Biosocial determinants of health outcomes:

New approaches and evidence



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A thesis submitted for the degree of

Doctor of Philosophy in Sociology

Trinity 2018

Word Count: 37,425

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Abstract

Health disparities among older adults are multifactorial. Risk factors are embedded from a matrix of biological, social, psychological, and contextual exposures, accumulated across the life trajectory. Sociologists have to date almost exclusively focused on the social aspects of health and overlooked biological and genetic potential, leading to estimation bias of social factors. Moreover, the majority of research examining the link between health and socioeconomic status (SES) seldom presents a causal inference. A knowledge gap also exists between the West and China. While there is a well-established relationship between SES and health among older people in Western societies, the SES-health gradient has not yet been established in different social and historical context.

The three independent essays in this thesis adopts a biosocial approach integrating life course perspective and fundamental causes theory, in order to bridge the disjointed knowledge on contextual, social and biological influences on health, measured by objective indicators of biomarkers and cognitive ability. I use data from the China Health and Retirement Longitudinal Survey (CHARLS) and the Health and Retirement Study (HRS) from the US to tackle the following three research questions:1) How do macro level contextual factors and individual socioeconomic status influence health in China? 2) Is the well-established relationship between socioeconomic status and health causal? 3) How do genetic factors moderate demographic and socio-economic effects on the decline of cognitive functions? The

key findings are: first, the individual level SES-health link is consistent across China and the U.S among the older population. Provincial variations in economic development, income inequality, and health infrastructure are associated with a range of health outcomes for Chinese midlife and older adults. Second, genetic risk score helps to identify a causal educational effect on health. Third, the genetic effect of education changes with age and across cognitive domains among the HRS sample.

Acknowledgements

The journey of writing this thesis was full of challenges and it was the constant support of a great number of people who helped me to meet them. I am deeply indebted to all of them. First and foremost, my thanks go to my supervisor Melinda C. Mills, who placed great trust in me right from the beginning when I switched to the socio-genome group. Not only will her depth of knowledge, clarity of thought, and precise style of writing continue to be an inspiration to me, with her unfailing support, patient guidance, and devoted mentorship, she is without a doubt a role model I look up to. I also own a great debt to my former supervisor, Francesco C. Billari, for his support and advice. After I started my MPhil in Sociology at the University of Oxford, in 2012, Francesco has guided me into the fields of demography and quantitative methods. Without his support, I would not have been able to pursue a DPhil in Oxford. He connected me with new perspectives and opportunities, and showed me how to build a sound foundation for sociological research. I am very grateful to my co-supervisor Nicola Barban, whose ideas and suggestions will reverberate through the pages to come. Nicola led me all the way through my transition to the field of socio-genomic studies with quicker-than-the-eye feedback and numerical statistical suggestions. Many thanks are also due to Stuart Gietel-Basten, who supported me both intellectually and personally during my MPhil in Oxford. I also wish to thank the examination and reading committee of my thesis, Benjamin Domingue, John Ermisch, Jan Jonsson, Christiaan Monden, Patrick Präg, Charles Rahal, Felix Tropf, for comments on my work.

The thesis would not have been possible without the loving support and sacrifices of my parents – Anlin Ding and Bojun Wang, to whom I am always grateful and to whom I would like to dedicate this thesis. It is my parents' faith in me that had made

me strive for higher educational goals. I would also like to express my gratitude to the memory of my grandmother Su Gong and to my aunt Boqiu Wang, who had a formative role in my life.

Finally, I want to thank Matthias Cheng Qian for his patience, kindness and constant encouragement. I am extremely fortunate to have had him as my pillar of support throughout this journey. Matthias has made my years in Oxford the best time of my life.

The research leading to this project was funded by the European Research Council Consolidator Grant SOCIOGENOME, awarded to Melinda Mills (Grant no. 615603); and China Oxford Scholarship Hoare Family Award in Social Science, awarded to Xuejie Ding.

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Abbreviation

AL-Allostatic Load

BMI-Body Mass Index

CHARLS-China Health and Retirement Longitudinal Study

DBP-diastolic blood pