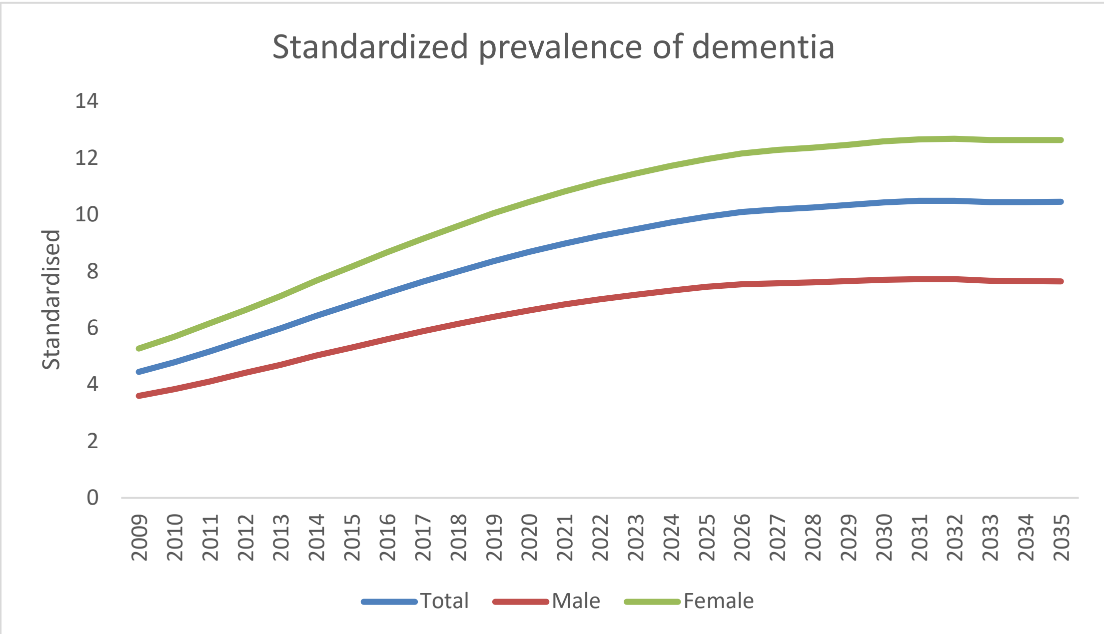


Table 6-1: The projected number of people with dementia in all population to 2035, with 95% UI (million)

Year	Predicted number of cases (million)	(95% UI) (million)
2009	5.94	(5.93-5.95)
2010	6.55	(6.53-6.56)
2011	7.28	(7.26-7.30)
2012	8.09	(8.06-8.11)
2013	8.98	(8.94-9.01)
2014	9.97	(9.93-10.01)
2015	11.02	(10.97-11.07)
2016	12.09	(12.03-12.15)
2017	13.28	(13.21-13.34)
2018	14.50	(14.42-14.58)
2019	15.80	(15.71-15.89)
2020	17.08	(16.98-17.17)
2021	18.28	(18.17-18.39)
2022	19.55	(19.43-19.66)
2023	20.72	(20.58-20.84)
2024	21.55	(21.41-21.69)
2025	22.15	(21.99-22.29)
2026	22.89	(22.73-23.04)
2027	23.81	(23.64-23.97)
2028	25.18	(25.00-25.35)
2029	26.20	(26.01-26.38)
2030	27.09	(26.90-27.29)
2031	27.87	(27.67-28.07)
2032	28.43	(28.21-28.64)
2033	29.25	(29.02-29.47)
2034	29.87	(29.63-30.10)
2035	30.56	(30.32-30.80)

Abbreviations: UI: uncertainty interval.

Table 6-2: The projected age-standardised prevalence of dementia in China to 2035 (standardised to population structure in 2015) (%)

Year	Total	Male	Female
2009	4.45	3.61	5.28
2010	4.79	3.84	5.69
2011	5.17	4.11	6.16
2012	5.58	4.41	6.63
2013	5.98	4.7	7.13
2014	6.43	5.02	7.67
2015	6.83	5.31	8.16
2016	7.24	5.6	8.67
2017	7.63	5.88	9.15
2018	7.99	6.14	9.6
2019	8.35	6.39	10.05
2020	8.68	6.62	10.44
2021	8.98	6.83	10.82
2022	9.25	7.01	11.16
2023	9.49	7.17	11.45
2024	9.72	7.32	11.72
2025	9.92	7.45	11.96
2026	10.09	7.54	12.16
2027	10.19	7.58	12.29
2028	10.25	7.61	12.36
2029	10.34	7.65	12.47
2030	10.43	7.7	12.59
2031	10.49	7.73	12.66
2032	10.5	7.72	12.69
2033	10.45	7.67	12.64
2034	10.45	7.66	12.63
2035	10.46	7.64	12.63

Note: Age structure was standardised to 2015,
as the closest to the last CLHLS data collection wave.

6.5 Sensitivity analysis

To explore the uncertainty in this study, a deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted. To explore how much the specific parameters affect the outputs of the LAM model, the deterministic sensitivity analysis was conducted by inputting the varied parameter (time effect on dementia incidence) manually. This step can also be called univariable sensitivity analysis. To explore the uncertainty driven from parameter imprecisions in the LAM model, the probabilistic sensitivity analysis was conducted. The selected probability distribution arose from a plausible range from observed data. Then the Monte Carlo simulation method was used as the sampling method in this step. The detailed information is shown in the following section.

6.5.1 Probabilistic sensitivity analysis (Monte Carlo simulation)

The probabilistic sensitivity analysis was conducted to estimate the uncertainty interval. The Monte Carlo simulation was performed as a sampling method from the plausible distribution. Table 6-3 shows the summary of parameters and functions used in the Monte Carlo simulation.

Table 6-3: The summary of parameters and functions used in Monte Carlo simulation.

Parameter	Description	Function
θ_{jm}	A vector includes age, sex and calendar specific value for the input parameters j at iteration m.	-
ω_{im}	A vector includes age, sex and calendar specific value for output j at iteration m.	-
I_m	A matrix includes all the age, sex and calendar-specific inputs employed in the Markov model at iteration m.	$I_m = \theta_{1m}, \theta_{2m}, \theta_{3m}, \ldots, \theta_{jm}$
O_m	A matrix includes all the age, sex and calendar-specific outputs in the Markov model at iteration m.	$O_m = \omega_{1m}, \omega_{2m}, \omega_{3m}, \ldots, \omega_{jm}$

The matrix I_m was used to calculate for the output matrix O_m by conducting the LAM model. 1000 times iterations were housed in the probabilistic sensitivity analysis. The 2.5th and 97.5th percentiles of the distribution of outputs in O_m were defined as the 95% uncertainty interval. Table 6-4 shows the selected distribution of the probabilistic sensitivity analysis.

Table 6-4: The distribution of probabilistic sensitivity analysis.

Input parameters	Types of distribution	Function	Data source
Prevalence proportion for state	Beta distribution	(Number of cases, the sample size minus the number of cases)	CLHLS
Incidence rate of hypertension	Normal distribution	(ln (mean), standard error)	The function predicted in R was used after logistic regression model was described in calculating transition probabilities to calculate the mean and standard error.
Incidence rate of stroke	Normal distribution	(ln(mean), standard error)	The function predicted in R was used after logistic regression model was described in calculating transition probabilities to calculate the mean and standard error.
Incidence rate of dementia	Normal distribution	(ln(mean), standard error)	The function predicted in R was used after logistic regression model was described in calculating transition probabilities to calculate the mean and standard error.
Probabilities to death	Normal distribution	(mean, standard error)	The all-cause and stroke-cause mortality and 95% confidence interval was obtained from the GBD. $\text{Standard error} = (\text{95\% upper confidence interval} - \text{mean})/1.96$

The choice of Beta distribution for the prevalence of states, and normal distribution for incidence of hypertension, stroke and dementia, all-cause and stroke-cause mortality is recommended by the ISPOR-SMDM Modeling Good Research Practices Task Working Group-6.[167] The ISPOR-SMDM Modeling Good Research Practices Task Working Group describe the recommendations for achieving transparency and validation developed by a task force, appointed by the International Society for Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making.

The mean and 95% confidence interval for probabilities to death were used to calculate the standard error. The mean and 95% confidence interval were obtained from the data source GBD Study 2019.[246] The characteristics of normal distribution are used to calculate the standard error - for a large sample, a 95% confidence interval is obtained as the values 1.96×SE either side of the mean.

Table 6-5 shows the estimated number of cases with dementia in 2035 in China and its uncertainty interval. Table 6-6 shows the estimated age-standardised prevalence of dementia for all the population, men and women in 2035 in China and associated uncertainty interval.

The number of people with dementia in China will reach 22.1 million (22.0 million-22.3million) in 2025, 27.1 million in 2030 (26.9 million-27.3 million) and 30.6 million (30.3 million-30.8 million).

Table 6-5: The estimated number of cases with dementia in 2035 in China and associated 95% uncertainty interval.

Year	Predicted number of cases	(95% UI)
2009	5936106	(5927198-5945244)
2010	6549234	(6534694-6563125)
2011	7278884	(7258113-7298614)
2012	8085160	(8057326-8110920)
2013	8979544	(8944312-9012674)
2014	9971574	(9928676-10011662)
2015	11024939	(10972310-11073509)
2016	12091860	(12029683-12147884)
2017	13276578	(13205536-13340403)
2018	14503589	(14423583-14577388)
2019	15802306	(15712987-15886743)
2020	17075733	(16976583-17167572)
2021	18284798	(18173544-18386560)
2022	19550495	(19426505-19664411)
2023	20715155	(20580047-20838853)
2024	21554224	(21408133-21688568)
2025	22149411	(21994843-22293520)
2026	22886787	(22725222-23040703)
2027	23806374	(23636496-23969426)
2028	25181871	(25003396-25354625)
2029	26198292	(26007860-26378745)
2030	27094979	(26896963-27285823)
2031	27874938	(27665537-28072279)
2032	28430228	(28210366-28636732)
2033	29249734	(29021350-29465829)
2034	29868655	(29631020-30097053)
2035	30563654	(30321674-30795883)

Abbreviations: UI: uncertainty interval.

Table 6-6: The estimated age-standardised prevalence of dementia for all the population, men and women to 2035 in China and the associated 95% uncertainty interval.

Year	All	95% lower UI	95% upper UI	Men	95% lower UI	95% upper UI	Women	95% lower UI	95% upper UI
2009	4.45	4.44	4.46	3.61	3.59	3.63	5.28	5.26	5.30
2010	4.79	4.77	4.80	3.84	3.82	3.86	5.69	5.66	5.71
2011	5.17	5.16	5.18	4.11	4.09	4.13	6.16	6.13	6.18
2012	5.58	5.56	5.59	4.41	4.39	4.43	6.63	6.61	6.65
2013	5.98	5.96	5.99	4.70	4.68	4.72	7.13	7.10	7.15
2014	6.43	6.41	6.44	5.02	5.00	5.04	7.67	7.65	7.69
2015	6.83	6.82	6.85	5.31	5.29	5.34	8.16	8.14	8.18
2016	7.24	7.22	7.26	5.60	5.58	5.62	8.67	8.64	8.69
2017	7.63	7.61	7.65	5.88	5.86	5.91	9.15	9.12	9.17
2018	7.99	7.97	8.01	6.14	6.11	6.16	9.60	9.57	9.62
2019	8.35	8.33	8.37	6.39	6.36	6.41	10.05	10.02	10.07
2020	8.68	8.65	8.69	6.62	6.59	6.64	10.44	10.41	10.46
2021	8.98	8.96	9.00	6.83	6.80	6.86	10.82	10.79	10.85
2022	9.25	9.23	9.27	7.01	6.98	7.04	11.16	11.12	11.19
2023	9.49	9.47	9.52	7.17	7.14	7.20	11.45	11.41	11.48
2024	9.72	9.70	9.75	7.32	7.28	7.35	11.72	11.69	11.76
2025	9.92	9.90	9.95	7.45	7.41	7.48	11.96	11.92	11.99
2026	10.09	10.06	10.11	7.54	7.51	7.58	12.16	12.12	12.19
2027	10.19	10.16	10.21	7.58	7.54	7.62	12.29	12.25	12.32

2028	10.25	10.22	10.27	7.61	7.57	7.64	12.36	12.33	12.40
2029	10.34	10.31	10.36	7.65	7.61	7.69	12.47	12.43	12.51
2030	10.43	10.40	10.45	7.70	7.66	7.74	12.59	12.55	12.62
2031	10.49	10.46	10.51	7.73	7.69	7.77	12.66	12.62	12.70
2032	10.50	10.47	10.53	7.72	7.68	7.76	12.69	12.65	12.73
2033	10.45	10.42	10.48	7.67	7.63	7.71	12.64	12.59	12.68
2034	10.45	10.42	10.48	7.66	7.62	7.70	12.63	12.59	12.67
2035	10.46	10.43	10.49	7.64	7.60	7.68	12.63	12.59	12.67

Abbreviations: UI: uncertainty interval.

6.5.2 Deterministic sensitivity analysis (Projected future prevalence of dementia in China based on different assumptions)

The time trend in stroke incidence was assumed at a declining trend of 0.9 % annual rate and the time trend in stroke mortality was assumed at a declining trend of 2.8% annual rate (as observed in GBD data).[246] The time trend in dementia incidence was assumed to increase first (as observed in CLHLS and also in other studies in China) and then decline (as observed in high-income countries). Appendix 11 shows the assumption of time trends in dementia incidence in China.

Two alternative assumptions on the time trend in dementia incidence were examined: a constant trend (no annual rate) over the time horizon (scenario 1), and a uniform increasing trend (at 2.5% annual rate) over the time horizon (scenario 2). Table 6-7 shows the detailed information about alternative assumptions in deterministic sensitivity analysis.

$$Time\ effects\ on\ dementia\ incidence = \begin{cases} 2.5 * \cos\left(\frac{year * \pi}{20}\right), year \leq 20 \\ -2.5, year > 21 \end{cases}$$

Table 6-7: Different assumptions in sensitivity analysis

Different assumptions	Explanation of assumption
Main projection	$Time\ effects\ on\ dementia\ incidence = \begin{cases} 2.5 * \cos\left(\frac{year * \pi}{20}\right), year \leq 20 \\ -2.5, year > 21 \end{cases}$
Scenario 1	$Time\ effects\ on\ dementia\ incidence = 0$ (no annual rate)
Scenario 2	$Time\ effects\ on\ dementia\ incidence = +2.5$ (at 2.5% annual rate)

Table 6-8 shows the number of cases with dementia based on different assumptions. Table 6-9 shows the age-standardised prevalence of dementia for all the population, men and women based on different assumptions.

Table 6-8: the number of cases with dementia based on different assumptions.

Year	Main Projection	Scenario 1	Scenario 2
2009	5936106	5901891	5936106
2010	6549234	6448097	6549665
2011	7278884	7079811	7281564
2012	8085160	7759938	8094230
2013	8979544	8501186	9002549
2014	9971574	9314629	10020730
2015	11024939	10169457	11118100
2016	12091860	11026731	12253108
2017	13276578	11985755	13539267
2018	14503589	12983343	14909254
2019	15802306	14051525	16403421
2020	17075733	15110761	17931688
2021	18284798	16133491	19461393
2022	19550495	17232120	21129868
2023	20715155	18273702	22776605
2024	21554224	19064963	24154476
2025	22149411	19678524	25343193
2026	22886787	20455302	26779357
2027	23806374	21433592	28525781
2028	25181871	22863376	30935162
2029	26198292	24015361	33035680
2030	27094979	25100122	35105567
2031	27874938	26116896	37140113
2032	28430228	26960849	38983812
2033	29249734	28087428	41296533
2034	29868655	29059745	43445301
2035	30563654	30139236	45818925

Table 6-9: The age-standardised prevalence of dementia for all the population, men and women based on different assumptions.

Year	Main Projection (All)	Scenario 1 (All)	Scenario 2 (All)	Main Projection (Men)	Scenario 1 (Men)	Scenario 2 (Men)	Main Projection (Women)	Scenario 1 (Women)	Scenario 2 (Women)
2009	4.45	4.43	4.45	3.61	3.59	3.61	5.28	5.26	5.28
2010	4.79	4.71	4.79	3.84	3.78	3.84	5.69	5.6	5.69
2011	5.17	5.03	5.17	4.11	4	4.11	6.16	5.99	6.16
2012	5.58	5.35	5.58	4.41	4.23	4.42	6.63	6.37	6.64
2013	5.98	5.66	6	4.7	4.45	4.71	7.13	6.75	7.15
2014	6.43	6	6.46	5.02	4.68	5.04	7.67	7.17	7.71
2015	6.83	6.3	6.89	5.31	4.9	5.36	8.16	7.53	8.23
2016	7.24	6.6	7.34	5.6	5.1	5.68	8.67	7.9	8.78
2017	7.63	6.88	7.78	5.88	5.3	6	9.15	8.26	9.33
2018	7.99	7.14	8.22	6.14	5.48	6.32	9.6	8.58	9.86
2019	8.35	7.42	8.68	6.39	5.66	6.64	10.05	8.92	10.42
2020	8.68	7.66	9.12	6.62	5.83	6.96	10.44	9.22	10.96
2021	8.98	7.91	9.57	6.83	6	7.29	10.82	9.53	11.51
2022	9.25	8.13	10.01	7.01	6.15	7.61	11.16	9.81	12.05
2023	9.49	8.35	10.46	7.17	6.29	7.93	11.45	10.08	12.58
2024	9.72	8.57	10.92	7.32	6.44	8.26	11.72	10.34	13.13
2025	9.92	8.78	11.38	7.45	6.58	8.6	11.96	10.59	13.68
2026	10.09	8.98	11.85	7.54	6.7	8.92	12.16	10.82	14.22
2027	10.19	9.13	12.26	7.58	6.79	9.21	12.29	11.02	14.72

2028	10.25	9.26	12.65	7.61	6.87	9.49	12.36	11.18	15.19
2029	10.34	9.43	13.12	7.65	6.98	9.83	12.47	11.38	15.73
2030	10.43	9.61	13.61	7.7	7.11	10.2	12.59	11.6	16.32
2031	10.49	9.78	14.09	7.73	7.22	10.56	12.66	11.8	16.89
2032	10.5	9.91	14.54	7.72	7.3	10.88	12.69	11.97	17.43
2033	10.45	9.99	14.92	7.67	7.36	11.17	12.64	12.06	17.87
2034	10.45	10.12	15.4	7.66	7.45	11.52	12.63	12.21	18.42
2035	10.46	10.27	15.91	7.64	7.54	11.89	12.63	12.38	19

Scenario 1 – Assuming no time effect on dementia incidence in China, the number of cases with dementia in 2035 will reach 30,139,236. If there is no time effect on dementia incidence over time horizon, the number of cases with dementia will decline by 424,418 in 2035, compared with our main prediction. Assuming no time effect on dementia incidence in China, the age-standardised prevalence for all the population in 2035 is estimated at 10.27%, the age-standardised prevalence for men and women in 2035 are estimated at 7.54% and 12.38%, respectively.

Scenario 2 – Assuming dementia incidence increased at an annual rate of 2.5%, the number of cases with dementia in 2035 will reach 45,818,925. If dementia incidence remains at 2.5% annual rate increasing over the time horizon, the number of cases with dementia will increase by 15,255,271 in 2035, compared with our main prediction. Assuming dementia incidence increase at 2.5% annual rate over the time horizon in China, the age-standardised prevalence for all the population in 2035 will reach 15.91%, the age-standardised prevalence for men and women in 2035 will reach 11.89% and 19.00%, respectively.

To conclude, the deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted to test different assumptions of the LAM model and exam the robustness of the LAM model. In deterministic sensitivity analysis, the assumptions in time trends in dementia incidence can affect the projection of dementia cases in the future. The constant increasing time trends in dementia incidence can lead to a larger number of dementia cases and a higher prevalence of dementia in 2035 compared with our main projection. On the other hand, the no time effect on dementia incidence leads to a small difference in projection results compared with our main projection. In probability sensitivity analysis, the estimated 95% uncertainty interval was calculated by Monte Carlo simulation.

6.6 Validation

To validate the model, the LAM model was used and the key outputs with internal and external resources were compared. The validation includes partially dependent validation and independent validation. Partially dependent validation refers to using the same partial data source as the developing model source during the model validation process and independent validation refers to employing the data sources that are not related and not used in this model during the model validation process. The projected five-year age group stroke-cause mortality and all-cause mortality 2009 to 2015 were compared again with GBD 2019 [246]. The projected dementia prevalence was compared with that in CMHS in 2014 and COAST II in 2017. The projected stroke prevalence was compared with that in GBD and NESS-China. Similarly, the projected hypertension prevalence was compared with that in the CNHS and PEACE Project. Moreover, the projected results in other studies were also compared with LAM projection prevalence in 2020 and 2030.

The five-year age group all-cause mortality and stroke-cause mortality estimated in this study from 2009 to 2015 were akin to those in GBD 2019. All estimations of dementia prevalence fall within the 95% confidence interval reported by CMHS and COAST II. The estimation of stroke prevalence and hypertension were close to those in GBD, NESS-China, CNHS and PEACE Project.

The projected number of dementia cases projected in this study in 2020 and 2030 were compared with that in the projection study MPDPCW. The projected dementia prevalence in LAM in 2020 is slightly higher than the projected dementia prevalence in MPDPCW, and the projected dementia prevalence in LAM in 2030 falls within the corresponding confidence interval of the projected dementia prevalence in MPDPCW. The MPDPCW did not account for the lengthening of life expectancy in China, which would lead to an underestimation of the number of dementia cases.

All-cause mortality

Figure 6-4: The all-cause mortality in GBD and LAM for males

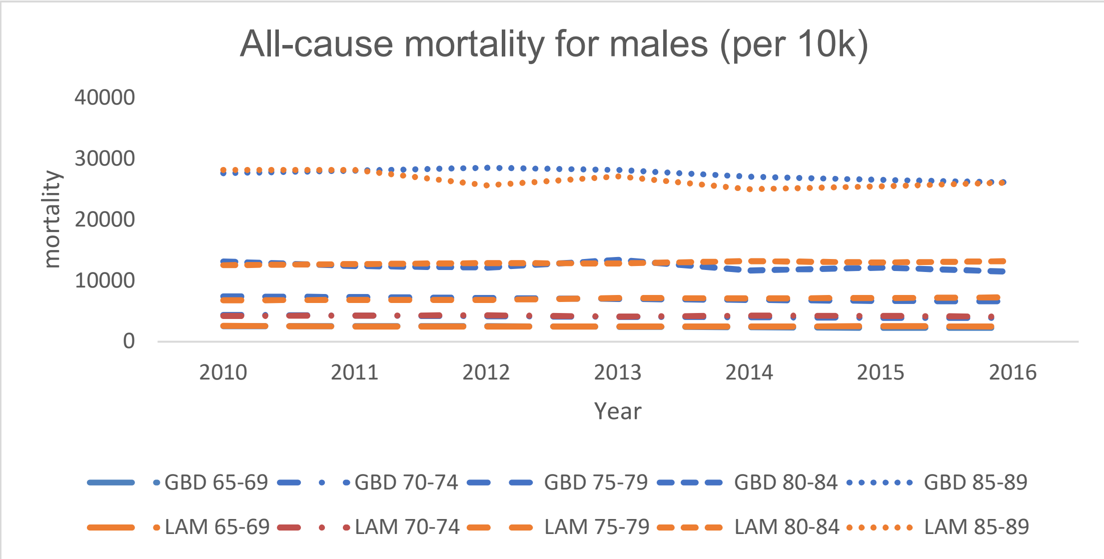
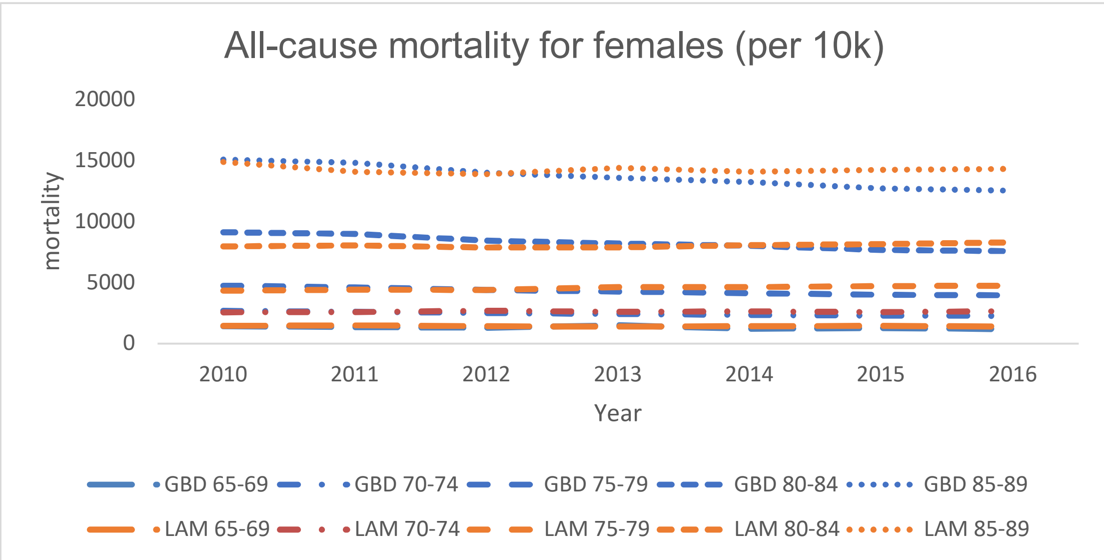


Figure 6-5: The all-cause mortality in GBD and LAM for females



The projected 5-year age group all-cause mortality from 2010 to 2015 from the LAM model was compared with that in the GBD dataset. The projected mortality for males and females in the LAM model were akin to those in the GBD dataset. The comparison of all-cause mortality in LAM and those in GBD for males and females are displayed in Figure 6-4 and Figure 6-5, respectively.

Stroke mortality

Figure 6-6: The stroke mortality in GBD and LAM for males

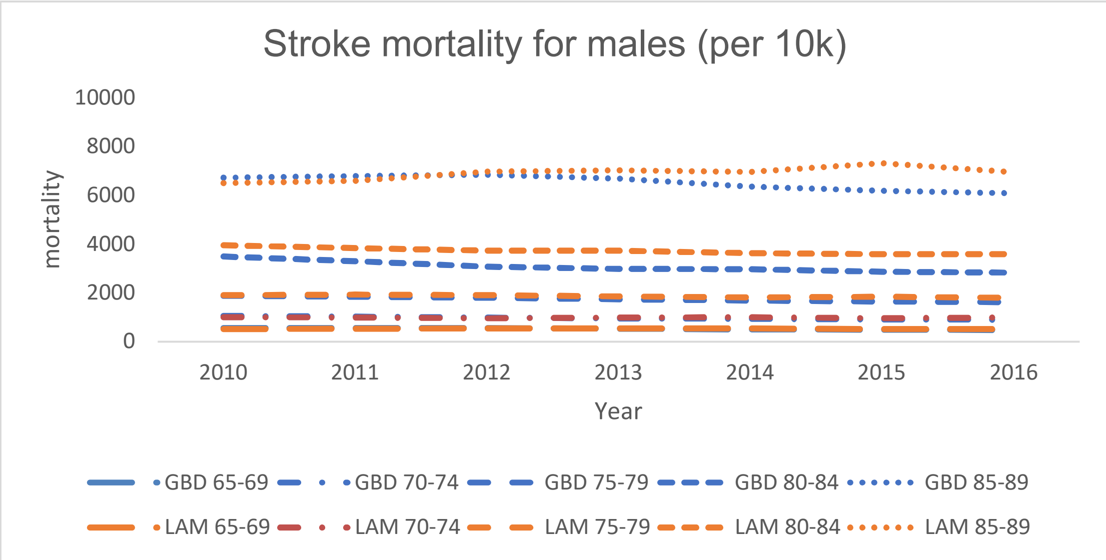
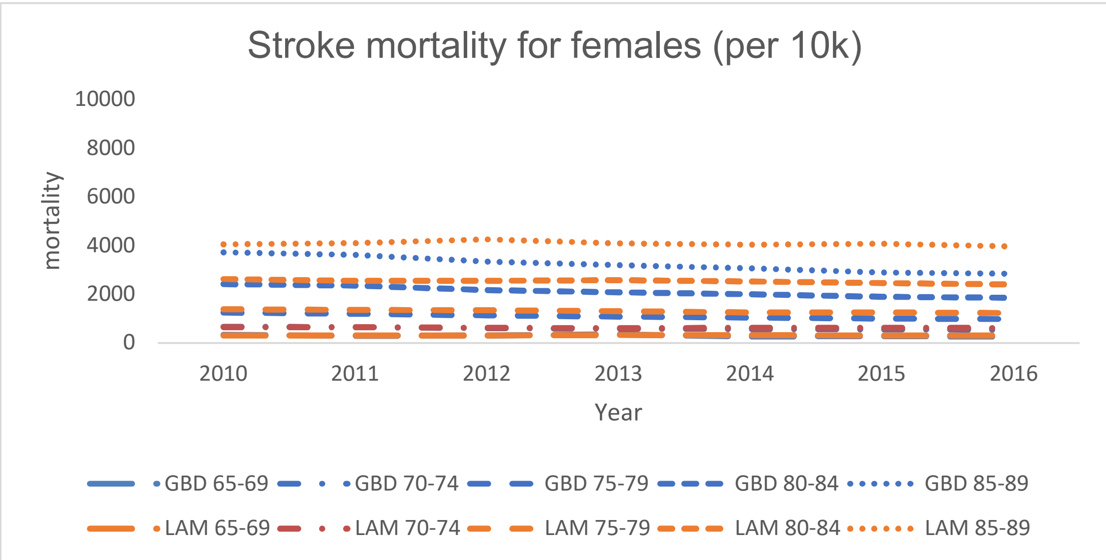


Figure 6-7: The stroke mortality in GBD and LAM for females



The projected 5-year age group stroke-cause mortality from 2010 to 2015 from the LAM model was compared with that in the GBD dataset. The projected stroke mortality for males and females in the LAM model were akin to those in the GBD dataset. The comparison of stroke cause mortality in LAM and those in GBD for males and females are displayed in Figure 6-6 and Figure 6-7, respectively.

Dementia prevalence

Figure 6-8: The dementia prevalence in CMHS and LAM.

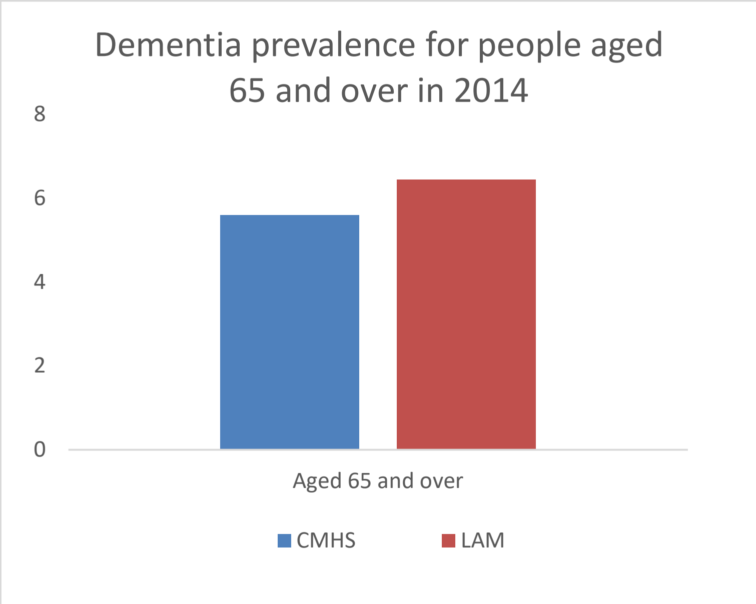
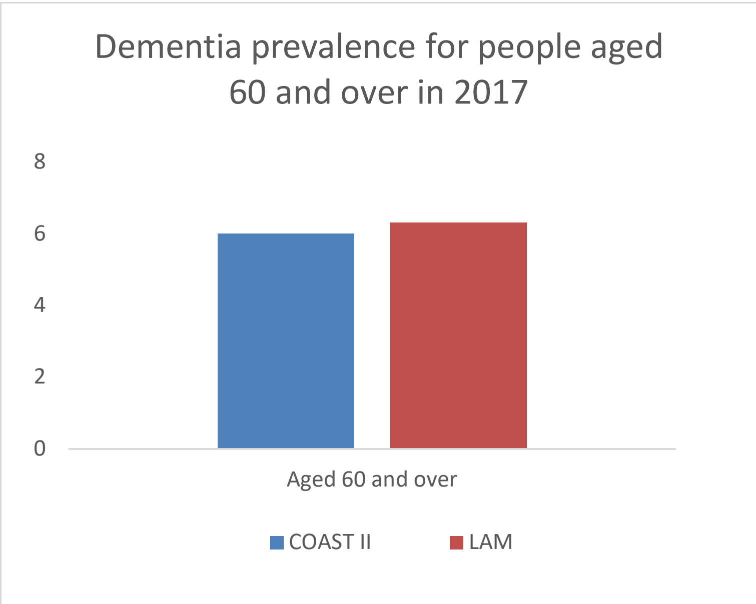


Figure 6-9: The dementia prevalence in COAST II and LAM.



The dementia prevalence projected in the LAM model was compared with that observed in CMHS. The dementia prevalence for people aged 65 and over in 2014 in CMHS is 5.6% (95%CI 3.5%-7.6%), and the projected dementia prevalence for people aged 65 and over in 2014 in the LAM model is 6.4%. The projected dementia prevalence in the LAM falls within the corresponding confidence interval of the observed prevalence in CMHS. Figure 6-8 shows the comparison of dementia prevalence for people aged 65 and over in CMHS and LAM.

The dementia prevalence projected in the LAM model was compared with that observed in COAST II. The dementia prevalence for people aged 60 and over in 2017 in COAST II is 6.0% (95%CI 5.8%-6.3%), and the projected dementia prevalence for people aged 60 and over in 2017 in LAM model is 6.3%. The projected dementia prevalence in LAM falls within the corresponding confidence interval of the observed prevalence in COAST II. Figure 6-9 shows the comparison of dementia prevalence for people aged 60 and over in COAST II and LAM.

Table 6-10: The dementia prevalence in CMHS, COAST II and LAM

Name of study	Study population	Year	Observed prevalence	95% CI	Name of study	Project prevalence
CMHS[21]	Aged 65 and over	2014	5.6	(3.5-7.6)	LAM	6.44
COAST II[22]	Aged 60 and over	2017	6	(5.8-6.3)	LAM	6.3

Abbreviations: CMHS: China Mental Health Survey; COAST II: China Cognition and Ageing Study II; LAM: Life-cycle Ageing Model; 95% CI: Confidence Interval
Data sources: [21,22]

Stroke prevalence

Stroke prevalence in GBD and LAM

Figure 6-10: The prevalence of stroke in GBD and LAM for males.

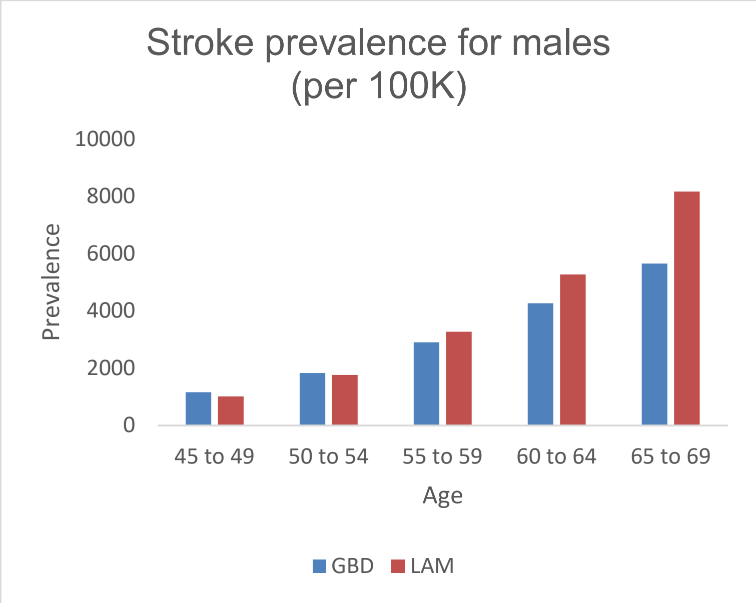
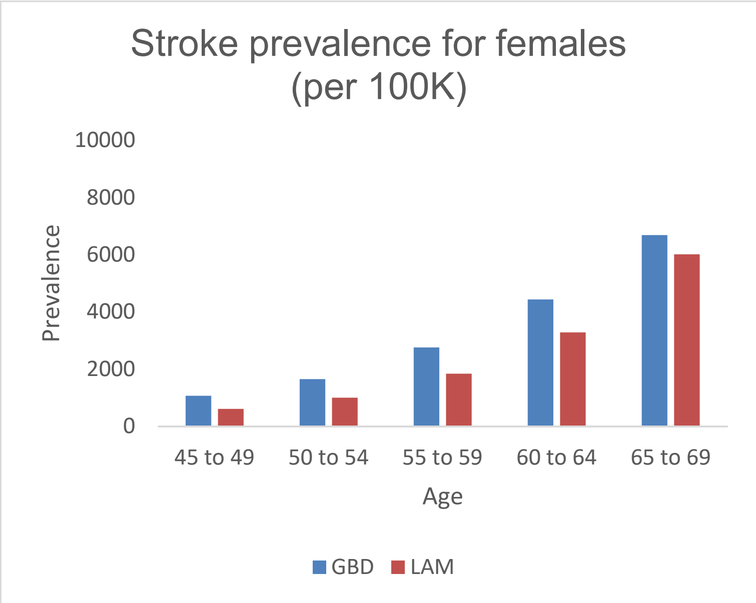


Figure 6-11: The prevalence of stroke in GBD and LAM for females.



Stroke prevalence

Stroke prevalence in NESS-China and LAM

Figure 6-12: The prevalence of stroke in NESS-China and LAM for males.

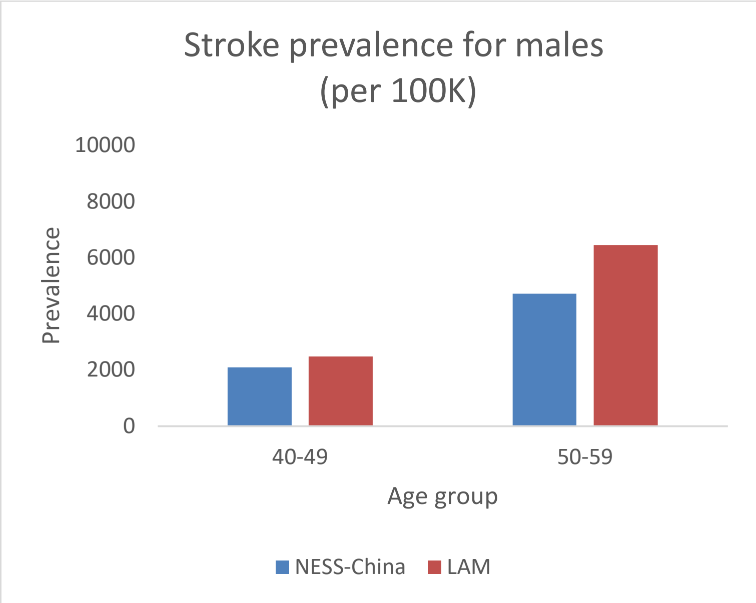
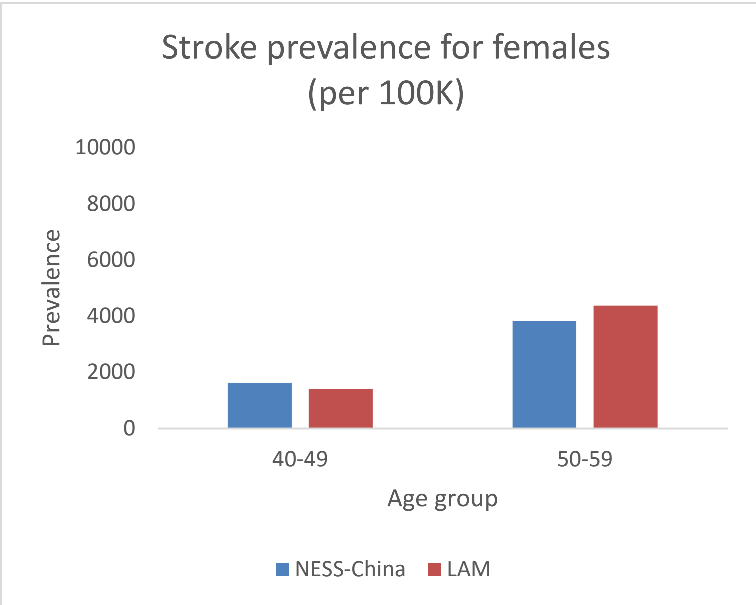


Figure 6-13: The prevalence of stroke in NESS-China and LAM for females.



The stroke prevalence projected in the LAM model was compared with that observed in the GBD dataset and NESS-China[247]. The projected stroke prevalence in LAM is akin to the observed stroke prevalence in GBD and NESS-China. Figure 6-10 and Figure 6-11 show the comparison of stroke prevalence in GBD and LAM for males and females, respectively. Figure 6-12 and Figure 6-13 show the comparison of stroke prevalence in NESS-China and LAM for males and females, respectively.

Hypertension prevalence

Figure 6-14: The prevalence of hypertension in CNHS and LAM.

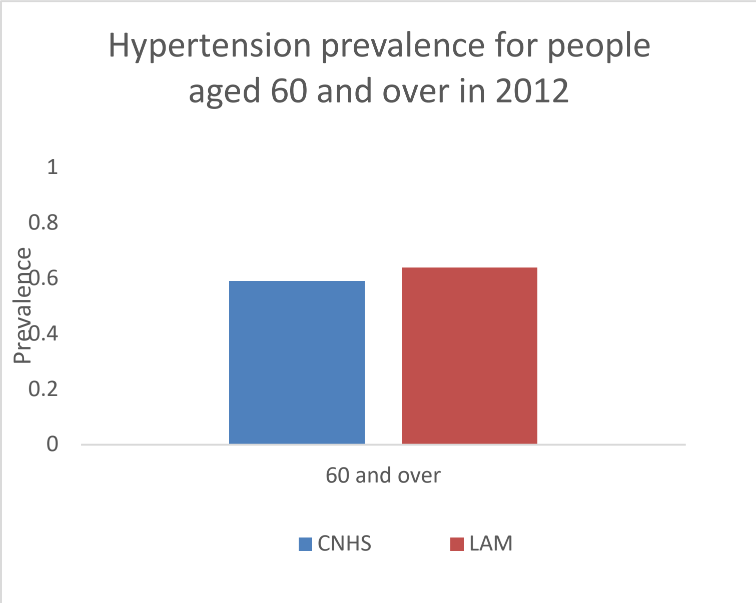
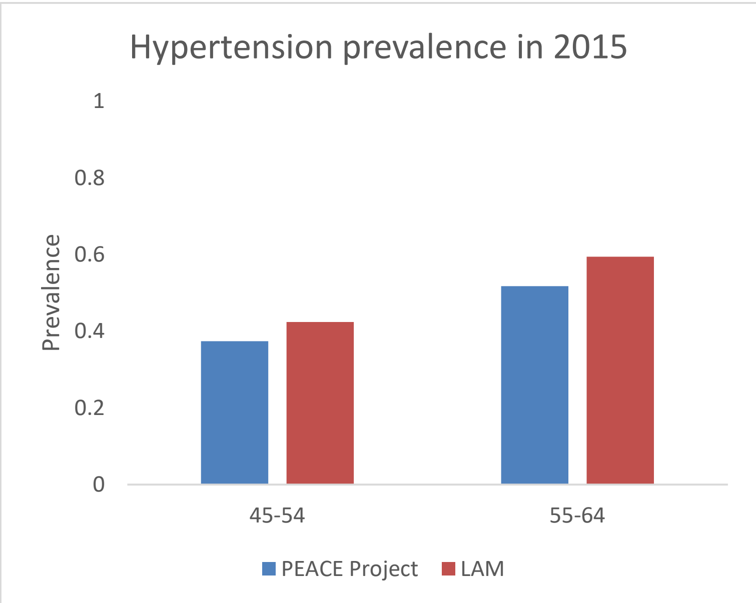


Figure 6-15: The prevalence of hypertension in PEACE Project and LAM.



The hypertension prevalence projected in the LAM model was compared with that observed in CNHS. The dementia prevalence for people aged 60 and over in 2012 in CNHS is 58.9%, and the projected hypertension prevalence for people aged 60 and over in 2012 in the LAM model is 63.7%. Figure 6-14 shows the comparison of hypertension prevalence for people aged 60 and over in CNHS and LAM. Figure 6-15 shows the comparison of hypertension prevalence for people aged 60 and over in PEACE Project and LAM.

Table 6-11: The prevalence of hypertension in CNHS, PEACE project and LAM model.

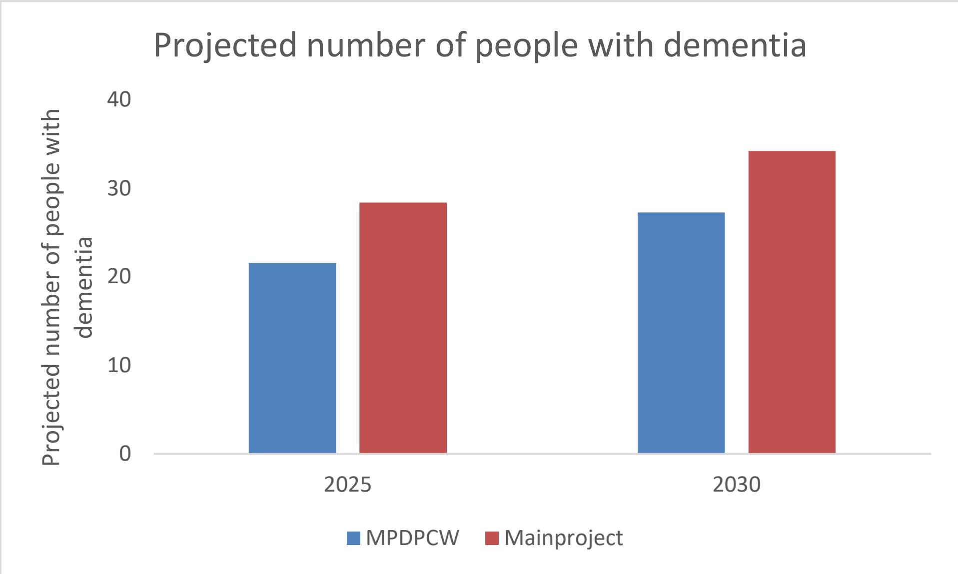
Name of study	Study population	Year	Observed prevalence	Name of study	Project prevalence
CNHS[248]	60+	2012	0.589	LAM	0.637
PEACE Project[249]	45-54	2015	0.374	LAM	0.424
PEACE Project[249]	55-64	2015	0.518	LAM	0.595

Abbreviations: CNHS: Chinese National Nutrition Survey 2012; PEACE Project: China Patient-Centred Evaluative Assessment of Cardiac Events (PEACE) Million Persons Project; LAM: Life-cycle Ageing Model.

Data sources: [248,249]

Projected number of people with dementia

Figure 6-16: The projected number of people with dementia MPDPCW and LAM in 2025 and 2030.



The number of people with dementia projected in the LAM model was compared with that projected in MPDPCW. The number of people with dementia for people aged 60 and over in 2025 in MPDPCW is 21.56 million (95% CI 15.59-27.92), and the projected number of people with dementia aged 60 and over in 2025 in the LAM model is 28.38 million. The number of people with dementia for people aged 60 and over in 2030 in MPDPCW is 27.29 million (95% CI 19.94-35.18), and the projected number of people with dementia aged 60 and over in 2030 in the LAM model is 34.21 million. The projected dementia prevalence in LAM in 2020 is slightly higher than the projected dementia prevalence in MPDPCW, and the projected dementia prevalence in LAM in 2030 falls within the corresponding confidence interval of the projected dementia prevalence in MPDPCW. The MPDPCW did not account for the time trends in mortality in China, which would lead to an underestimation of the number of dementia cases. Figure 6-16 shows the comparison of projected dementia prevalence for people aged 60 and over in MPDPCW and LAM.

Table 6-12: The projected number of people with dementia in 2025 and 2030 (million).

Year	MPDPCW[10]	95% CI	LAM
2025	21.56	(15.59-27.92)	28.38
2030	27.29	(19.94-35.18)	34.21

Abbreviations: MPDPCW: Model-Based Projection of Dementia Prevalence in China and Worldwide study; LAM: Life-cycle Ageing Model; CI: Confidence Interval.
Data sources: [10]

6.7 Implications

This study shows that the number of dementia cases in China is projected to increase to more than 30 million by 2035. Through the projection model, this thesis suggests that the Chinese government and society need to extend the coverage of healthcare, access to care, treatment, and support for people with dementia.

The vision of future work could involve the following points:

- The LAM model includes various outputs other than dementia. To be specific, the LAM model could be employed to project future trends in stroke-cause mortality and all-cause mortality.

- The LAM model might be used to assess how the number of dementia cases could be reduced or increased by various intervention actions. For instance, the LAM model might be employed to investigate the benefits of possible interventions for lowering smoking, controlling obesity, and increasing vegetable consumption.

- The LAM model simulates the transit between hypertension, stroke, dementia and mortality. Thus, the LAM model could be used to simulate how vascular factors influence the total population in the future.

Such a model can not only provide an accurate projection of the number of dementia cases, but also can provide a model base for forecasting the health gains from the interventions to prevent dementia.

6.8 Discussion

As far as is known, this is the first study to explore the future burden of dementia in China, considering the calendar changes in dementia incidence, stroke incidence, stroke mortality as well as population structure changing based on a state-transition Markov model. This section discusses the strengths and limitations, compares with other studies with a similar purpose and method conducted in other countries in the world, and explores the possible causes that lead to the results in this study.

6.8.1 Strengths of this study

This study has two strengths in terms of study design and application possibility.

First, from the perspective of study design, this thesis provides the first study to explore the future burden of dementia, considering the calendar changes in dementia incidence, stroke incidence, stroke mortality as well as population structure changing based on a state-transition Markov model.

Secondly, from the perspective of application possibility, this study developed the probabilistic Markov model - LAM - which could provide outcomes including hypertension, stroke, dementia and death, and simulate the population diseases progress. The Markov model developed in this thesis provides scholars with a possible tool to explore the potential impacts of possible preventive interventions on the burden of dementia in the future. The results of this prediction model can be used as a benchmark to measure the impact of possible dementia interventions.

6.8.2 Limitations of this study

This study also has some limitations that need to be considered. This study has two limitations in terms of recall bias and model assumption.

First, the limitation of recall bias needs to be noticed in this study. To be specific, although the LAM model applied a standardised assessment of cognitive ability and functional ability to define dementia cases and conducted model validation again with internal and external data sources, the information of stroke in CLHLS was collected by self-reporting. This process of covariate definition may lead to recall bias and changes of diagnosis criteria over time.

The second limitation of this study is about model assumption. The LAM model is based on the assumption that survival with health conditions changes in proportion to changes in overall life expectancy. This assumption, despite being reasonable and widely used in modelling research [250], has not been verified, as evidence on the exact age and gender survival with dementia is rare and difficult to collect.[251]

The third limitation of this study is possible changing factors. The LAM model considers the time trends in dementia incidence, stroke incidence, stroke mortality and population structure, but do not account for other factors that might change over time, such as education attainment improving, diets changing and depression levels changing, which might cause changes in the projection results.

Thus, the limitations about recall bias, model assumption and possible changing factor need to be taken into consideration in this study.

6.8.3 Comparison with other studies

Several studies projected the future number and prevalence of ageing-related diseases in high-income countries. Among these studies, the IMPACT-BAM model [94] in England and Wales and the CFAS modelling study [109] (conducted by Jagger and published in 2009) in England are good-practice studies. These two studies and the LAM model study have three common points. The first point is that all three studies employed the modelling method. To be specific, both the LAM model and IMPACT-BAM model used the state-transition Markov model (discrete-time model), and CFAS modelling study used the dynamic macro-simulation model. The second common point is that the purposes of all three studies were projecting the future burden of ageing-related diseases in one specific country. The IMPACT-BAM model was used to forecast the burden of dementia cases in England and Wales up to 2040, the CFAS modelling study was used to predict the burden of disabilities in the United Kingdom up to 2026, and the LAM model was used to project the burden of dementia cases in China up to 2035. The third point to which attention should be paid is model advantages. All these three projection studies consider the time trends in dementia incidence.

Li's study projected the future number of dementia cases in China using

Brookmeyer and Gray's approach of modelling.[10] However, the primary analysis of this study did not account for the time trends in mortality in China, which could lead to an underestimation of future dementia cases in China.

The studies that project the dementia burden in the high- and middle-income countries reveal some points about dementia in the world. First, dementia is projected to be a global challenge in the world. As a result of life expectancy lengthening in these countries, the number of dementia patients is expected to increase. Second, although the number of dementia patients is expected to rise in both China and the United Kingdom, the rate of increase is higher in China. There could be two reasons for this difference. First, the time trend in dementia incidence in the United Kingdom is declining, but the recent time trend in dementia incidence in China is estimated to be upward. Second, due to the baby boom in the 1960s and life expectancy increases, China is the country with a faster ageing rate than the United Kingdom. Taking into account the different time effects on dementia incidence and the different rates of ageing, the projected number of people with dementia in China may be greater than in the United Kingdom.

Thus, according to the existing projection studies, dementia is expected to be a global challenge, both in high-income countries and middle-income countries, and the increase in the number of dementia patients in China may be more significant than in the United Kingdom. Table 6-13 shows the comparison of studies in middle-income countries and high-income countries.

Table 6-13: The comparison of LAM study, IMPACT-BAM study and CFAS study

Model name	LAM	IMPACT-BAM [94]	MRC CFAS modelling study [109]
Model type	Probabilistic Markov model	Probabilistic Markov model	Dynamic macro-simulation
Location	China	England and Wales	United Kingdom
Outputs	Dementia, hypertension, stroke, stroke-cause mortality, all-cause mortality	Cardiovascular diseases, cognitive impairment, functional impairment, dementia, cardiovascular death, non-cardiovascular death	Dementia and disability
Time horizon	2009-2035	2016-2040	2006-2026
Increase degree	5,936,106 (2009) - 30,563,654 (2035)	766,600 (2016) - 1,205,000 (2040)	-

Data sources: [94,109]

6.8.4 Exploration

In this study, the number of people with dementia in China is projected to increase 5-fold from 2009 to 2035 (an increase from 5.9 million in 2009 to 30.6 million in 2035). The main increase is in the age group 65-75 years old, which might be due to the baby boom in the 1960s in China.

There are three reasons that lead to the increase in the number of people with dementia in China. First of all, the baby boom that occurred in the 1960s contributed to the significant increase in the number of people with dementia in China.[252] The baby boom began after the end of the three-year natural disaster in 1962. This baby boom wave peaked in 1965 and lasted until 1973. It is the main baby boom with the largest birth population and the greatest impact on the subsequent economy in China's history. During this period, the national economic situation gradually improved, and compensatory fertility came in a strong momentum. The population birth rate was between 3% and 4%, with an average of 3.3%.[253] In these 10 years, nearly 260 million people were born in China.[254] Thus, the baby boom plays an important role leading to a large population on the cusp of entering ageing life in the future 30 years, which also contributes to the increase in the number of people with dementia.

Secondly, the increasing time trends in dementia incidence also play an important role in the significant increase in the number of people with dementia in China. According to the sensitivity analysis in this study, the increasing time trends in dementia incidence can contribute to the increasing number of people with dementia in China. Thirdly, increasing life expectancy also leads to the increase in the number of people with dementia in China. Recently, the life expectancy in China prolongates with the improving levels of medical care. To be specific, the life expectancy in China increased by 9.5 years from 1990 to 2015.[255] The prolongated life expectancy can also lead to the increase in the number of old people in China. To conclude, the baby boom in the 1960s, the increasing dementia incidence, and the prolongation of life expectancy in China will lead to the increasing number of people with dementia in China in the future.

6.9 Conclusion

To conclude, the number of dementia cases is projected to increase significantly in 2035. The number of people with dementia is predicted to be five times higher in 2035 than in 2010. This significant increase could pose a huge burden on society and health care services, inspiring the society and public health sector to prepare earlier and take action before the changes come to realisation. The results of this prediction model can be used as a benchmark to measure the impact of possible dementia interventions.

7 Study 3: Modelling the impact of the reduction in salt intake on dementia burden to 2035 in China

In this chapter, the LAM model was applied to explore the impact of reduction in salt intake on the burden of dementia to 2035 in China. Different scenarios of reduction in salt intake were assessed. Deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted to explore the uncertainty of the model analysis.

7.1 Background

Elevated salt intake was associated with a high risk of non-communicable diseases, and the salt intake reduction could reduce blood pressure and the risk of non-communicable diseases.[256,257] Chinese people consumed 12 grams salt per day, which is more than twice the WHO recommended salt intake (less than 5 g per day).[258,259] The 2011 Lancet report, initiated by the WHO and prepared in cooperation with about 100 scientists, included reducing salt intake as one of the five priority interventions for member states to address the crisis of non-communicable diseases.[260] Higher salt intake was associated with a higher risk of incident hypertension and stroke, and mortality.[90,261,262] The strong positive relationship between blood pressure and these outcomes provides indirect evidence that reducing sodium intake can decrease the dementia burden through a beneficial effect on blood pressure. The accurate exploration of the impacts of reduction in salt intake on dementia needs to consider the effects of this intervention on the incidence of hypertension, stroke and dementia as well as mortality.

Little is known about the impacts of salt intake reduction on the number of dementia cases and prevalence of dementia in China in the future.

7.2 Aims

The overall objective of this study is to explore the impact of salt intake reduction on the burden of dementia in China in the future based on the state-transition Markov model.

- To explore the prevalence proportion and number of people with dementia in China up to 2035 under salt intake reduction using a state-transition Markov model.

- To compare the prevalence proportion and number of people with dementia in China in 2035 under the public health intervention on salt intake reduction, 5g/per day (recommended salt intake by World Health Organization-WHO), 3g/per day (recommended salt intake by Consensus and Action on Salt and Health-CASH), and 8.5g/per day (the midpoint between WHO recommended salt intake value and current salt intake value).

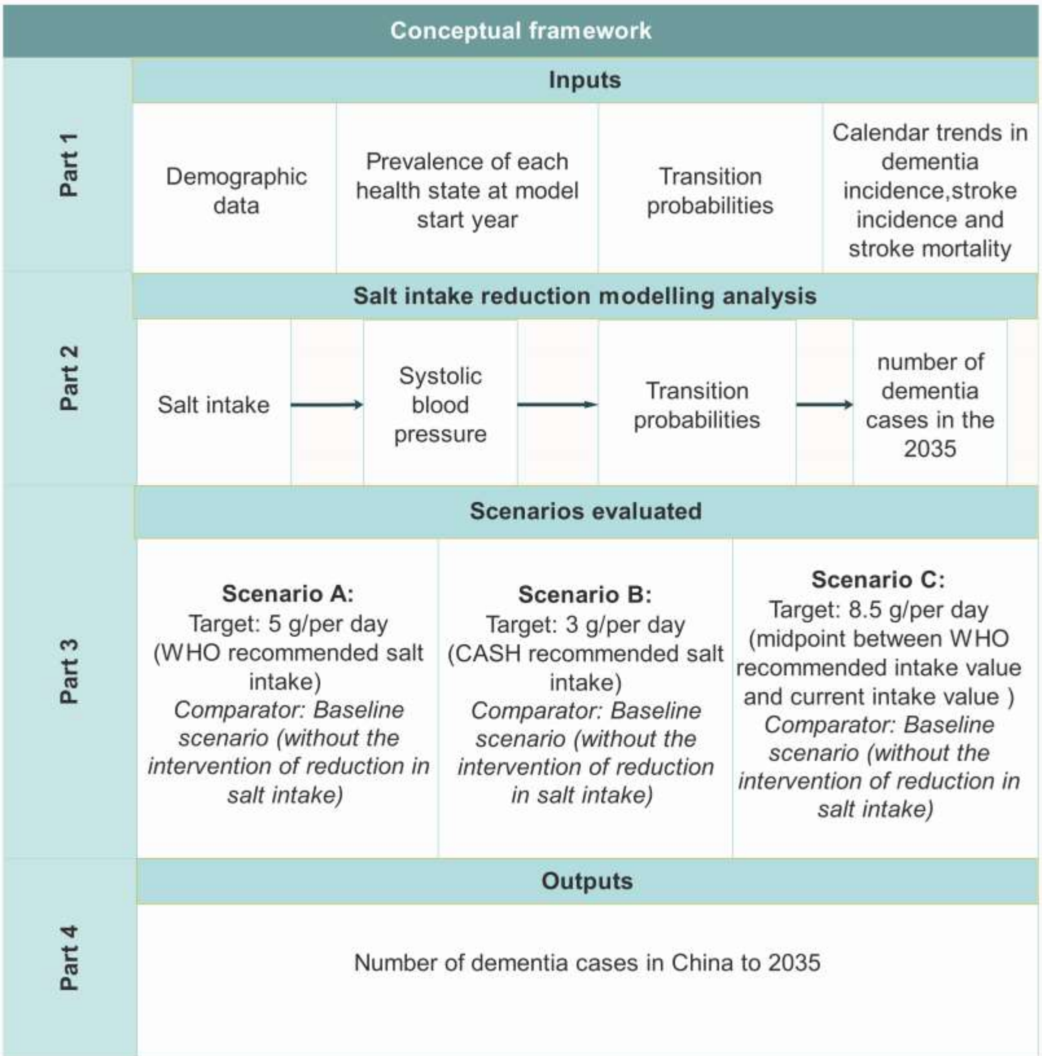
- To project the number of people with dementia in China to 2035 under the public health intervention on salt intake reduction, based on the assumption that the change in systolic blood pressure does not affect mortality and compare the results with primary results.

- To explore the uncertainty in these predictions using a Monte Carlo simulation with the state-transition Markov model.

7.3 Methods

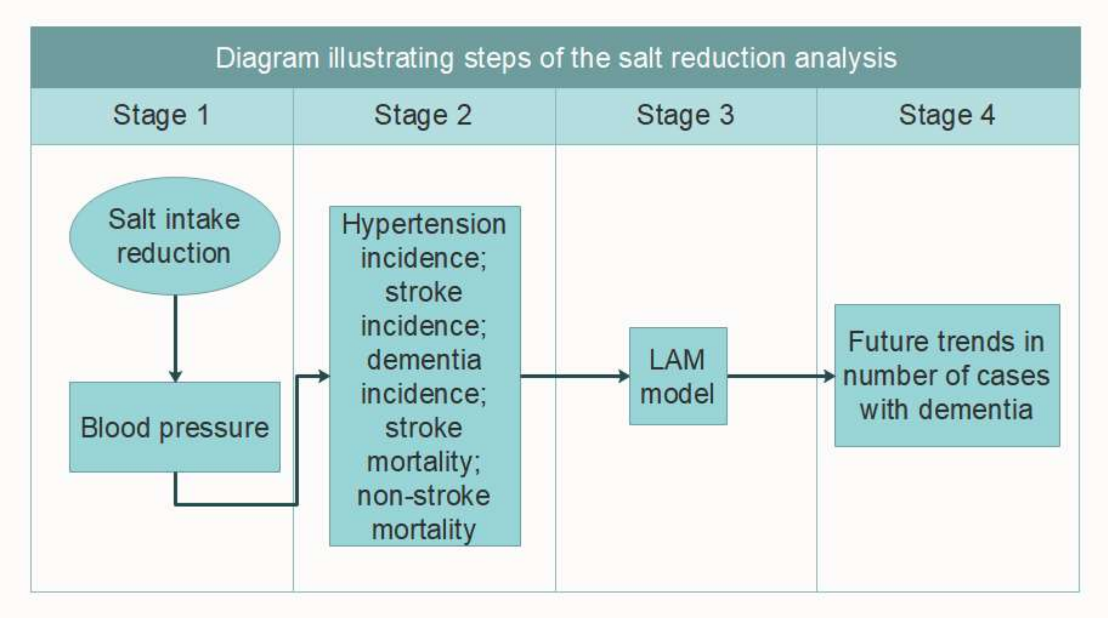
To explore the impact of salt reduction intervention on the number of dementia cases in China in the future, the state-transition Markov model-LAM model was employed. Figure 7-1 shows the conceptual framework of this study.

Figure 7-1: Conceptual framework of this study.



The analysis included four stages: first, the intervention effect on systolic blood pressure in hypertensives and normotensives were estimated from meta-analysis; second, the effects of changes in systolic blood pressure on hypertension incidence, stroke incidence, dementia incidence, stroke mortality and no-stroke mortality were estimated from observational study or meta-analysis; third, the changed parameters were input to the LAM model; four, the number of people with dementia was output from the LAM model and was compared with the baseline scenario. Figure 7-2 displays the diagram illustrating steps of the salt reduction analysis.

Figure 7-2: Diagram illustrating steps of the salt reduction analysis.



Overview of LAM model

The life-cycle ageing model (LAM model) is a state-transition Markov model, which follows the progression of a healthy Chinese population from 2008 to 2035 into 8 states characterized by the presence of absence of hypertension, stroke and dementia, and 2 states for stroke death or no-stroke death. The prevalence of disease situation at the start year (2008) was estimated from the CLHLS. The LAM simulation allows people to move from one state to other states in the model. The possible movements of people between these health states are driven by one-year transition probabilities. For instance, a healthy 60-year-old woman starts the simulation in state 1 (healthy state) in 2008. She moves to state 2 (hypertension) in 2009, and then moves to state 3 (hypertension and stroke) in 2010. In 2010 she could die from stroke (she moves to state 9). As above, movements to any health state are driven by transition probabilities. Transition probabilities were estimated by combining data from CLHLS and GBD 2019.

Salt intake and salt intake reduction

The China Health and Nutrition Survey (CHNS) provided the average salt intake in Chinese population at 1991, 1993, 1997, 2000, 2004, 2006 and 2009.[258] A linear regression model was fitted to obtain the salt intake in China at the model start year (2008). The salt intake value in 2008 rounded to the nearest integer was 12g/per day. The WHO guideline provided a recommended daily salt intake of 5g/per day.[259] The salt intake of Chinese people is assumed to reduce to the daily salt intake recommended by WHO (5g/per day) by 2025 and keep the recommended salt intake until 2035. The annual reduction in salt consumption is assumed to be constant.

Salt reduction effect on transition probabilities

For this study, the salt intake was assumed to be reduced to 5g/day in the Chinese population, which would affect blood pressure and modify some of the LAM transition probabilities, then ultimately would result in changes in the number of people with dementia. The hypertension incidence, stroke incidence, dementia incidence, stroke death and non-stroke death were affected by salt intake and blood pressure change. The effect of salt intake reduction on blood pressure was obtained from a Cochrane systematic review and meta-analysis of trials.[90] The result of this systematic review was employed because this study only included the trials where salt reduction interventions were evaluated over a minimum duration of 4 weeks, which was considered as an important factor when evaluating salt intake reduction public health intervention.[90,263] In this Cochrane systematic review of trials, each 4.40-g dietary salt reduction was associated with a reduction of 5.39 mm Hg in systolic blood pressure (95% CI: -6.62 to -4.15 mm Hg) and 2.42 mm Hg (95% CI: -3.56 to -1.29 mm Hg) in hypertensive people and normotensive people respectively.[90] The Cochrane review includes studies covering different ethnic groups (Black, White and Asian). Meta-regression showed that a modest reduction in salt intake for four or more weeks causes significant and important falls in blood pressure in both hypertensive and normotensive individuals, irrespective of sex and ethnic group, the subgroup analysis also showed that showed a significant fall in blood pressure with the salt reduction in the Asian group. Because the effects of blood pressure changes on stroke incidence, stroke mortality and non-stroke mortality are influenced by the individuals with the presence or absence of hypertension, the effects of the intervention on stroke incidence and mortality are estimated in hypertensive and normotensives separately.[92,264] The relative risks and hazards ratio of comparing every exposure group with unexposed group were obtained from meta-analysis, a large observational study and a trial study.[92,264-266] The following formula was applied to transfer the effects of changes in systolic blood pressure on incidence and mortality from 5/10 mm Hg to 1 mm Hg.

$$\alpha_2 = 1 - e^{((\ln(1-\alpha_1))/n)}$$

n denotes the change/difference in systolic blood pressure presented in the published evidence, α_1 denotes the published coefficient for systolic blood pressure effect on incidence and mortality, α_2 denotes the transformed coefficient for the effect of systolic blood pressure per mm Hg on incidence and mortality.

The detailed information about input parameters and data sources is shown in Table 7-2, Table 7-3, Table 7-4. Transition probabilities affected by the change in each mm Hg systolic blood pressure are shown in Appendix 17. The equation and derivation process used for transferring the parameters of effects on incidence and mortality for n mm Hg to 1 mm Hg is shown in Appendix 18.

Alternative scenarios of salt reduction

The first scenario of this study is Scenario A, assuming the salt intake in the Chinese population reduces to 5 g/per day. Two alternative scenarios on the different reductions in salt intake were evaluated. The first alternative scenario assumes the salt intake in Chinese people reduces to 3 g/per day (Scenario B) - recommended by CASH, and the second alternative scenario is if the salt intake in Chinese population reduces to 8.5 g/per day (Scenario C) - the midpoint between WHO recommended intake value and current intake value were evaluated. Table 7-1 shows the detailed information about three scenarios in this study.

Table 7-1: The detailed information about scenarios in salt intake reduction study.

Name of analysis	Assumptions on the target of salt intake	Source
Scenario A	5g per person per day	WHO

Scenario B	3g per person per day	CASH
Scenario C	8.5g per person per day	The midpoint between WHO recommended intake value and current intake value
Baseline scenario analysis	12g per person per day (No intervention on salt intake)	-

Abbreviations: WHO: World Health Organization; CASH: Consensus and Action on Salt and Health.

Sensitivity analysis

To explore the uncertainty of this model analysis, a deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted. For the deterministic sensitivity analysis, the alternative assumption on the different reductions in salt intake was assessed. The alternative assumption is that reducing salt intake has no effect on mortality in Chinese people. For the probabilistic sensitivity analysis, a Monte Carlo simulation was conducted to estimate the parameter uncertainty. The procedure entailed iterative sampling from selected distributions for parameters that were applied in the LAM, and then recalculation of the outputs. 1000 iterations were applied and 2.5th and 97.5th of outputs were used to estimate the 95% uncertainty intervals.

The state-transition Markov model was constructed by R (version 3.4.2, https://cran.r-project.org). The Markovchain R package was employed to develop the Markov model.

Table 7-2: The effects of reduction in salt intake on systolic blood pressure

Overview of parameters	Input parameters	Affected population	Value	Description	Source
Effect of reduction in salt intake on systolic blood pressure	Effect of reduction in salt intake on systolic blood pressure in hypertensive population	Hypertensive population	-5.39 (95% CI: -6.62 to -4.15 mm Hg) per 4.40-g reduction	Meta-analysis	He et al. [90]
	Effect of reduction in salt intake on systolic blood pressure in normotensive population	Normotensive population	-2.42 (95% CI: -3.56 to -1.29 mm Hg) per 4.40-g reduction	Meta-analysis	He et al. [90]

Conversions: 1 g salt (sodium chloride) = 0.393 g sodium, 1 g sodium = 43.5 mmol sodium

Abbreviations: CI: confidence interval.

Table 7-3: The effects of reduction in systolic blood pressure on the incidence of hypertension, stroke and dementia

Overview of parameters	Input parameters	Affected population	Value	Description	Source
The effects of change in systolic blood pressure on hypertension incidence	Systolic blood pressure on hypertension incidence	-	HR 1.07 (95% CI 1.06-1.08) per 5 mm Hg	Population-based, observational cohort study	FHS [265]
The effects of change in systolic blood pressure on stroke incidence	Systolic blood pressure effect on stroke incidence in hypertensive population	Hypertensive population	RR 0.64 (95% CI 0.58–0.71) per 10 mm Hg	Meta-analysis	Thomopoulos et al. [92]
	Systolic blood pressure effect on stroke incidence in normotensive population	Normotensive population	RR 0·85 (95% CI 0.68- 1.06) per 10 mm Hg	Meta-analysis	Mattias Brunström [264]
The effects of change in systolic blood pressure on dementia incidence	Systolic blood pressure effect on dementia incidence	-	a −0.009 (−0.026 to 0.007) reduction in the risk of dementia per mm Hg SBP	Randomized controlled trial study	SPRINT-MIND[266,267]

Abbreviations: FHS: Framingham Heart Study; SPRINT-MIND: Systolic Blood Pressure Intervention Trial—Memory and Cognition in Decreased Hypertension; RR: Relative risk; HR: Hazards ratio; CI: confidence interval.

Table 7-4: The effects of reduction in systolic blood pressure on mortality

Overview of parameters	Input parameters	Affected population	Value	Description	Source
The effects of reduction in systolic blood pressure on the mortality in hypertensive population	Systolic blood pressure effect on stroke mortality in hypertensive population	Hypertensive population	RR 0.84 (95% CI 0.77–0.92) per 10 mm Hg	Meta-analysis	Thomopoulos et al. [92]
	Systolic blood pressure effect on no-stroke mortality in hypertensive population*	Hypertensive population	RR 0.90 (95% CI 0.85–0.95) per 10 mm Hg	Meta-analysis	Thomopoulos et al.[92]
The effects of reduction in systolic blood pressure on the mortality in normotensive population	Systolic blood pressure effect on stroke mortality in normotensive population	Normotensive population	RR 1.03 (95% CI 0.87- 1.20) per 10 mm Hg	Meta-analysis	Mattias Brunström [264]
	Systolic blood pressure effect on no-stroke mortality in normotensive population*	Normotensive population	RR 0.98 (95% CI 0·90–1.06) per 10 mm Hg	Meta-analysis	Mattias Brunström [264]

*The effects of the reduction in systolic blood pressure on all-cause mortality were used to represent no-stroke mortality

Abbreviations: RR: Relative risk; HR: Hazards ratio; CI: confidence interval.

7.4 Results

This section reports the results of the impacts of salt intake reduction on dementia in the future in China for Scenario A, Scenario B and Scenario C.

7.4.1 Scenario A

Scenario A assumes that the salt intake of Chinese people is to reduce the daily intake to 5g/per person per day by 2025 and keep the salt intake value until 2035. This section reported the results of the impacts of salt intake reduction on dementia in the future in China for Scenario A, including the number of cases and prevalence of dementia as well as the comparison of Scenario A and Baseline Scenario analysis (no intervention on salt intake).

The number of dementia cases and prevalence in Scenario A

The potential impacts of reducing the salt intake on dementia burden in the Chinese population were assessed from the LAM model. Scenario A, assuming the target of salt consumption is 5 grams per day, would result in the number of dementia cases reaching 22,162,646 by 2025 (95% UI 22,012,039-22,301,284), 27,291,813 by 2030 (95% UI 27,098,597-27,474,999) and 30,994,901 by 2035 (95% UI 30,759,149-31,220,898).

The crude prevalence of dementia in China for aged 65 and over was projected to be 9.75% in 2025 (95% UI 9.72-9.78%), 10.23% in 2030 (95% UI 10.20%-10.26%) and 10.33% in 2035 (95% UI 10.30%-10.37%).

For men, the number of cases was estimated to reach 7,494,580 in 2025, 8,906,128 in 2030 and 9,783,446 in 2035. The crude prevalence of dementia for men in China was projected to be 7.35% in 2025, 7.60% in 2030 and 7.60% in 2035. For women, the number of cases was estimated to reach 14,668,066 in 2025, 18,385,685 in 2030 and 21,211,455 in 2035. The crude prevalence of dementia for women in China was projected to be 11.70% in 2025, 12.28% in 2030 and 12.46% in 2035.

Figure 7-3 shows the number of dementia cases under the intervention of reduction in salt intake (Scenario A analysis).

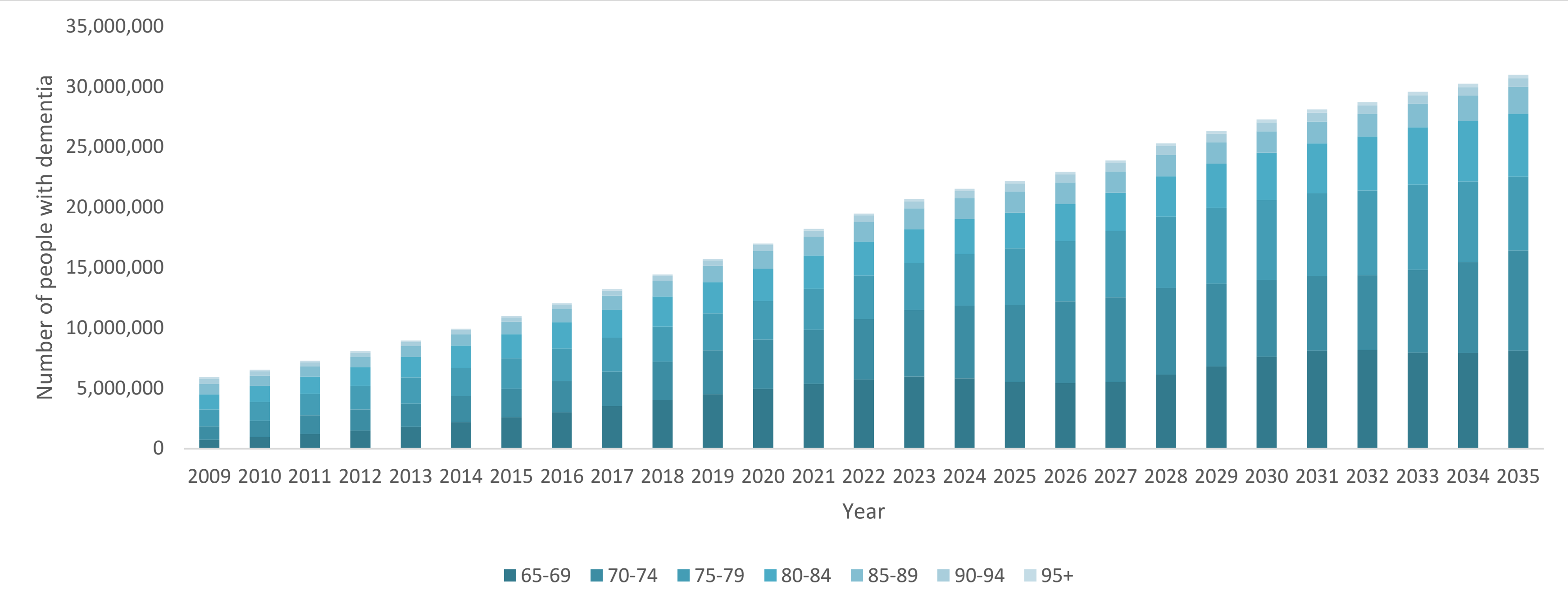
The comparison of Scenario A and baseline scenario analysis

Compared to the baseline analysis (no intervention on salt intake), the intervention on salt intake reduction (with a target of 5g/per person per day in salt intake) would probably cause fewer cases in the near future but would probably cause more additional cases later on.

For Scenario A analysis, compared with the baseline scenario (no intervention on salt intake), the salt reduction intervention might result in approximately 77,806 fewer cases of dementia by 2020, approximately 13,230 more cases of dementia by 2025, approximately 196,830 additional cases of dementia by 2030, approximately 431,250 additional cases of dementia by 2035. As compared with the baseline scenario, Scenario A will have 1.4% more dementia cases in 2035.

For Scenario A, compared with baseline scenario (no intervention on salt intake), the salt reduction intervention might result in approximately 0.21% lower in the prevalence of dementia by 2025, approximately 0.23% lower in the prevalence of dementia by 2030, approximately 0.23% lower in the prevalence of dementia by 2035.

Figure 7-3: The number of dementia cases under the intervention of reduction in salt intake (Scenario A analysis)



7.4.2 Scenario B

Scenario B assumes that the salt intake of Chinese people is to be reduced to a daily intake of 3g/per person per day by 2025 and keep the salt intake value until 2035.

The number of dementia cases and prevalence for Scenario B

For Scenario B, with the target of salt intake of 3g/per day, the number of dementia cases for the total population was estimated to reach 22,159,436 in 2025 (95% UI 22,010,093-22,296,535), 27,333,951 in 2030 (95% UI 27,142,146-27,516,175) and 31,098,236 in 2035 (95% UI 30,862,484-31,322,280). The crude prevalence of dementia in China for aged 65 and over was projected be 9.69% in 2025 (95% UI 9.66%-9.72%), 10.16% in 2030 (95% UI 10.13%-10.19%) and 10.26% in 2035 (95% UI 10.24%-10.30%).

The comparison of Scenario B and baseline scenario analysis

For scenario B analysis, compared with the baseline scenario (no intervention on salt intake), the salt reduction intervention might result in approximately 10,030 more cases of dementia by 2025, approximately 238,970 additional cases of dementia by 2030, approximately 534,580 additional cases of dementia by 2035. As compared with the baseline scenario, Scenario B will have 1.7% more dementia cases in 2035.

7.4.3 Scenario C

Scenario C assumes that the salt intake of Chinese people is to be reduced to a daily intake of 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

The number of dementia cases and prevalence for Scenario C

For Scenario C, with the target of salt intake of 5g/per day, the number of dementia cases for the total population was estimated to reach 22,160,970 in 2025 (95% UI 22,008,201-22,301,656), 27,203,378 in 2030 (95% UI 27,007,749-27,389,278) and 30,793,340 in 2035 (95% UI 30,555,187-31,022,542).

The crude prevalence of dementia in China for aged 65 and over was projected to be 9.85% in 2025 (95% UI 9.83%-9.88%), 10.34% in 2030 (95% UI 10.31%-10.38%) and 10.45% in 2035 (95% UI 10.41%-10.49%).

The comparison of Scenario C and baseline scenario analysis

For scenario C analysis, compared with the baseline scenario (no intervention on salt intake), the salt reduction intervention might result in approximately 11,560 more cases of dementia by 2025, approximately 108,400 additional cases of dementia by 2030, approximately 229,690 additional cases of dementia by 2035. As compared with the baseline scenario, Scenario C will have 0.8% more dementia cases in 2035.

Appendix 20, Appendix 21 and Appendix 22 display the number of people with dementia for different scenarios (in millions), in total, males and females. Appendix 23, Appendix 24, and Appendix 25 show the specific number of dementia cases for different scenario analyses in total, males and females. Appendix 26 shows the projected number with 95% UI. Appendix 27 shows the dementia prevalence for different scenario analysis. Detailed information about the probabilities sensitivity analysis to calculate the 95% uncertainty interval is shown in the following section.

Table 7-5: The projected number of dementia cases (Scenario A, Scenario B, Scenario C, Baseline analysis)

Year	Scenario A*	Scenario B†	Scenario C‡	Baseline analysis
2020	16997927 (16901214-17088045)	16973917 (16877895-17063751)	17038099 (16940154-17128862)	17075733 (16976583-17167572)
2025	22162646 (22012039-22301284)	22159436 (22010093-22296535)	22160970 (22008201-22301656)	22149411 (21994843-22293520)
2030	27291813 (27098597-27474999)	27333951 (27142146-27516175)	27203378 (27007749-27389278)	27094979 (26896963-27285823)
2035	30994901 (30759149-31220898)	31098236 (30862484-31322280)	30793340 (30555187-31022542)	30563654 (30321674-30795883)

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to the daily rate of 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption that the salt intake of Chinese people is to be reduced to the daily rate of 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption that the salt intake of Chinese people is assumed to reduce the daily intake to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Table 7-6: Number of new cases of dementia changed for scenarios A, scenario B, scenario C vs baseline scenario: China, population aged 65 and over (unit: thousands)

Gender	Scenario A*	95% UI	Scenario B†	95% UI	Scenario C‡	95% UI
All						
2025	13.23	(-137.37 to 151.87)	10.03	(-139.32 to 147.12)	11.56	(-141.21 to 152.24)
2030	196.83	(3.62 to 380.02)	238.97	(47.17 to 421.2)	108.4	(-87.23 to 294.3)
2035	431.25	(195.5 to 657.24)	534.58	(298.83 to 758.63)	229.69	(-8.47 to 458.89)
Men						
2025	39.66	(-57.43 to 144.43)	48.07	(-48.22 to 151.69)	21.89	(-76.71 to 128.41)
2030	127.47	(-0.52 to 262.67)	158.18	(31.65 to 292.25)	67.75	(-62.77 to 205.51)
2035	220.66	(72.11 to 371.31)	276.15	(128.57 to 425.02)	115.63	(-34.59 to 269.3)
Women						
2025	-26.42	(-141.99 to 83.76)	-38.05	(-152.4 to 70.91)	-10.33	(-128.04 to 101.11)
2030	69.37	(-88.02 to 216.62)	80.8	(-74.87 to 227.06)	40.65	(-120.24 to 191.17)
2035	210.59	(12.57 to 396.33)	258.43	(61.49 to 442.69)	114.06	(-87.8 to 301.29)

Abbreviations: UI: uncertainty interval.

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to the daily intake of 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to the daily intake of 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to reduce the daily intake to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Table 7-7: Prevalence of dementia changed for scenarios A, scenario B, scenario C vs baseline scenario: China, population aged 65 and over (%)

Gender	Scenario A*	95% UI	Scenario B†	95% UI	Scenario C‡	95% UI
All						
2025	-0.21	(-0.18 to -0.24)	-0.27	(-0.24 to -0.3)	-0.11	(-0.08 to -0.13)
2030	-0.23	(-0.2 to -0.26)	-0.3	(-0.27 to -0.33)	-0.12	(-0.08 to -0.15)
2035	-0.23	(-0.19 to -0.26)	-0.3	(-0.26 to -0.32)	-0.11	(-0.07 to -0.15)
Men						
2025	-0.15	(-0.11 to -0.19)	-0.2	(-0.16 to -0.23)	-0.08	(-0.04 to -0.11)
2030	-0.16	(-0.11 to -0.2)	-0.21	(-0.16 to -0.25)	-0.08	(-0.03 to -0.12)
2035	-0.15	(-0.1 to -0.19)	-0.19	(-0.14 to -0.24)	-0.07	(-0.02 to -0.12)
Women						
2025	-0.24	(-0.19 to -0.27)	-0.31	(-0.26 to -0.34)	-0.12	(-0.07 to -0.15)
2030	-0.27	(-0.21 to -0.3)	-0.35	(-0.29 to -0.38)	-0.13	(-0.08 to -0.17)
2035	-0.26	(-0.2 to -0.3)	-0.34	(-0.27 to -0.37)	-0.13	(-0.07 to -0.17)

Abbreviations: UI: uncertainty interval.

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to the daily intake of 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to the daily intake of 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to the daily intake of 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

7.5 Sensitivity analysis

To explore the uncertainty in this study, a deterministic sensitivity analysis and probabilistic sensitivity analysis were conducted. To explore how much the reduction in salt intake can affect the outputs of the LAM model, the deterministic sensitivity analysis was conducted by inputting the different parameters in the LAM manually. To explore the uncertainty arising from parameter imprecision in the LAM model, a probabilistic sensitivity analysis was conducted. The selected probability distribution emerged from the plausible range from observed data. Then a Monte Carlo simulation method was used as the sampling method in this step.

7.5.1 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis was conducted to estimate the uncertainty interval. A Monte Carlo simulation was performed as the sampling method from the plausible distribution. 1000 iterations were performed to estimate 95% uncertainty intervals (95% UI) for the outputs in the LAM model. Appendix 25 shows the projected number of dementia cases for different scenario analyses with 95% UI.

7.5.2 Deterministic sensitivity analysis

The deterministic sensitivity analysis was to project the impacts of intervention on reduction with different assumptions on the future burden of dementia in China. One alternative assumption (test 1) was examined but with no effect on the reduction in salt intake on mortality.

For test 1 (assuming there is no effect of reduction in salt intake on the stroke mortality and all-cause mortality), the number of dementia cases is projected to be fewer in the future compared with scenario A analysis (with the target of salt intake 5g/per day) and baseline analysis (no intervention on salt intake). To be specific, for test 1 (assuming there is no effect of reduction in salt intake on stroke mortality and all-cause mortality), the number of dementia cases is projected to be 29.3 million, which is 1.7 million fewer than the scenario A analysis and 1.2 million fewer than the baseline scenario analysis. The decrease in mortality may explain the growing number of dementia cases caused by the intervention on salt intake reduction.

Table 7-8: The comparison of test 1, Scenario A analysis and baseline analysis

Year	Test 1*	Scenario A†	Baseline analysis
2009	5,931,454	5,934,616	5,936,106
2010	6,535,223	6,543,768	6,549,234
2011	7,250,685	7,267,102	7,278,884
2012	8,037,902	8,065,349	8,085,160
2013	8,907,998	8,950,300	8,979,544
2014	9,870,130	9,932,198	9,971,574
2015	10,888,065	10,975,511	11,024,939
2016	11,914,568	12,033,607	12,091,860
2017	13,052,208	13,210,062	13,276,578
2018	14,226,435	14,430,691	14,503,589
2019	15,465,990	15,725,007	15,802,306
2020	16,675,842	16,997,927	17,075,733
2021	17,818,223	18,211,663	18,284,798
2022	19,011,449	19,485,291	19,550,495
2023	20,102,229	20,664,476	20,715,155
2024	20,873,360	21,530,057	21,554,224
2025	21,405,843	22,162,646	22,149,411
2026	22,082,914	22,938,241	22,886,787
2027	22,941,331	23,894,705	23,806,374
2028	24,243,715	25,297,938	25,181,871
2029	25,202,472	26,352,615	26,198,292
2030	26,048,507	27,291,813	27,094,979
2031	26,784,626	28,117,789	27,874,938
2032	27,306,806	28,724,684	28,430,228
2033	28,085,174	29,588,490	29,249,734
2034	28,672,236	30,255,517	29,868,655
2035	29,333,796	30,994,901	30,563,654

* Test 1 based on the assumption that the changed blood pressure had no effects on mortality.

† Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to the daily intake of 5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

7.6 Discussion

7.6.1 Key findings

This study is the first, to our knowledge, to estimate the potential impacts of reduction in salt intake on the future burden of dementia in China.

This study suggests that compared with persisting with the 2008 average salt intake level, assuming the intake is reduced to 5 g/person per day by 2025 and remained stable to 2035, the intervention might result in 431,250 additional dementia cases by 2035 in China.

7.6.2 Strengths and limitations

There are three strengths of this study from the perspective of study design, study outcome and data sources.

Firstly, from the perspective of the study design, this study allowed the simulation of the transitions between hypertension, stroke, dementia, and death, according to age, sex and calendar year. This makes these estimations closer to real-life settings. The closer to a real-life model provides a more accurate estimation of the possible impacts of reduction in salt intake on dementia burden in China.

Secondly, from the perspective of the study outcome, this study selected dementia as the model outputs to explore the potential impacts of reduction in salt intake on the future burden of dementia in China. To our knowledge, there are no previous studies modelling the impacts of reduction in salt intake on the future burden of dementia in China. This study can fill this research gap.

Thirdly, modelling work also benefited from relatively high-quality data about the association between salt intake and blood pressure. To be specific, this study employed the Cochrane meta-analysis of trials, only including the trials for which salt reduction interventions were evaluated over a minimum duration of 4 weeks, which was considered as an important factor when evaluating salt intake reduction public health intervention.[90,263] The high-quality data sources on parameters of modelling development laid the foundation of this study. To conclude, the more real-life study design, the specific modelling outcome and high-quality data sources are the strengths of this study.

Despite the more real-life study design, the specific modelling outcome and high-quality data sources, this study also has some limitations that need to be mentioned. The first limitation of this study is that this study did not consider the effect of reduction in salt intake on gastric cancer, oesophageal cancer, kidney disease or osteoporosis, which meant this study might underestimate the health benefits of the salt reduction intervention.

Moreover, this study did not account for the potential benefits of using a salt substitute. For example, some manufacturers in China provided the reduced-sodium, high-potassium salt substitute (65% sodium chloride, 25% potassium chloride, 10% magnesium sulphate) to replace normal salt (100% sodium chloride). This type of salt substitute might have some other health benefits on hypertension and stroke, which are difficult to account for in the model.

The third limitation might be due to the uncertainty of the public response to the intervention on reduction in salt intake. For example, the food industry manufacturers might reduce the salt by adding flavour-compensating ingredients such as more sugar, which could counteract some of the health benefits of sodium reductions. This might lead to other unexpected effects on health outcomes.

The fourth limitation is that in the baseline scenario analysis, the LAM model assumes the declining trend in salt intake is accounted in the time trends in dementia incidence and does not separate the effects of the reduction in salt intake on each health state. This assumption, although reasonable and commonly applied in modelling studies, lacks verification, as evidence on the extent of reduction in salt intake on time trends in dementia incidence and overall health status is difficult to estimate.

Thus, the effects of the reduction in salt intake on other diseases, the assumptions on modelling design, the uncertainty of the response from the public and industry on the salt reduction intervention and the assumption in the baseline scenario analysis are the limitations of this study.

7.6.3 Comparison with other studies

This study employed a state-transition Markov model to explore the potential impacts of reduction in salt intake on the future burden of dementia in China.

Several studies have used modelling methods to explore the health gains of reduction in salt intake, but the majority of these studies examine the number of people who avoid cardiovascular disease and the number of lives saved in the future. In the past, the majority of studies concentrated on the effects of salt reduction in high-income nations[130,138-140]; however, more and more studies are now focusing on the impacts of salt reduction in middle-income countries[11,134-136].

While one study suggested that reducing hypertension prevalence might reduce the prevalence of dementia or Alzheimer's disease, the authors did not account for the reduction in mortality that would result from better vascular health.[268] One recent study employed microsimulation model methods (the Future Elderly Model) [269], which account for the effects on the incidence and mortality, and reported that the lowering of hypertension incidence would result in more additional dementia cases. This result is consistent with this study.

7.7 Conclusion

To conclude, this study employed a state-transition Markov model to explore the potential impacts of the reduction in salt intake on the future burden of dementia in China. The reduction in salt intake might result in further cases by 2035. Compared with maintaining the 2008 average salt intake level, assuming the intake is reduced to 5 g/person per day by 2025 and remained stable to 2035, the intervention might result in 431,250 additional dementia cases by 2035 in China.

8 Discussion

This chapter brings together the work of three studies in this thesis, the subject of which is dementia in China. The content of this thesis is organized according to (1) examining the recent time trends in dementia incidence in China, (2) projecting the future burden of dementia in China, and (3) exploring the impact of the reduction in salt intake on the burden of dementia in China in the future. This chapter summarises the key findings of three studies in this thesis, interprets the results, reviews the strengths and limitations, discusses the implications and outlines the potential future research work in China.

8.1 Summary of key findings

Three studies were linked together by research progress. Three sequential questions were answered: (1) Is dementia incidence increasing in China? (2) What will be the burden of dementia in China in the future? (3) How will interventions about reducing salt intake impact on the burden of dementia in China in the future?

To examine the recent time trends in dementia incidence in China, CLHLS wave 3 to wave 8 were used as the data source. Dementia was ascertained at each wave using standardised cognitive and functional impairment criteria. The competing risk events of mortality and non-random losses to follow-up were accounted for in analysing the time trend in dementia incidence. A joint model was employed to study the time trend in dementia incidence in longitudinal cohort data. R package JM was employed to fit the joint model.

To project the future trends in the number of dementia cases and prevalence of dementia in China, this thesis developed a novel state-transition Markov model - LAM - which simulates the Chinese population ageing process. The data on people aged 40 years and over from CLHLS (2002, 2005, 2008, 2011 and 2014) were harmonized and combined to obtain the information about whether the participants had hypertension, stroke, dementia, and on their information about death and death causes. The population structure in the initial year was driven from the Chinese Statistical Yearbook. The stroke-cause and all-cause mortality was obtained from the GBD 2019. Changes in calendar trends in disease incidence or mortality were the input in the model. R package Markovchain was employed to develop a state-transition Markov model.

To explore the impact of reduction in salt intake on future dementia burden in China, CHNS (1991, 1993, 1997, 2000, 2004, 2006 and 2009) were used as data sources. A linear regression model was fitted to obtain the salt intake in China at the model start year (2008). The WHO guideline recommended daily salt intake of 5g/per day. The salt intake of Chinese people is assumed to be reduced to the daily intake recommended by WHO (5g/per day) by 2025 and keep the recommended salt intake until 2035. The developed state-transition Markov model, LAM, was used to explore the impact of reduction in salt intake on the number of dementia cases and prevalence of dementia in China.

Study one indicates that the dementia incidence was increasing in China between 2002 to 2014. An annual 2.5% increase in dementia incidence was found from this study after correcting for competing risks of mortality and non-random losses to follow-up.

Study two indicates that the number of dementia cases is projected to increase substantially by 2035. The number of people with dementia is projected to be 22.15 million by 2025, 27.09 million by 2030 and 30.56 million by 2035 and the prevalence of dementia is projected to be 9.96% by 2025, 10.46% by 2030 and 10.56% by 2035.

Study three indicates that the reduction in salt intake might result in further cases by 2035. Compared with the persisting 2008 average salt intake level, assuming salt intake is reduced to 5 g/person per day by 2025 and remained stable to 2035, the intervention might result in 431,250 additional dementia cases by 2035 in China.

8.2 Interpretation of the results

8.2.1 Comparison with other studies

The results in this thesis are compared with existing evidence in the following ways:

(1) Providing an estimate of recent time trends in dementia incidence in China

To our knowledge, **Study one** is the first nationally representative studies of recent time trends in dementia incidence in China using longitudinal data and joint modelling technique.

The evidence that is available, indicates that high-income countries have downward or stable time trends in dementia incidence. Some studies using regional data and the traditional statistical methods without accounting for non-random losses to follow-up and deaths, have reported an upward trend in the incidence of dementia over time in China. There appears to be no study examining the recent time trends in dementia incidence in China using an appropriate method and representative national data.[9] This gap in the literature is filled by this thesis.

(2) Providing a projection of future trends in the burden of dementia in China in the future

As far as is known, **Study two** is the first study to explore the future burden of dementia, considering the time trends in dementia incidence, stroke incidence, stroke mortality as well as the change in population ageing simultaneously based on a novel epidemiological prediction model.

Some epidemiological dementia projection studies conducted in high-income countries take time trends in dementia incidence into account[94], while it appears that the epidemiological dementia projection study conducted in China did not. This study, based on the associations between hypertension, stroke, dementia, and death, according to age, sex and calendar year provides a more accurate projection of future trends in the burden of dementia in the Chinese population.

(3) Providing explorations of the impacts of the reduction in salt intake on the burden of dementia in China in the future

Study three is the first, to our knowledge, to estimate the potential impacts of reduction in salt intake on the future burden of dementia in China.

Several countries and regions, including China[134], the United Kingdom[130], India[135], Brazil[136], Cameroon[137], New Zealand[138], and Europe[139], have conducted studies to examine the effects of reducing salt consumption on health.

The majority of these studies used the state-transition Markov modelling method, whereas only one study used a combination method involving a macro-simulation model and a micro-simulation model. Moreover, the majority of these studies selected cardiovascular disease or a related condition as the outcome. This study considers dementia to be the output of a modelling method that can both fill a gap in academia and assist the government in enhancing its capacity for accurate public health policy projections based on evidence.

8.2.2 Integration of chapters

The main purpose of this thesis is to project the future burden of dementia in China. The projection of the future number of people with dementia in China, only based on the constant prevalence of dementia, is not accurate. The accurate projection requires accounting for the time trends in dementia incidence, complex effects of epidemiological trends in stroke and population structure. On the one hand, the reduction in stroke incidence leads to a decrease in dementia incidence. On the other hand, the prolongation of life expectancy resulting from the reduction in stroke mortality leads to an increase in the number of dementia cases. Thus, the time trends in dementia incidence, stroke incidence, stroke mortality as well as the change in population ageing need to be accounted for simultaneously in the epidemiological projection study.

Study one estimates the recent time trends in dementia incidence in China. Study one showed an annual 2.5% increase in dementia incidence in China. This incidence trend contributed input data for a novel state-transition Markov model to project the future burden of dementia in China.

Study two develops a novel state-transition Markov model, LAM model, to project the future burden of dementia in China. The LAM model accounts for the time trends in dementia incidence, stroke incidence, stroke mortality as well as the change in population ageing simultaneously. Study two indicates that the number of people with dementia is projected to be 22.15 million by 2025, 27.09 million by 2030 and 30.56 million by 2035. The finding of Study two not only projects the future number of dementia cases in China but also provides a model base for Study three.

Study three explores the impacts of reduction in salt intake in the future in China. Study three applied the LAM model, which was developed in study two. Study three suggests that compared to a scenario of persistent 2008 levels, assuming that the salt intake is reduced to 5 g/per person per day by 2025 and maintained this value by 2035, this intervention is projected to avoid 77.81 thousand dementia cases by 2020 and add a further 431.25 thousand dementia cases by 2035 in China. Study three is an application of the LAM model.

In conclusion, the thesis is comprised of three sequential and progressively deeper studies of dementia in China. These three studies are connected by the logical progression of research. The research procedure progresses from data analysis to model development to the application of models. Estimates of recent time trends in dementia incidence pave the way for later analysis. The process of developing the LAM model involves projecting the future burden of dementia, and a future application of the LAM model examining the potential impacts of salt intake reduction on the burden of dementia in China.

8.3 Strengths and limitations

8.3.1 Strengths

There are two strengths of this thesis from the perspective of methodology and data source.

From a methodological standpoint, this thesis employed two advanced statistical techniques, namely the joint modelling method and state-transition Markov modelling. The joint modelling is used to estimate the recent temporal trends in dementia prevalence in China. Through tracking changes in intrinsic biomarkers and linking the longitudinal model and survival analysis model, the joint model is able to avoid the possibility of selection bias in the cohort data, as compared to conventional statistical modelling (the Cox regression model). The state-transition Markov modelling method – LAM – is developed to project the future burden of dementia in China by 2035 and to investigate the impacts of reducing salt intake on the number of dementia cases and prevalence proportion of dementia in China by 2035. The LAM model is a state-transition Markov model that allows us to simultaneously consider the temporal trends in dementia incidence, stroke incidence, stroke mortality, and population ageing. Compared to conventionally available statistical methods (extrapolation and linear regression model), the LAM represents and synthesises the observed transitions between the health states of interest to provide a more accurate projection.

From the perspective of data sources, this thesis employed a representative data source-CLHLS, which has with two features - a large study sample containing all levels of educational attainment and a long follow-up time. These characteristics enable us to investigate the recent time trends in the incidence of dementia and simulate the transitions between these health states among the older people in China.

8.3.2 Limitations

Some limitations also need to be considered in this thesis.

The first limitation of this study was about the study population sample. Initially, although CLHLS covers a large sample of China (23 provinces in China), it still does not possess data from other areas (Guizhou, Yunnan, Xizang, Gansu, Qinghai, Ningxia, Xinjiang, Inner Mongolia, Hong Kong, Taiwan, and Macau). Because the trends in dementia incidence may be dissimilar between the east-west area and urban-rural region, the fact that the sample data do not cover all the Chinese regions may influence the representativeness of the data.

The second potential limitation is caused by the recall bias and covariate definition change over time. The health status (chronic disease) and lifestyle factors of CLHLS were collected by self-reporting. This process of covariate definition may lead to recall bias and changes of diagnosis criteria over time.

This study employed an operational case definition based on standardised assessments of cognition and function to define dementia (standardised assessment of cognition and function to define dementia is more appropriate for dementia definition in the time trends analysis, as the clinical diagnosis of dementia is changing over time), because lack of available clinical assessments and the complexity of sub-types of dementia (Alzheimer's disease, Vascular dementia, mixed dementia, frontotemporal dementia, Parkinson's disease dementia, Lewy body dementia), this study has to consider dementia as a homogenous condition and cannot monitor the subtypes.

The fourth limitation of this thesis is practice effects. This thesis employed CMMSE to assess the cognitive ability of the Chinese population. The repeated application of such tests might lead to improvements in performance, which might lead to an underestimate of dementia incidence.

8.4 Implication of the findings

8.4.1 Implication of the findings inside and outside academia

The work in this thesis has important implications inside and outside academia.

The burden of dementia has been growing and will continue to increase in future decades, driven by population ageing, and possibly an increasing dementia incidence rate. An epidemiological prediction model is developed to estimate the number of dementia cases in the future in China, and to use as a tool to estimate the number of cases that may be prevented by salt intake reduction intervention in the Chinese population.

The benefits of this thesis inside academia can be divided into knowledge and methodology. In terms of knowledge, this thesis fills some academic research gaps. To be specific, this thesis provides the first study to estimate the trend in dementia incidence in a middle-income country, to explore the future burden of dementia, considering the calendar changes in dementia incidence, stroke incidence, stroke mortality as well as population structure changing based on a state-transition Markov model, and to explore the potential impacts of reduction in salt intake on the future burden of dementia in China. In terms of methodology, the state-transition Markov model developed in this thesis also provides scholars with a possible tool to explore the potential impacts of possible preventive interventions on the burden of dementia in the future.

This thesis also has some important implications for policymakers and other stakeholders outside the academic sector. First, it is important to improve the awareness of dementia in China. The new evidence presented in this thesis confirms a worrying trend toward an increase in the incidence of dementia over the last 12 years. The potential for preventing dementia is of widespread interest. Specific and effective actions for reducing dementia risk factors across the life course are needed, such as reducing the prevalence of diabetes. It is never too early and never too late in the life course for dementia prevention.

Second, there is a clear and urgent need to improve healthcare coverage in China for people living with dementia now and in the future. This study shows that the number of dementia cases in China is projected to increase to more than 30 million by 2035. Through the projection model, this thesis suggests that the Chinese government and society need to extend the coverage of healthcare, access to care, treatment, and support for people with dementia.

Third, reduction in salt intake and mid- and late-life blood pressure may reduce risk in those susceptible to dementia. However, this anti-hypertension intervention has effects on other health outcomes, with unexpected consequences for population health, for example, prolonging life expectancy in the older people could lead to increased dementia cases. Dementia is accompanied by cognitive and functional impairment, which has a profound effect on the patient’s quality of life, caregiver burden, and need for and cost of care. This study suggests that public health policy should not be isolated, particular in vascular diseases. Interventions require overall planning and coordination as they involve many supporting policies and measures, such as increasing the number of social care givers.

8.4.2 Policy implications in the Chinese context

The Chinese government has identified dementia as a priority in Chinese public mental health. The Chinese government aims to establish a public health service system that can more accurately monitor the trend of dementia and provide care services for the older people with dementia. The work in this shows the time trends in the dementia incidence between 2002 to 2014, projects the future number of dementia cases in the China up to 2035, and explores the potential impacts of reduction in salt intake on dementia burden in China. The work in this thesis helps to estimate the trends of dementia incidence and suggests the needs of dementia care in China will increase in the future due to the increasing number of dementia cases. The scenario analysis in this thesis also suggests that interventions require overall planning and coordination as they involve many supporting policies and measures, such as increasing the number of social care givers (because declining trends in salt intake will result in higher burden of dementia cases in China in the future, as a consequence of reduced competing mortality risks). This study provided answers to significant concerns regarding dementia in China (current time trends in dementia incidence and future time trends in dementia burden) and shed light on the impacts of the intervention policy on dementia burden in the future in China (intervention on reduction in salt intake).

8.5 Future work

This is the first study to estimate the recent time trends in dementia incidence in China, to project the future burden of dementia in China, and to investigate the potential impact of an intervention of reducing salt consumption on the number of dementia cases in China. However, our understanding of dementia in China is incomplete, and many questions remain unanswered on this subject. These questions concern the field of methodology, the application of the model, and the outcome of the study. In this section, we discuss the questions that we can concentrate on in the future.

8.5.1 Exploration of impacts of alternative interventions to prevent dementia on the number of dementia cases in China in the future

Changes in dementia incidence may be influenced by a complex interplay of lifestyle changes with regard to risk factors. The Lancet Report 2020 indicated that, if twelve potentially reversible risk factors are accounted for, 40% of the dementia cases may be preventable.[38] These risk factors include early-life, mid-life and later life risk factors.[38] Nonetheless, it remains unknown how interventions aimed at modifying risk factors would impact on the dementia burden in China. The LAM can be used to examine, for instance, how interventions such as quitting smoking and using hearing aids would impact on the prevalence of dementia. In the future, LAM can be used to investigate the impacts of alternative interventions to prevent dementia on the number of dementia cases in China by scenario analysis.

8.5.2 Development of alternative forecasting models to project the future burden of dementia in China in the future

The LAM, the state-transition model developed in this thesis, represents and synthesises the observed transitions between the health states of interest and provides a more accurate projection of the dementia burden in

China. The development of a micro-simulation model to project the future burden of dementia in China is a possible future work direction. For example, Canada's Population Health Model and FEM employ individual level data on social, behavioural and health factors to project the future burden of specific disease and evaluate different scenarios.[270,271] A micro-simulation would also aid in the external validation of the LAM model, despite the fact that micro-simulation development is complex and requires a high level of computational capability [270]. In short, alternative forecasting models to project the future burden of dementia in China can be a research direction in the future.

8.5.3 Projection of economic cost of dementia in China in the future

This study projects the number of dementia cases and dementia prevalence in China. The economic cost of dementia is an additional important and potential research topic for epidemiological forecasting. The projection study about dementia cost in China requires data concerning direct medical costs (e.g. inpatient and outpatient services with related medications and other therapies), direct non-medical costs (e.g. the costs of caregiving and the costs of transportation and special equipment) and indirect costs (e.g. loss of productivity by both patients and their informal caregivers). For example, Hurd in 2015 forecasted the economic costs of dementia in the United States by 2040 and Huang in 2022 forecasted the burden of care for individuals with dementia in China from 2010 to 2050 by extrapolation.[31,272] The combination of projection model and health economic cost estimation can provide a more accurate projection for the future economic cost of dementia in China. In brief, the economic cost of dementia in China can also be studied in the future by combining epidemiological data and health economic data.

In conclusion, there are possible future research directions in the fields of model application, model development and study subject. Examining the impacts of alternative interventions on the number of dementia cases in China by scenario analysis, developing alternative forecasting models to project the future burden of dementia in China, and projecting the economic cost of dementia in the future are the three possible research directions.

9 Conclusion

The burden of dementia has been growing and will continue to increase in future decades, driven by population ageing, and possibly an increasing dementia incidence rate. A novel epidemiological prediction model was developed to estimate the number of dementia cases in the future in China, and to use as a tool to estimate the number of cases that may be prevented by salt intake reduction intervention in the Chinese population.

This thesis employed joint modelling to study for the time trends in dementia incidence in China and develop a state-transition Markov model to project the future burden of dementia in China and applied this model to explore the impacts of reduction in salt intake on dementia cases in China in the future. An annual 2.5% increase in dementia incidence was found from this study after accounting for competing risks of mortality and non-random losses to follow-up. For the burden of dementia in the future, the number of people with dementia is projected to be 22.1 million by 2025, 27.1 million by 2030 and 30.6 million by 2035. Prevalence of dementia is projected to be 10.0% in 2025, 10.5% in 2030 and 10.6% in 2035. An intervention scenario was examined using the Markov model. Compared with the persisting 2008 average salt intake level, assuming the intake is reduced to 5 g/person per day by 2025 and remained stable to 2035, the intervention might result in 431,250 additional dementia cases by 2035 in China.

2,300 years ago, curious about an ideal society, people asked Mencius, one of the most famous philosophers in China, what an “ideal society” looks like. Mencius answered: “Treat with respect and care for the elders in my family, and then by extension, also the elders in other families.”[273] This reflects the ancient Chinese people's beautiful compassionate vision of society with the older people. Dementia is one of the most important diseases that occur in old age and poses a huge challenge for China. What this thesis has shown here is the view of dementia in China in the past, present, and future, and the perspective on intervention. In light of the upward trends in dementia cases in China, it still needs increased efforts to address the growing challenges of dementia in China.

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Appendix

Appendix 1: The Global Plan of Action on Public Health Responses to Dementia 2017-2025.

The Global Plan of Action sets out specific objectives in seven areas to move from plan to action in order to address the global challenge of dementia. Firstly, WHO hopes that by 2025, 75% of Member States (Number=146) adopt national dementia response plans, policies and frameworks. Up to now, there are only 31 countries in the world that have adopted their national dementia plan to act on dementia (27 WHO members, 4 no-WHO members), which only reaches 19% of the target. Secondly, the Global Action Plan proposed that, 50% of countries have initiatives to promote dementia friendly societies by 2025. Thirdly, countries around the world should reduce the risk of developing dementia for the individual. Governments need to reduce the risk of developing dementia for individuals by controlling the risk factors for dementia. Fourthly, governments need to take action to improve the proportion of people who could get a timely diagnosis of dementia by 2025. The WHO wants 50% of people with dementia in 50% of countries to be timely diagnosed by 2025. Fifthly, 75% of countries are expected to be able to run support and training programmes for caregivers and dementia patients' families by 2025. Sixth, 50% of countries are expected to be able to collect a core set of indicators of dementia by 2025. Seventh, the number of outputs of global research on dementia will double between 2017 and 2025. In this unprecedented time, The Global Action Plan emphasized that strengthening dementia as a public health priority has become particularly important, especially in middle-and low-income countries.

Appendix 2: Historical development of national policies related to dementia in China since 2010

Table: Historical development of national policies related to dementia in China since 2010

Period	Date	The title of policy	The aim or main content related to dementia	The institute
14th Five-Year Plan (2021-2025)	01 Mar 2022	The 14th-Five Year Plan for Healthy Ageing	Strengthen health education and improve the active health ability of the elderly. Improve the prevention and health care service system that pays equal attention to physical and mental health. Focus on continuous services and improve the level of medical services for the older people. Improve the care service system coordinated by home, community, and institutions for the disabled older people. Further, promote the development of the combination of medical service and nursing. Develop traditional Chinese medicine for older people health services. Strengthen the construction of older people health service institutions. Improve the capacity of older people health service.	National Health Commission, Department of ageing health

			Promote the development of science, technology and industry for healthy ageing.	
13th Five-Year Plan (2015-2020)	11 Sep 2020	National Dementia Plan (To explore the service program of Alzheimer's disease prevention and treatment)	Aim to raise public awareness of the prevention and treatment of dementia to 80% by 2022.	National Health Commission
13th Five-Year Plan (2015-2020)	Sep 2019	Core information on prevention and intervention of Alzheimer's disease	To enhance the whole society's awareness of Alzheimer's disease prevention, promote the prevention gateway to move forward, improve the level of prevention knowledge, reduce the growth rate of Alzheimer's disease incidence, and improve the health of the older people.	General Office of National Health Commission
13th Five-Year Plan (2015-2020)	15 July 2019	The Action Plan for Healthy China 2030	Objectives: by 2022 and 2030, the disability rate of the elderly aged 65-74 will decrease; the growth rate of senile dementia among people aged 65 and above will decrease; the proportion of medical and health services provided by pension institutions for the older people in different forms, and the proportion of green channel for convenient services such as registration and treatment provided by	National Health Commission

			medical institutions for the older people will reach 100% respectively; The community day-care centres and other communities will be strengthened. The construction of older people care institutions in the district provides support for home-based care. Gradually establish a policy system to support family care, support adult children and older people parents to live together, and promote the home-based and community-based care services.	
13th Five-Year Plan (2015-2020)	25 Oct 2016	The Planning Outline of Healthy China 2030	Strengthen the health guidance and comprehensive intervention of common and chronic diseases of the older people and strengthen the health management of the older people. Promote the development of mental health and care services for the older people and strengthen the effective intervention of the Alzheimer's disease.	State Council
12th Five-Year Plan (2010-2015)	18 June 2015	National mental health five-year plan (2015-2020)	Make dementia (as well as autism, schizophrenia and depression) as a priority. The main objectives of the plan include the development of integrated services, the training of mental health professionals, the improvement of rehabilitation services and community-based and family-based support, as well as the promotion of social awareness and the alleviation of social stigma.	State Council

12th Five-Year Plan (2010-2015)	17 Sep 2011	The 12th-Five Year Plan for the cause of the ageing in China	It is encouraged to provide special training and support for family members of the older people and give full play to the role of family members in spiritual care and psychological support. The early recognition rate of senile dementia, depression and other mental diseases reached 40%.	State Council

Data sources: National Health Commission of China (http://www.nhc.gov.cn/)

Appendix 3: Search terms used for systematic review

Search terms used for systematic review

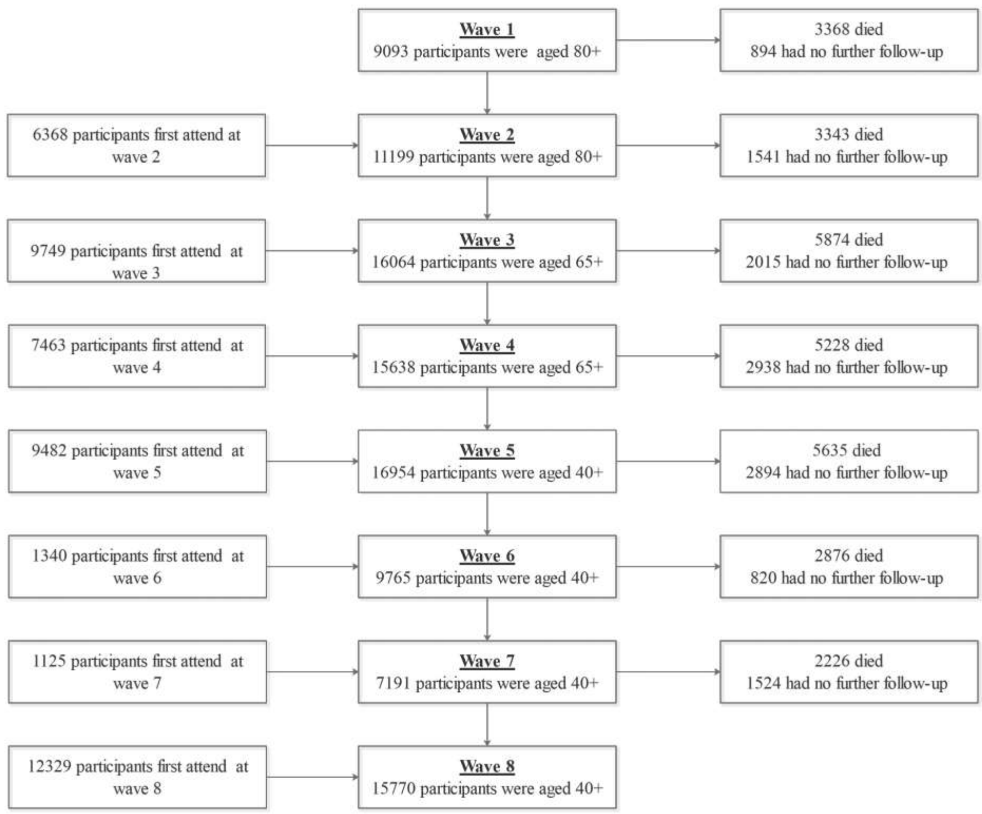
The existing evidence were reviewed on 01 March 2022, searching the PubMed for studies projecting future trends in stroke, dementia and life expectancy in China. The search terms used for research in context were as follows:

Search terms (PubMed)	"Dementia" OR "Stroke" OR "Hypertension"[212] OR "Life expectancy"[212] OR Dementi*[ti] OR Longeviti[ti] OR Life expectan* [ti]
	AND
	"Computer Simulation" OR "Forecasting"[212] OR "Population Forecast" OR Simulation*[ti] OR Model*[ti] OR forecast*[ti] OR Project*[ti]
	AND
	"China"[212] OR "Chinese"[212] OR "China"[ti] OR "Chinese"[ti]

Papers which were not relevant were removed manually. The additional searches were using the references of relevant studies. The results of the searching can be found in Table 2-8.

Appendix 4: The flow-diagram of participants in CLHLS between 1998 to 2018.

Figure: The flow-diagram of all participants in CLHLS between 1998 to 2018.



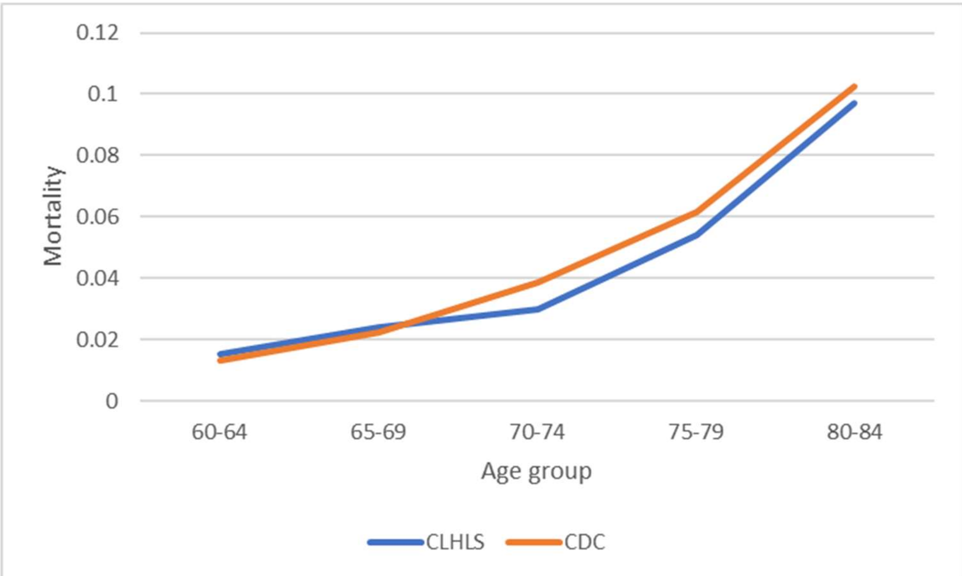
Appendix 5: The number and proportion of missing value in CLHLS

	Wave 3 N (%)	Wave 4 N (%)	Wave 5 N (%)	Wave 6 N (%)	Wave 7 N (%)
Sex	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Age	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Cognitive assessment	8(0.0)	19(0.1)	88(0.5)	336(3.5)	457(6.4)
Functional assessment	0(0.0)	0(0.0)	0(0.0)	65(0.7)	126(1.8)
Education	78(0.5)	10(0.0)	22(0.2)	2(0.0)	5(0.0)
Stroke	640(4.0)	926(5.9)	288(1.7)	360(3.7)	270(3.8)
Hypertension	8(0.0)	24(0.2)	1(0.0)	9(0.0)	3(0.0)
Hear loss	691(4.3)	466(3.0)	1654(17.0)	561(5.8)	258(3.6)
Diabetes	726(4.5)	972(6.2)	335(3.4)	426(4.4)	303(4.2)
Smoke	31(0.2)	3(0.0)	0(0.0)	7(0.0)	2(0.0)
Drink	34(0.2)	4(0.0)	0(0.0)	1(0.0)	1(0.0)
Exercise	34(0.2)	0(0.0)	1(0.0)	5(0.0)	5(0.0)
Social isolated	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Region differences	65(0.4)	31(0.2)	15(0.2)	7(0.0)	1(0.0)

Appendix 6: The comparison of mortality in CLHLS and CDC

To explore the reliability of deaths measured by proxy-reported in CLHLS, the mortality from CLHLS and mortality reported by the Chinese Center for Disease Control and Prevention (CDC) were compared. The mortality from CLHLS was measured by proxy reported and the three-year mortality was transferred to one-year mortality by the equation. The mortality from the CDC was obtained from the “National disease surveillance system-death cause surveillance data set”. The wave 4 death information was selected and compared with mortality from CDC 2004 (the mid-point of two interview waves). The five-year age group mortality from CLHLS was akin to that of the CDC. The figure shows the comparison of mortality from CLHLS and CDC.

Figure: The comparison of mortality from CLHLS and CDC.



Appendix 7: The process of developing LAM

In order to build a realistic, representative and accurate model, data sources were used from a longitudinal study. Quantitative rules were derived from this longitudinal study to drive simulation, thus, to project the future burden of population ageing. Change in calendar trends in health status incidence can then be posed by inputting calendar trends in both the dementia incidence and stroke incidence trends to assess the likely effects on the outcome of interest. Data cleaning and manipulation were carried out using Stata Model implementation and simulation was programmed in R.

The process of constructing, implementing and simulating the model followed several steps:

(1) Design simulation processes to mimic actual pathways to population ageing.

(2) Establish the starting sample and calculate different prevalence and number of participants with different health states at the start year.

(3) Undertake analysis on available data to drive transition probabilities related to different health states.

(4) Add the factor of calendar trends in disease incidence related to health states.

(5) Beginning with the starting sample, apply equations to the stochastic simulation process to drive change in number and prevalence of different

health states in the Chinese older people.

(6) Validate the results of the LAM simulation process and outcomes against other studies and later record.

(7) Employ a Monte Carlo simulation method to perform probabilistic sensitivity analysis.

(8) Using different calendar trends in disease incidence to carry out a deterministic sensitivity analysis.

Appendix 8: The data sources and input parameters in LAM

Data sources

Data sources are from CLHLS (2002-2018) and China Statistical Yearbook Information estimation and projection. Data on people aged 40 years and over from CLHLS (2002, 2005, 2008, 2011 and 2014) were harmonized and combined to obtain the information about whether the participants had hypertension, stroke, dementia, and on their information about death and death causes. The China Statistical Yearbook provides the population structure and National Bureau of Statistics (NBS) of China provides the total population at the initial year. The GBD 2019 provides the stroke-cause and all-cause mortality at the initial year.

These data sources were used in the following ways:

(1) To form an initial sample at the start year (2008), by providing the proportion of each health state of people (aged 40 and over) in China. The proportion of each health state was obtained from CLHLS and the population for each 5-year age group for males and females respectively, was obtained from the China Statistical Yearbook and the NBS of China. The basic characteristics of the initial sample can be found in Table 5-1.

(2) To derive the 3-year transition probabilities from the longitudinal data, an equation was used to transfer the 3-year transition probabilities to one-year transition probabilities. The CLHLS wave 3 to wave 7 were used to estimate the transition probabilities for disease-free, hypertension, stroke, dementia, and deceased status.

(3) Time trends in stroke and stroke-cause mortality in China were provided by the GBD Study 2019.

(4) To provide the prevalence of dementia, hypertension, stroke and mortality (stroke-cause mortality and all-cause mortality) in later years with which to compare the simulated results of the running model in this study.

Table: Input parameters and data sources in the LAM model

Parameters	Data sources
Prevalence proportion of each health state at start year	● CLHLS
Transition probabilities	● CLHLS-Transition probabilities from health state to alive state. ● CLHLS and GBD 2019-Transition probabilities from health state to death state.
Parameters related with time effects	● Time trends in dementia incidence- CLHLS ● Time trends in stroke incidence-GBD 2019 ● Time trends in stroke mortality-GBD 2019
Population structure	● China Statistical Yearbook
Chinese population	● NBS of China

Appendix 9: Description of health states in LAM

LAM model (Life-cycle Ageing Model) is a state-transition Markov model that follows the progression of the Chinese population aged over 35 from 2002 to 2014 through states of hypertension, stroke and dementia to death. The model structure is presented in Figure 6-1, the description of health state is presented in this table.

Table: Description of health states

Number of health state	**Name**	**Description**
1	Disease-free state	People without hypertension, cognitive impairment, functional impairment
2	Hypertension state	People only with hypertension
3	Stroke state	People with stroke
4	Dementia state	People with dementia
5	Hypertension and stroke state	People with hypertension and stroke
6	Stroke and dementia state	People with stroke and dementia
7	Hypertension and dementia state	People with hypertension and dementia
8	Hypertension, dementia and stroke state	People with hypertension, stroke and dementia
9	Stroke death state	People die because of stroke
10	Non-stroke death state	People die because of other causes rather than stroke

Appendix 10: Description of transition probabilities in LAM

Table: The detailed information of transition probabilities

Transition probabilities	From state	To state
$p_{1,1}$	Disease-free state	Disease-free state
$p_{1,2}$	Disease-free state	Hypertension state
$p_{1,3}$	Disease-free state	Stroke state
$p_{1,4}$	Disease-free state	Dementia state
$p_{1,9}$	Disease-free state	Stroke death state
$p_{1,10}$	Disease-free state	Non-stroke death state
$p_{2,2}$	Hypertension state	Hypertension state
$p_{2,5}$	Hypertension state	Hypertension and stroke state
$p_{2,7}$	Hypertension state	Hypertension and dementia state
$p_{2,9}$	Hypertension state	Stroke death state
$p_{2,10}$	Hypertension state	Non-stroke death state
$p_{3,3}$	Stroke state	Stroke state
$p_{3,5}$	Stroke state	Hypertension and stroke state
$p_{3,9}$	Stroke state	Stroke death state
$p_{3,10}$	Stroke state	Non-stroke death state
$p_{4,4}$	Dementia state	Dementia state
$p_{4,9}$	Dementia state	Stroke death state
$p_{4,10}$	Dementia state	Non-stroke death state
$p_{5,5}$	Hypertension and stroke state	Hypertension and stroke state
$p_{5,8}$	Hypertension and stroke state	Hypertension, stroke and dementia state
$p_{5,9}$	Hypertension and stroke state	Stroke death state
$p_{5,10}$	Hypertension and stroke state	Non-stroke death state
$p_{6,6}$	Stroke and dementia state	Stroke and dementia state
$p_{6,8}$	Stroke and dementia state	Hypertension, dementia and stroke state
$p_{6,9}$	Stroke and dementia	Stroke death state

	state	
$p_{6,10}$	Stroke and dementia state	Non-stroke death state
$p_{7,7}$	Hypertension and dementia state	Hypertension and dementia state
$p_{7,8}$	Hypertension and dementia state	Hypertension, dementia and stroke state
$p_{7,9}$	Hypertension and dementia state	Stroke death state
$p_{7,10}$	Hypertension and dementia state	Non-stroke death state
$p_{8,8}$	Hypertension, dementia and stroke state	Hypertension, dementia and stroke state
$p_{8,9}$	Hypertension, dementia and stroke state	Stroke death state
$p_{8,10}$	Hypertension, dementia and stroke state	Non-stroke death state

Appendix 11: Calendar effects on transition probabilities

Calendar trends in stroke incidence and stroke mortality in China

The GBD 2019 provided the value in stroke incidence and mortality from 2002 to 2014 in China.[1] The age-standardised stroke incidence decreased from 199.68 per 100k in 2002 to 142.20 per 100k in 2014. The age-standardised stroke mortality decreased from 227.40 per 100k in 2002 to 203.22 per 100k in 2014. The annual change rates are assumed to be the same over the time horizon. The equation for calculating the time effects on stroke incidence and mortality are as follows:

$$time\ effect = \sqrt[12]{value\ _{2014} / value_{2002}} - 1$$

The stroke incidence in China fell by 0.9% per year, and the stroke mortality in China fell by 2.8% per year.

In order to obtain the mortality of stroke allowing for a calendar effect, we multiplied $P(stroke\ mortality)_{a,t+1} = \Delta_{a,t+1} * P(stroke\ mortality)_{a,t}$

Denote $P(stroke\ mortality)$ to be the mortality of stroke, and $\Delta_{a,t+1}= \frac{m\_stroke_{a,t+1}}{m\_stroke_{a,t},}$. And $m\_stroke_{a,t+1}$ is the age-specific probability of death because of stroke in year t.

Reference:

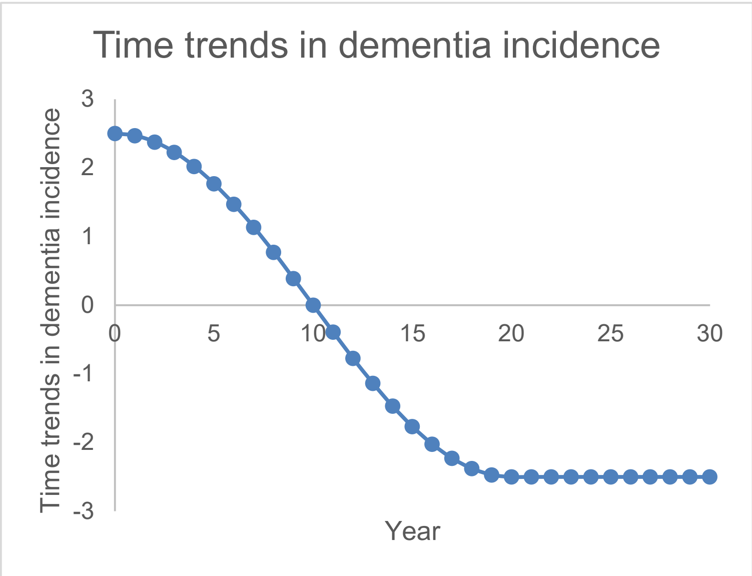
1 Network GBD. Global burden of disease study 2019 (GBD 2019) results. *Seattle, United States: Institute for Health Metrics and Evaluation (IHME).* 2019.

Calendar trends in dementia incidence in China

The time trend in dementia incidence was assumed to increase first (as observed in CLHLS and also in other studies in China) and then decline (as observed in high-income countries). To make the numeric value transition smoothly, the curve was fitted with a piecewise function. The function and figure for time effects on dementia incidence were as follows. The figure shows the assumption of time trends in dementia incidence rate in China.

$$Time\ effects\ on\ dementia\ incidence = \begin{cases} 2.5 * \cos\left(\frac{year * \pi}{20}\right), year \leq 20 \\ -2.5, year > 21 \end{cases}$$

Figure: Assumption of time trends in dementia incidence in China



In order to obtain the incidence of dementia allowing for a calendar effect, we multiplied $P(Dementia)_{a,t+1} = Time\ effects_{a,t+1} * P(Dementia)_{a,t}$

Denote *P(Dementia)* to be the incidence of dementia, and

$Time\ effect_{a,t+1} = \frac{m\_dementia_{a,t+1}}{m\_dementia_{a,t},}$. And $m\_dementia_{a,t}$ is the age-specific probability of getting dementia in year t. Table shows the calendar effects on transition probabilities.

Table: Calendar effects on transition probabilities

Type of calendar effects	Equation	Annual percentage change	Detailed Processes	Effected transition probability
Mortality of stroke	$P(stroke\ mortality)_{a,t+1} = \Delta_{a,t+1} * P(stroke\ mortality)_{a,t}$	Decline at annual rate of 2.8%	$P(CVD\ mortality)_{a,t+1} = 0.972 * P(CVD\ mortality)_{a,t}$	$p_{1,9}, p_{2,9}, p_{3,9}, p_{4,9}, p_{5,9}, p_{6,9}, p_{7,9}, p_{8,9}$
Incidence of dementia	$P(Dementia)_{a,t+1} = Time\ effects_{a,t+1} * P(Dementia)_{a,t}$	Time effects in dementia incidence $Time\ effects\ on\ dementia\ incidence = \begin{cases} 2.5 * \cos\left(\frac{year * \pi}{20}\right), year \leq 20 \\ -2.5, year > 21 \end{cases}$	$P(Dementia)_{a,t+1} = Time\ effects * P(Dementia)_{a,t}$	$p_{1,4}, p_{2,7}, p_{5,8}$
Incidence of stroke	$P(stroke)_{a,t+1} = \Delta_{a,t+1} * P(stroke)_{a,t}$	Decline at annual rate of 0.9%	$P(CVD)_{a,t+1} = 0.991 * P(CVD)_{a,t}$	$p_{1,3}, p_{2,5}, p_{7,8}$

Appendix 12: Matrix calculations

The steps to calculate and simulate processes are given by the following:

Example: the LAM model for male

- Step 1: calculate the prevalence of ten health states

The prevalence rates of ten health states for males at age a in LAM are described in the column vector given by

$$p\_m_a = [p\_m_{a,1}, p\_m_{a,2}, p\_m_{a,3}, p\_m_{a,4}, p\_m_{a,5}, p\_m_{a,6}, p\_m_{a,7}, p\_m_{a,8}, p\_m_{a,9}, p\_m_{a,10}]$$

- Step 2: estimate the transition probabilities

The transition probabilities for males in LAM are described in the matrix given by

$$P = \begin{pmatrix} p_{1,1} & \cdots & 0 \\ \cdots & \cdots & \cdots \\ p_{1,10} & \cdots & p_{10,10} \end{pmatrix}$$

- Step 3: estimate the time effect on the incidence and mortality

- Step 4: calculate the number of males

  aged a in each health state at time t and output results

When $t = 0$

$$m_{a,0} = M_{a,0} * p\_m_a$$

Denote $m_{a,0}$ to be the initial population for males at age a, p_m_a to be the prevalence for ten health states for males at age a, and $m_{a,0}$ to be the number of the male age at a in each health state at time t.

When $t = n$

$$m_{a,t} = m_{a-1,t-1} * [T_{a-1}]^T$$

Denote $m_{a,t}$ to be the column vector containing the number of population for males in each health state at age a at time t, $m_{a-1,t-1}$ to be the column vector containing the number of population for males in each health state at age a-1 at time t-1, and T_{a-1} to be the matrix containing transition probabilities for males aged a. Table displays an example of outputs from LAM (for males).

Table: The outputs in LAM model

Example: the LAM model for male

Output variables in LAM (example or male)	**Description**	**Equation**
$alive\_m_{a,t}$	Number of males alive at age a at the beginning of cycle t.	$m_{a,t,1} + m_{a,t,2} + m_{a,t,3} + m_{a,t,4} + m_{a,t,5} + m_{a,t,6} + m_{a,t,7} + m_{a,t,8}$
$death\_m_{a,t}$	Number of males deceased at age a at the beginning of the cycle t.	$m_{a,t,9} + m_{a,t,10}$
$dementia\_m_{a,t}$	Number of males with dementia at age a at the beginning of the cycle t.	$m_{a,t,4} + m_{a,t,6} + m_{a,t,7} + m_{a,t,8}$
$stroke\_m_{a,t}$	Number of males with stroke at age a at the beginning of the cycle t.	$m_{a,t,3} + m_{a,t,5} + m_{a,t,6} + m_{a,t,8}$
$hypertension\_m_{a,t}$	Number of males with hypertension at age a at the beginning of the cycle t.	$m_{a,t,2} + m_{a,t,5} + m_{a,t,7} + m_{a,t,8}$
$sd\_m_{a,t}$	Number of males deceased because of stroke at age a at the beginning of the cycle t.	$m_{a,t,9}$

$nsd\_m_{a,t}$	Number of males deceased not because of stroke at age a at the beginning of the cycle t.	$m_{a,t,10}$
$pd\_m_{a,t}$	Prevalence of dementia for males at age a at the beginning of cycle t	$\frac{dementia\_m_{a,t}}{alive\_m_{a,t}}$
$ps\_m_{a,t}$	Prevalence of stroke for males at age a at the beginning of cycle t.	$\frac{stroke\_m_{a,t}}{alive\_m_{a,t}}$
$ph\_m_{a,t}$	Prevalence of hypertension for males at age a at the beginning of cycle t.	$\frac{hypertension\_m_{a,t}}{alive\_m_{a,t}}$
$sm\_m_{a,t}$	New stroke deaths for males at age a at the beginning of cycle t.	$m_{a,t,9} - m_{a,t-1,9}$
$nm\_m_{a,t}$	New no stroke deaths for males at age a at the beginning of cycle t.	$m_{a,t,10} - m_{a,t-1,10}$
$am\_m_{a,t}$	New deaths for males at age a at the beginning of cycle t.	$m_{a,t,9} + m_{a,t,10} - m_{a,t-1,9} - m_{a,t-1,10}$

The stating sample for simulation comprised data on the older people in the base year 2008. The simulation process for next year (one-year interval) followed a sequence of steps from demographic characteristics, through the disease-free state (healthy state), to hypertension state, stroke state or dementia state, to final stroke-cause death state or non-stroke death state.

The base information in the simulation includes initial prevalence, transition probabilities, calendar effects in dementia incidence, stroke incidence, and stroke mortality. These were records from 2008 and the future that simulated forward in the one-time iteration of the simulation, leading to outcomes for 2008 and the future.

The R package Markovchain was employed to construct the state-transition Markov model. The curve fitting tool in MATLAB was used to calculate the age-specific prevalence at the start year. The VBA (Visual Basic for Applications) for Excel was employed to draw figures. The STATA was employed for data cleaning and management.

Appendix 13: The calculation of transition probabilities

Type	Probability	Method
Incidence of dementia	$p_{1,4}, p_{2,7}, p_{5,8}$	To calculate the one-year transition probability, a logistic regression model was fitted for the CLHLS. The form of logistic regression model: $logit\ incidence\ dementia = \beta_0 + \beta_{age} * age + \beta_{sex} * sex + \beta_{state} * state$ When fitting the logistic regression models, the incidence of dementia was considered as the outcome, and adjusted for sex, age and state (state 1, state 2 and state 5). From the logistic regression model, three-year transition probability was obtained. Then the three-year transition probability (TTP) was transferred to one-year transition probability (OTP). The equation is as follows: $OTP = 1 - e^{((\ln(1-TTP))/3}$
Incidence of hypertension	$p_{1,2}, p_{3,5}, p_{6,8}$	To calculate the one-year transition probability, a logistic regression model was fitted for the CLHLS. The form of logistic regression model: $logit\ incidence\ hypertension = \beta_0 + \beta_{age} * age + \beta_{sex} * sex + \beta_{state} * state$

		When fitting the logistic regression model, the incidence of hypertension was considered as the outcome, and adjusted for sex, age and state (state 1, state 3 and state 6). Considering that the incidence of hypertension is not linear with age, a piecewise function with the age of 70 as the boundary was fitted. From the logistic regression model, a three-year transition probability was obtained. Then the three-year transition probability (TTP) was transferred to one-year transition probability (OTP). The equation is as follows: $$OTP = 1 - e^{((\ln(1-TTP))/3}$$
Incidence of stroke	$p_{1,3}, p_{2,5}, p_{7,8}$	To calculate the one-year transition probability, a logistic regression model for the CLHLS was fitted. The form of logistic regression model: $$logit\ incidence\ stroke = \beta_0 + \beta_{age} * age + \beta_{sex} * sex + \beta_{state} * state$$ When fitting the logistic regression model, the incidence of stroke as the outcome was considered and adjusted for sex, age and state (state 1, state 2 and state 7). Considering that the incidence of stroke is not linear with age, a piecewise function with the age of 70 as the boundary was adopted. From the logistic regression model, a three-year transition probability was obtained. Then the three-year transition probability (TTP) was transferred to one-year transition probability (OTP). The equation is as

		follows: $$OTP = 1 - e^{((\ln(1-TTP))/3}$$
Stroke death	$p_{i,9}$	Firstly, the five-year age group stroke-cause mortality in 2008 was obtained from GBD 2019 (35-40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94). The Curve Fitting Tool in MATLAB was employed to calculate the age and sex specific stroke-cause mortality. Secondly, the transition probabilities were calculated by two equations: $$logit\ stroke\ cause\ death = \beta_0 + \beta_{age} * age + \beta_{sex} * sex + \beta_{state} * state$$ $$logit\ stroke\ cause\ death = \beta_0 + \beta_{age} * age + \beta_{sex} * sex$$ The state-specific probability was calculated from the first equation ($p_{i,9,age,sex}$), and all-cause probability was calculated from the second equation ($p_{0,9,age,sex}$). The coefficient was calculated by the following equation $$coefficient = \frac{p_{i,9,age,sex}}{p_{0,9,age,sex}}$$ Thirdly, to calculate the age, sex and state specific transition probabilities, the age-sex specific stroke-cause mortality was multiplied

		by the factor $coefficient$. The equation was as follows: $$P_{i,9} = motality * coeffiecient$$
No-stroke death	$p_{i,10}$	Firstly, the five-year age group all-cause mortality in 2008 was obtained from GBD 2019 (35-40, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, 90-94). The Curve Fitting Tool in MATLAB was employed to calculate the age and sex specific all-cause mortality. Secondly, to obtain the non-stroke-cause mortality, all-cause mortality minus stroke-cause mortality. Thirdly, the transition probabilities were calculated by two equations: $$logit\ non\ stroke\ cause\ mortality = \beta_0 + \beta_{age} * age + \beta_{sex} * sex + \beta_{state} * state$$ $$logit\ non\ stroke\ cause\ mortality = \beta_0 + \beta_{age} * age + \beta_{sex} * sex$$ The state-specific probability was calculated from the first equation ($p_{i,9,age,sex}$), and non-stroke-cause probability was calculated from the second equation ($p_{0,9,age,sex}$). The coefficient was calculated by the following equation $$coefficient = \frac{p_{i,9,age,sex}}{p_{0,9,age,sex}}$$ Fourthly, to calculate the age, sex and state specific transition probabilities, the age-sex specific non-stroke-cause mortality was

		multiplied by the factor $coefficient$. The equation was as follows: $$P_{i,9} = \ motality * coeffiecient$$
Recurrent state	$p_{1,11}, p_{2,2}, p_{3,3}, p_{4,4}, p_{5,5}, p_{6,6}, p_{7,7}, p_{8,8}$	To calculate the recurrent state-transition probabilities, the formula was used containing other transition probabilities. The formula was given as follows: $$P_{i,i} = 1 - \sum_{j=1}^{j} P_{i,j}$$ J denotes the column vector containing the state (except i) to where a transition pathway from state i is possible.

Appendix 14: The assumptions in the LAM model.

Table: The assumptions in the LAM model.

Assumption	**Justification**
LAM models health state transitions in the population of China aged 35 and over from health to death. The inputs for the state transition Markov model-LAM involve the number of population size at each age and sex, initial health state prevalence at the start year, and transition probabilities between states by age, sex and specific calendar year.	
Population number by age and sex	
Estimates for population numbers by 5-year age group and sex in model at the start year were from the China Statistical Yearbook. The number of people aged 35 at start year were from NBS. Assumption 1: NBS data are accurate and realistic. Assumption 2: The China Statistical Yearbook data is realistic.	China Statistical Yearbook provides the estimation of population demographics. NBS provides the total estimation of population number.
Initial health state prevalence value	
Initial health states prevalence in the LAM model by specific age and sex were driven from the CLHLS. Assumption 3: CLHLS provides a representative population sample of China.	The CLHLS is a randomly selected population sample of the older people in China, and this dataset represents 85% of the total Chinese population. A detailed and comprehensive description of the sample design and data quality of the CLHLS can be

	seen in section 4.1 The study design. The data quality indicated that the CLHLS could represent the Chinese population.
To improve the data statistical power and avoid any bias, five waves of CLHLS were pooled. Prevalence estimates of hypertension, stroke and dementia that define the health states were obtained from the pooled data and attributed to start year 2008, which is the midpoint of the CLHLS data collection timeframe and the start year of model. Assumption 4: The estimations of prevalence from five waves of data are precise and accurate for the midpoint of data collection timeframe.	
Assumption 5: from the start year of 2008, the number of people at the health state equals the number of people at that health state at the previous year plus the new cases of that health state and minus the number of people transit to other health states and death states. The number of new cases depends on the related transition probabilities.	Epidemiological concept and principles applied to state-transition Markov models
Transition probability	
The age-sex specific transition probabilities were driven from CLHLS and attributed to the midpoint (2008) of the data collection framework. Assumption 6: The transition probabilities for hypertension, stroke, dementia and mortality in CLHLS are similar to those for China.	The independent external data sources and dependent internal data sources were obtained to validate the accurate of transition probabilities. The mortality predicted in LAM in the future were matched with those observed in GBD 2019.

Assumption 7:	
Calendar trends	
Transition probabilities (incidence of stroke and dementia, mortality of stroke) change over time	
Assumption 8: The incidence of stroke and mortality of stroke from the GBD 2019 represent the real situation in China.	Data driven from GBD shows that the stroke incidence and stroke mortality followed downward trends over 2002-2014. The trends in stroke incidence and mortality are assumed to be continued in the future.
Assumption 9: The estimation of life expectancy is amenable to being increased.	The estimation of life expectancy depends on mortality. The life expectancy will increase with the decrease in mortality
Assumption 10: The incidence of dementia increases initially and declines later.	The recent dementia incidence in China observed in CLHLS and other studies increased. The United States, United Kingdom and some high-income countries reported the dementia incidence downward. Then the dementia incidence was assumed to increase initially and decline later with development. In order to examine the uncertainty, the

	sensitivity analysis was conducted assuming the constant dementia incidence (no time effect) and upward dementia incidence (increase at an annual rate 2.5%).
Assumption 11: The survival of hypertension, stroke and dementia change with mortality over time.	
Assumption 12: The future changes in risk factors will continue with the time trends in mortality and incidence of stroke.	This study based on the situation at the baseline of the start year. The risk factors and other public health interventions could have an impact on the future health status of the Chinese population. LAM model could simulate these scenarios in the future.
Competing risks	
Assumption 13: Due to causes of death is the competing risk of dementia.	The stroke-cause death and non-stroke death are final health states in the LAM model. Once the people die because of stroke or non-stroke, they will not have the risk of developing dementia. Thus, stroke-cause death and non-stroke death are competing risks in this study.

Appendix 15: The projected number of people with dementia in all population.

Year	Predicted number of cases	(95% UI)
2009	5936106	(5927198-5945244)
2010	6549234	(6534694-6563125)
2011	7278884	(7258113-7298614)
2012	8085160	(8057326-8110920)
2013	8979544	(8944312-9012674)
2014	9971574	(9928676-10011662)
2015	11024939	(10972310-11073509)
2016	12091860	(12029683-12147884)
2017	13276578	(13205536-13340403)
2018	14503589	(14423583-14577388)
2019	15802306	(15712987-15886743)
2020	17075733	(16976583-17167572)
2021	18284798	(18173544-18386560)
2022	19550495	(19426505-19664411)
2023	20715155	(20580047-20838853)
2024	21554224	(21408133-21688568)
2025	22149411	(21994843-22293520)
2026	22886787	(22725222-23040703)
2027	23806374	(23636496-23969426)
2028	25181871	(25003396-25354625)
2029	26198292	(26007860-26378745)
2030	27094979	(26896963-27285823)
2031	27874938	(27665537-28072279)
2032	28430228	(28210366-28636732)
2033	29249734	(29021350-29465829)
2034	29868655	(29631020-30097053)
2035	30563654	(30321674-30795883)

Abbreviations: UI: uncertainty interval.

Appendix 16: The projected number of dementia cases in China to 2035, in total, males and females

Year	Total	Male	Female
2009	5,936,106	2,429,443	3,506,663
2010	6,549,234	2,570,469	3,978,765
2011	7,278,884	2,778,579	4,500,305
2012	8,085,160	3,035,918	5,049,242
2013	8,979,544	3,325,701	5,653,843
2014	9,971,574	3,656,173	6,315,401
2015	11,024,939	4,004,320	7,020,619
2016	12,091,860	4,356,024	7,735,836
2017	13,276,578	4,761,119	8,515,459
2018	14,503,589	5,166,695	9,336,894
2019	15,802,306	5,596,202	10,206,104
2020	17,075,733	6,008,895	11,066,838
2021	18,284,798	6,393,276	11,891,522
2022	19,550,495	6,795,964	12,754,531
2023	20,715,155	7,129,922	13,585,233
2024	21,554,224	7,336,220	14,218,004
2025	22,149,411	7,454,922	14,694,489
2026	22,886,787	7,614,301	15,272,486
2027	23,806,374	7,860,762	15,945,612
2028	25,181,871	8,247,943	16,933,928
2029	26,198,292	8,515,984	17,682,308
2030	27,094,979	8,778,662	18,316,317
2031	27,874,938	8,994,360	18,880,578
2032	28,430,228	9,120,541	19,309,687
2033	29,249,734	9,329,231	19,920,503
2034	29,868,655	9,438,982	20,429,673
2035	30,563,654	9,562,788	21,000,866

Appendix 17: Transition probabilities for incidence of hypertension, stroke and dementia, and mortality affected by the changes in systolic blood pressure

Table: Transition probabilities for incidence of hypertension, stroke and dementia, and mortality affected by the changes in systolic blood pressure

Overview of parameters	Effected population	Assumed decrease in risk for each mm Hg of reduction in systolic blood pressure
The effects of reduction in systolic blood pressure on the incidence		
The effects of change in systolic blood pressure on hypertension incidence	-	-1.4%
The effects of change in systolic blood pressure on stroke incidence	hypertensive population	-4.4%
	normotensive population	-1.6%
The effects of change in systolic blood pressure on dementia incidence	-	-0.9%
The effects of reduction in systolic blood pressure on mortality		
	hypertensive population-stroke mortality	-1.7%

The effects of reduction in systolic blood pressure on the in hypertensive population	hypertensive population-non-stroke mortality	-1.0%
The effects of reduction in systolic blood pressure on the mortality in the normotensive population	normotensive population-stroke mortality	+0.3%
	normotensive population-non-stroke mortality	-0.2%

Appendix 18: The equation used for transferring the parameters of effects on incidence and mortality for n mm Hg to 1 mm Hg

The following equation was used to transfer the parameters of effects on incidence and mortality for n mm Hg to 1 mm Hg:

$$\alpha_2 = 1 - e^{((\ln(1-\alpha_1))/n)}$$

n denotes the change/difference in systolic blood pressure presented in the published evidence, α_1 denotes the published coefficient for systolic blood pressure effect on incidence and mortality, α_2 denotes the transformed coefficient for the effect of systolic blood pressure per mm Hg on incidence and mortality.

Derivation process

$$(1-\alpha_2)^n = 1-\alpha_1$$

$$1-\alpha_2 = (1-\alpha_1)^{1/n}$$

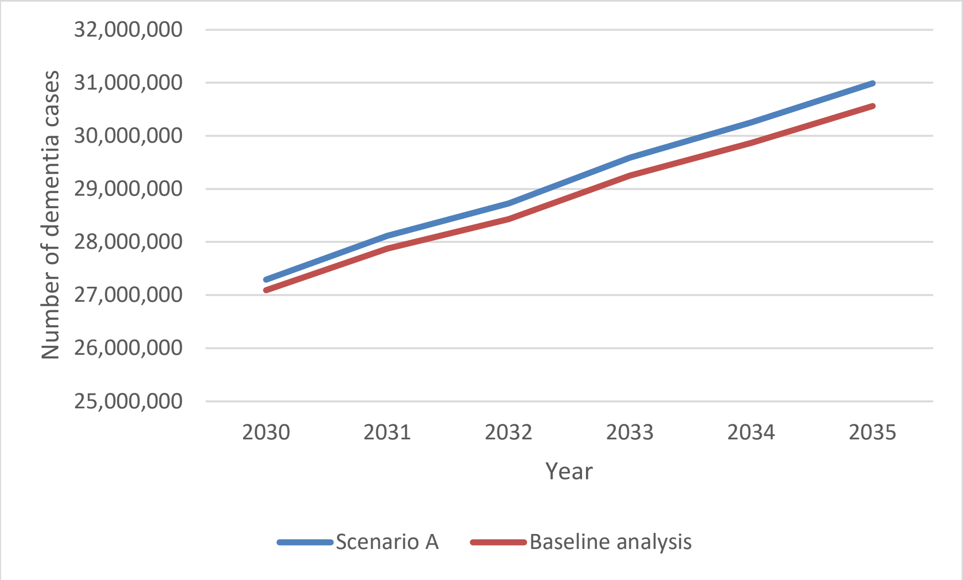
$$\ln(1-\alpha_2) = \ln(1-\alpha_1)^{1/n}$$

$$1-\alpha_2 = e^{\ln(1-\alpha_1)^{1/n}}$$

$$\alpha_2 = 1 - e^{((\ln(1-\alpha_1))/n)}$$

Appendix 19: The projected number of dementia cases for different scenarios to 2035 (Scenario A and Baseline analysis)

Figure: The projected number of dementia cases for different scenarios to 2035 (Scenario A and Baseline analysis)



Appendix 20: The projected number of dementia cases for different scenarios to 2035, total (millions)

Table: The projected number of dementia cases for different scenarios to 2035, total (millions)

Year	Scenario A*	Scenario B†	Scenario C‡	Baseline Analysis
2009	5.93	5.93	5.94	5.94
2010	6.54	6.54	6.55	6.55
2011	7.27	7.26	7.27	7.28
2012	8.07	8.06	8.08	8.09
2013	8.95	8.94	8.96	8.98
2014	9.93	9.92	9.95	9.97
2015	10.98	10.96	11.00	11.02
2016	12.03	12.02	12.06	12.09
2017	13.21	13.19	13.24	13.28
2018	14.43	14.41	14.47	14.50
2019	15.73	15.70	15.76	15.80
2020	17.00	16.97	17.04	17.08
2021	18.21	18.19	18.25	18.28
2022	19.49	19.46	19.52	19.55
2023	20.66	20.65	20.69	20.72
2024	21.53	21.52	21.55	21.55
2025	22.16	22.16	22.16	22.15
2026	22.94	22.94	22.92	22.89
2027	23.89	23.91	23.86	23.81
2028	25.30	25.32	25.25	25.18
2029	26.35	26.38	26.28	26.20
2030	27.29	27.33	27.20	27.09
2031	28.12	28.17	28.01	27.87
2032	28.72	28.79	28.59	28.43
2033	29.59	29.67	29.43	29.25
2034	30.26	30.35	30.08	29.87
2035	30.99	31.10	30.79	30.56

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 21: The projected number of dementia cases for different scenarios to 2035, males (millions)

Table: The projected number of dementia cases for different scenarios to 2035, males (millions)

Year	Scenario A*	Scenario B†	Scenario C‡	Baseline Analysis
2009	2.43	2.43	2.43	2.43
2010	2.57	2.57	2.57	2.57
2011	2.78	2.77	2.78	2.78
2012	3.03	3.03	3.03	3.04
2013	3.32	3.31	3.32	3.33
2014	3.64	3.64	3.65	3.66
2015	3.99	3.99	4.00	4.00
2016	4.34	4.34	4.35	4.36
2017	4.74	4.74	4.75	4.76
2018	5.15	5.14	5.16	5.17
2019	5.58	5.57	5.59	5.60
2020	6.00	5.99	6.00	6.01
2021	6.38	6.38	6.39	6.39
2022	6.79	6.79	6.80	6.80
2023	7.14	7.14	7.13	7.13
2024	7.36	7.36	7.35	7.34
2025	7.49	7.50	7.48	7.45
2026	7.67	7.69	7.65	7.61
2027	7.94	7.95	7.90	7.86
2028	8.34	8.36	8.30	8.25
2029	8.63	8.65	8.57	8.52
2030	8.91	8.94	8.85	8.78
2031	9.14	9.18	9.07	8.99
2032	9.29	9.33	9.21	9.12
2033	9.51	9.56	9.43	9.33
2034	9.64	9.69	9.55	9.44
2035	9.78	9.84	9.68	9.56

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 22: The projected number of dementia cases for different scenarios to 2035, females (millions)

Table: The projected number of dementia cases for different scenarios to 2035, females (millions)

Year	Scenario A*	Scenario B†	Scenario C‡	Baseline Analysis
2009	3.51	3.50	3.51	3.51
2010	3.97	3.97	3.98	3.98
2011	4.49	4.49	4.50	4.50
2012	5.04	5.03	5.04	5.05
2013	5.63	5.63	5.64	5.65
2014	6.29	6.28	6.30	6.32
2015	6.99	6.98	7.00	7.02
2016	7.69	7.68	7.71	7.74
2017	8.47	8.45	8.49	8.52
2018	9.28	9.27	9.31	9.34
2019	10.15	10.13	10.18	10.21
2020	11.00	10.98	11.04	11.07
2021	11.83	11.81	11.86	11.89
2022	12.69	12.67	12.72	12.75
2023	13.53	13.51	13.56	13.59
2024	14.17	14.16	14.20	14.22
2025	14.67	14.66	14.68	14.69
2026	15.27	15.26	15.27	15.27
2027	15.96	15.96	15.96	15.95
2028	16.96	16.96	16.95	16.93
2029	17.73	17.73	17.71	17.68
2030	18.39	18.40	18.36	18.32
2031	18.98	19.00	18.94	18.88
2032	19.44	19.46	19.38	19.31
2033	20.07	20.11	20.01	19.92
2034	20.61	20.65	20.53	20.43
2035	21.21	21.26	21.11	21.00

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 23: The number of people with dementia for different scenario analysis to 2035, total

Table: The number of people with dementia for different scenario analysis to 2035, total

Year	Scenario A*	Scenario B†	Scenario C‡	Baseline analysis
2009	5,934,616	5,934,196	5,935,365	5,936,106
2010	6,543,768	6,542,205	6,546,487	6,549,234
2011	7,267,102	7,263,752	7,272,978	7,278,884
2012	8,065,349	8,059,686	8,075,248	8,085,160
2013	8,950,300	8,941,949	8,964,916	8,979,544
2014	9,932,198	9,920,911	9,951,916	9,971,574
2015	10,975,511	10,961,267	11,000,293	11,024,939
2016	12,033,607	12,016,710	12,062,918	12,091,860
2017	13,210,062	13,190,569	13,243,658	13,276,578
2018	14,430,691	14,409,069	14,467,701	14,503,589
2019	15,725,007	15,701,704	15,764,520	15,802,306
2020	16,997,927	16,973,917	17,038,099	17,075,733
2021	18,211,663	18,188,270	18,249,991	18,284,798
2022	19,485,291	19,463,318	19,520,257	19,550,495
2023	20,664,476	20,645,614	20,692,898	20,715,155
2024	21,530,057	21,517,542	21,546,105	21,554,224
2025	22,162,646	22,159,436	22,160,970	22,149,411
2026	22,938,241	22,944,524	22,918,466	22,886,787
2027	23,894,705	23,910,092	23,857,497	23,806,374
2028	25,297,938	25,319,832	25,247,884	25,181,871
2029	26,352,615	26,384,005	26,284,446	26,198,292
2030	27,291,813	27,333,951	27,203,378	27,094,979
2031	28,117,789	28,171,743	28,007,302	27,874,938
2032	28,724,684	28,792,119	28,589,284	28,430,228
2033	29,588,490	29,667,389	29,431,764	29,249,734
2034	30,255,517	30,347,096	30,075,469	29,868,655
2035	30,994,901	31,098,236	30,793,340	30,563,654

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 24: The number of people with dementia for different scenario analysis to 2035, males

Table: The number of people with dementia for different scenario analysis to 2035, males

Year	Scenario A*	Scenario B†	Scenario C‡	Baseline analysis
2009	2,429,306	2,429,264	2,429,373	2,429,443
2010	2,569,207	2,568,852	2,569,835	2,570,469
2011	2,775,338	2,774,414	2,776,948	2,778,579
2012	3,030,121	3,028,452	3,033,015	3,035,918
2013	3,316,979	3,314,483	3,321,343	3,325,701
2014	3,644,586	3,641,250	3,650,402	3,656,173
2015	3,990,258	3,986,177	3,997,329	4,004,320
2016	4,340,230	4,335,593	4,348,226	4,356,024
2017	4,743,986	4,738,854	4,752,718	4,761,119
2018	5,149,355	5,144,034	5,158,286	5,166,695
2019	5,579,748	5,574,493	5,588,366	5,596,202
2020	5,995,106	5,990,377	6,002,559	6,008,895
2021	6,384,361	6,380,720	6,389,578	6,393,276
2022	6,793,444	6,791,290	6,795,719	6,795,964
2023	7,137,068	7,137,241	7,134,805	7,129,922
2024	7,357,655	7,361,410	7,348,608	7,336,220
2025	7,494,580	7,502,996	7,476,807	7,454,922
2026	7,672,593	7,685,768	7,645,904	7,614,301
2027	7,936,662	7,954,305	7,901,562	7,860,762
2028	8,339,004	8,360,398	8,296,734	8,247,943
2029	8,625,173	8,651,188	8,574,226	8,515,984
2030	8,906,128	8,936,839	8,846,410	8,778,662
2031	9,140,921	9,176,600	9,072,008	8,994,360
2032	9,287,524	9,328,622	9,208,680	9,120,541
2033	9,514,024	9,559,817	9,426,543	9,329,231
2034	9,642,556	9,693,416	9,545,889	9,438,982
2035	9,783,446	9,838,937	9,678,414	9,562,788

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 25: The number of people with dementia for different scenario analysis to 2035, females

Table: The number of people with dementia for different scenario analysis to 2035, females

Year	Scenario A*	Scenario B†	Scenario C‡	Baseline analysis
2009	3,505,310	3,504,932	3,505,992	3,506,663
2010	3,974,561	3,973,353	3,976,652	3,978,765
2011	4,491,764	4,489,338	4,496,030	4,500,305
2012	5,035,228	5,031,234	5,042,233	5,049,242
2013	5,633,321	5,627,466	5,643,573	5,653,843
2014	6,287,612	6,279,661	6,301,514	6,315,401
2015	6,985,253	6,975,090	7,002,964	7,020,619
2016	7,693,377	7,681,117	7,714,692	7,735,836
2017	8,466,076	8,451,715	8,490,940	8,515,459
2018	9,281,336	9,265,035	9,309,415	9,336,894
2019	10,145,259	10,127,211	10,176,154	10,206,104
2020	11,002,821	10,983,540	11,035,540	11,066,838
2021	11,827,302	11,807,550	11,860,413	11,891,522
2022	12,691,847	12,672,028	12,724,538	12,754,531
2023	13,527,408	13,508,373	13,558,093	13,585,233
2024	14,172,402	14,156,132	14,197,497	14,218,004
2025	14,668,066	14,656,440	14,684,163	14,694,489
2026	15,265,648	15,258,756	15,272,562	15,272,486
2027	15,958,043	15,955,787	15,955,935	15,945,612
2028	16,958,934	16,959,434	16,951,150	16,933,928
2029	17,727,442	17,732,817	17,710,220	17,682,308
2030	18,385,685	18,397,112	18,356,968	18,316,317
2031	18,976,868	18,995,143	18,935,294	18,880,578
2032	19,437,160	19,463,497	19,380,604	19,309,687
2033	20,074,466	20,107,572	20,005,221	19,920,503
2034	20,612,961	20,653,680	20,529,580	20,429,673
2035	21,211,455	21,259,299	21,114,926	21,000,866

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 26: The number of people with dementia for different scenario analysis to 2035, total with 95% UI

Table: The number of people with dementia for different scenario analysis to 2035, total with 95% UI

Year	Scenario A* (95% UI)	Scenario B† (95% UI)	Scenario C‡ (95% UI)	Baseline analysis (95% UI)
2009	5934616 (5925748-5943729)	5934196 (5925337-5943302)	5935365 (5926473-5944484)	5936106 (5927198-5945244)
2010	6543768 (6529289-6557617)	6542205 (6527748-6556049)	6546487 (6531985-6560368)	6549234 (6534694-6563125)
2011	7267102 (7246463-7286736)	7263752 (7243142-7283352)	7272978 (7252280-7292671)	7278884 (7258113-7298614)
2012	8065349 (8037695-8090831)	8059686 (8032094-8085100)	8075248 (8047505-8100864)	8085160 (8057326-8110920)
2013	8950300 (8915507-8983120)	8941949 (8907277-8974694)	8964916 (8929917-8997881)	8979544 (8944312-9012674)
2014	9932198 (9890035-9971855)	9920911 (9878939-9960445)	9951916 (9909387-9991790)	9971574 (9928676-10011662)
2015	10975511 (10923662-11023284)	10961267 (10909636-11008775)	11000293 (10948073-11048548)	11024939 (10972310-11073509)
2016	12033607 (11972476-12088554)	12016710 (11955863-12071359)	12062918 (12001267-12118405)	12091860 (12029683-12147884)
2017	13210062 (13140510-13272970)	13190569 (13121419-13253217)	13243658 (13173400-13307026)	13276578 (13205536-13340403)
2018	14430691 (14352276-14503012)	14409069 (14331097-14480972)	14467701 (14388493-14540757)	14503589 (14423583-14577388)
2019	15725007 (15637750-15807613)	15701704 (15614975-15783788)	15764520 (15676286-15848032)	15802306 (15712987-15886743)
2020	16997927 (16901214-17088045)	16973917 (16877895-17063751)	17038099 (16940154-17128862)	17075733 (16976583-17167572)
2021	18211663 (18103925-18311025)	18188270 (18081440-18287152)	18249991 (18140656-18350307)	18284798 (18173544-18386560)
2022	19485291 (19363731-19596614)	19463318 (19342807-19573869)	19520257 (19396930-19632886)	19550495 (19426505-19664411)
2023	20664476 (20534648-20785310)	20645614 (20516972-20765039)	20692898 (20560466-20816267)	20715155 (20580047-20838853)
2024	21530057 (21389447-21660687)	21517542 (21378102-21646959)	21546105 (21402623-21678659)	21554224 (21408133-21688568)
2025	22162646 (22012039-22301284)	22159436 (22010093-22296535)	22160970 (22008201-22301656)	22149411 (21994843-22293520)

2026	22938241 (22780077-23086551)	22944524 (22787471-23091306)	22918466 (22759176-23069859)	22886787 (22725222-23040703)
2027	23894705 (23730543-24053123)	23910092 (23746418-24067157)	23857497 (23689969-24018275)	23806374 (23636496-23969426)
2028	25297938 (25124464-25465777)	25319832 (25148314-25486066)	25247884 (25071144-25418223)	25181871 (25003396-25354625)
2029	26352615 (26169196-26527128)	26384005 (26203440-26557034)	26284446 (26096300-26461503)	26198292 (26007860-26378745)
2030	27291813 (27098597-27474999)	27333951 (27142146-27516175)	27203378 (27007749-27389278)	27094979 (26896963-27285823)
2031	28117789 (27913281-28309565)	28171743 (27968730-28361898)	28007302 (27800260-28201691)	27874938 (27665537-28072279)
2032	28724684 (28508983-28923429)	28792119 (28578012-28989145)	28589284 (28370972-28791351)	28430228 (28210366-28636732)
2033	29588490 (29362999-29795440)	29667389 (29444407-29872649)	29431764 (29204105-29642264)	29249734 (29021350-29465829)
2034	30255517 (30026005-30471351)	30347096 (30119571-30560514)	30075469 (29841822-30297352)	29868655 (29631020-30097053)
2035	30994901 (30759149-31220898)	31098236 (30862484-31322280)	30793340 (30555187-31022542)	30563654 (30321674-30795883)

Abbreviations: UI: uncertainty interval.

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 27: The prevalence of dementia for different scenario analysis to 2035, total

Table: The prevalence of dementia for different scenario analysis to 2035, total

Year	Scenario A* (95% UI)	Scenario B† (95% UI)	Scenario C‡ (95% UI)	Baseline analysis (95% UI)
2009	4.46 (4.46-4.47)	4.46 (4.46-4.47)	4.47 (4.46-4.47)	4.47 (4.46-4.47)
2010	4.8 (4.79-4.81)	4.8 (4.79-4.8)	4.8 (4.79-4.81)	4.81 (4.8-4.81)
2011	5.18 (5.18-5.19)	5.18 (5.17-5.19)	5.19 (5.18-5.2)	5.2 (5.19-5.21)
2012	5.6 (5.59-5.61)	5.59 (5.58-5.6)	5.61 (5.6-5.62)	5.62 (5.61-5.63)
2013	6 (5.99-6.02)	6 (5.98-6.01)	6.02 (6.01-6.04)	6.04 (6.03-6.05)
2014	6.39 (6.38-6.41)	6.38 (6.37-6.39)	6.41 (6.4-6.43)	6.44 (6.43-6.45)
2015	6.77 (6.76-6.79)	6.76 (6.74-6.77)	6.8 (6.79-6.82)	6.83 (6.82-6.85)
2016	7.16 (7.14-7.18)	7.14 (7.12-7.15)	7.19 (7.18-7.21)	7.23 (7.22-7.25)
2017	7.49 (7.47-7.51)	7.46 (7.45-7.48)	7.53 (7.52-7.55)	7.58 (7.56-7.6)
2018	7.81 (7.79-7.83)	7.78 (7.76-7.8)	7.86 (7.84-7.88)	7.92 (7.9-7.94)
2019	8.1 (8.08-8.13)	8.07 (8.05-8.09)	8.16 (8.14-8.19)	8.22 (8.2-8.25)
2020	8.39 (8.37-8.42)	8.36 (8.33-8.38)	8.46 (8.44-8.49)	8.53 (8.51-8.55)
2021	8.68 (8.66-8.71)	8.64 (8.62-8.66)	8.76 (8.73-8.78)	8.83 (8.81-8.86)
2022	8.93 (8.91-8.95)	8.88 (8.86-8.91)	9.01 (8.99-9.04)	9.09 (9.07-9.12)
2023	9.18 (9.16-9.21)	9.13 (9.1-9.15)	9.27 (9.24-9.29)	9.36 (9.33-9.38)
2024	9.46 (9.44-9.49)	9.41 (9.38-9.44)	9.56 (9.53-9.59)	9.66 (9.63-9.68)
2025	9.75 (9.72-9.78)	9.69 (9.66-9.72)	9.85 (9.83-9.88)	9.96 (9.93-9.99)
2026	9.96 (9.93-9.99)	9.9 (9.87-9.93)	10.07 (10.04-10.1)	10.18 (10.15-10.21)

2027	10.08 (10.06-10.12)	10.02 (9.99-10.05)	10.2 (10.17-10.23)	10.31 (10.28-10.34)
2028	10.1 (10.08-10.14)	10.04 (10.01-10.07)	10.22 (10.19-10.25)	10.33 (10.3-10.37)
2029	10.17 (10.14-10.21)	10.1 (10.08-10.14)	10.29 (10.26-10.32)	10.4 (10.37-10.44)
2030	10.23 (10.2-10.26)	10.16 (10.13-10.19)	10.34 (10.31-10.38)	10.46 (10.43-10.49)
2031	10.28 (10.25-10.31)	10.21 (10.18-10.25)	10.39 (10.36-10.43)	10.51 (10.48-10.55)
2032	10.34 (10.31-10.37)	10.27 (10.24-10.31)	10.45 (10.42-10.49)	10.57 (10.54-10.61)
2033	10.33 (10.31-10.37)	10.27 (10.24-10.3)	10.45 (10.42-10.49)	10.57 (10.53-10.6)
2034	10.35 (10.32-10.39)	10.28 (10.25-10.32)	10.46 (10.43-10.5)	10.58 (10.55-10.62)
2035	10.33 (10.3-10.37)	10.26 (10.24-10.3)	10.45 (10.41-10.49)	10.56 (10.53-10.6)

Abbreviations: UI: uncertainty interval.

* Scenario A analysis based on the assumption that the salt intake of Chinese people is to be reduced to 5g/per person per day by 2025 and keep the salt intake value until 2035.

† Scenario B analysis based on the assumption the salt intake of Chinese people is to be reduced to 3g/per person per day by 2025 and keep the salt intake value until 2035.

‡ Scenario C analysis based on the assumption the salt intake of Chinese people is assumed to be reduced to 8.5g/per person per day by 2025 and keep the salt intake value until 2035.

Note: The baseline scenario analysis assumes that the current value in salt intake in the Chinese population will continue.

Appendix 28: Public response to the intervention on reduction in salt intake

To reduce the salt intake of the Chinese population, the Chinese government has adopted a number of actions, such as promoting the correct usage rate of restriction-salt-spoon. Specifically, many local governments in China have distributed two-gram salt-restriction spoons to citizens, and the majority of Beijing residents had received them by 2008. Those who received this spoon should have been instructed to consume less than 6g of salt daily. With a 5cm handle and a 1.1cm calibre, this teaspoon was designed to hold 2g of table salt, making 3 teaspoons equal to 6g of salt. The widespread use of such a spoon in China is due to the fact that it facilitates salt measurement in the kitchen. For instance, a household of three should consume no more than 18g of salt each day. If this family does not consume salt at breakfast, they can consume 9g at lunch or dinner, or 4 to 5 teaspoons of salt each meal.

It has been demonstrated that increasing the rate at which salt-restriction spoons are used correctly will reduce the salt consumption and blood pressure of individuals. For instance, Li Yuqing [1] and Yang Jun [2] observed that using a salt-restriction-spoon properly or consuming low sodium salt can reduce salt consumption and lower blood pressure; the effect would be more pronounced if both acts were conducted concurrently. However, many recipients of salt-restriction spoons either do not utilise them or cannot use them properly. Only 61.8% and 47.7% of Beijing residents who received a salt-restriction spoon in 2007 and 2008 owned and used it, respectively, according to a 2011 survey, and only

17.1% knew how to use it properly (according to the standard of 6g/per day/per person).[3] In 2011, researchers discovered that the receipt rate and usage rate of salt-restriction-spoons in Beijing were 72.1% and 32.0%, respectively.[4] The fact that the restriction-spoon usage rate in Beijing is higher than in Dalian is positive, as it shows that the salt-restriction-spoon campaign in Beijing, particularly in urban areas, has achieved initial success.

These effects of interventions on reduction in salt intake show that despite there is uncertainty on public response to reduction in salt intake, it is important to improve the current usage rate salt-restriction-spoon and education on the right usage of the salt-restriction-spoon.

Reference:

1 Yuqing, L., Xiurong, L., Feng, L., & Ailan, F. (2008). Effect evaluation of salt restriction intervention to hypertension. *Chinese Journal of Health Education*, 24, 5012504.

2 Jun, Y., Xiaoli, X., Feng, L., & Na, W. (2007). Survey on the salt intake of people in Beijing and evaluation of salt-restriction intervention. *Public health management in China*, 542-544.

3 Chen, J., Liao, Y., Li, Z., Tian, Y., Yang, S., He, C., ... & Sun, X. (2013). Determinants of salt-restriction-spoon using behavior in China: Application of the health belief model. *PLoS One,* 8(12), e83262.

4 Chen, J., Liao, Y., Li, Z., Tian, Y., Yang, S., He, C., ... & Sun, X. (2013). Determinants of salt-restriction-spoon using behavior in China: Application of the health belief model. PLoS One, 8(12), e83262.

Appendix 29: The current and future healthcare coverage in China for people living with dementia

Traditionally, it is a family responsibility to take care of the older people with dementia in China. However, with the change of the Chinese population structure, especially the implementation of the one-child policy, it is difficult for the children to take care of the older people with dementia by themselves. Chinese people have to shift to employ others to take care of the older people with dementia.

The “New Era Actively Responding to Population Aging Development Report (2018)” shows that the older people care service system is a comprehensive and systematic livelihood project, and it is necessary to further clarify that the responsibility of “family”, “community” and “institutions” to meet the needs of older people care. The Chinese government is committed to establishing an older people care service system with “family”, “community” and “family”.

A 2016 study in Lanxi found that though in recent years, older people service institutions have been emphasized, the number of older people care institutions for dementia patients (such as providing medical record management or providing psychological support) is still very small.[1] And researchers found that the cost of caring for patients with dementia is high, and there is no older people care service that could provide professional medical, psychological or rehabilitation support for dementia.

Another good trend is that the number of people covered by national endowment insurance increases with years. The number of people covered by endowment insurance has tripled in the past 20 years. Specifically, the number of people participate in the national endowment insurance increased from 136.2 million in 2000 to 257.1 million in 2010, to 434.8 million in 2019 (see Table).

Table: The number of people participated in national endowment insurance in China from 2010 to 2019.

	Number of people participating in endowment insurance (thousand)	Number of employees participating in endowment insurance (thousand)	Number of retirees participating in endowment insurance (thousand)
2010	257,073	194,023	63,050
2011	283,913	215,650	68,262
2012	304,268	229,811	74,457
2013	322,184	241,773	80,410
2014	341,244	255,310	85,934
2015	353,612	262,192	91,419
2016	379,297	278,263	101,034
2017	402,933	292,676	110,257
2018	419,016	301,040	117,977
2019	434,820	-	-

Data sources: National Bureau of Statistics

To conclude, the increased number of dementia cases continues to pose significant challenges for public health system throughout the world and China is no exception. Although the Chinese government has invested a lot of money in national insurance to reduce the burden of dementia patients and their families and released a blanket of policy document to guarantee the policy landscape of dementia-related public system in China, China still faces great challenges in terms of the burden and economic cost of dementia. Due to the characteristics of dementia, it may exert great pressure on Chinese dementia patients themselves, their families, national public health service system and clinicians in the future. In order to help national policy makers and clinicians cope with the challenges of dementia in the future, it is important to estimate the current incidence trend of dementia accurately and project the future burden of dementia in China accurately.

Reference:

1 Wu, C., Gao, L., Chen, S., & Dong, H. (2016). Care services for elderly people with dementia in rural China: a case study. *Bulletin of the World Health Organization*, 94(3), 167.

Appendix 30: Research Outputs

Publication:

Li Y, Araghi M, Liao J, Brunner E. P30 Trend in dementia incidence in China 2002–2014: population-based longitudinal study *J Epidemiology Community Health* 2021;75: A56.

Conference:

Poster presentation at the Society for Social Medicine & Population Health 2021 virtual meeting, Wednesday 15 September - Friday 17 September 2021, Title: Trend in dementia incidence in China 2002–2014: population-based longitudinal study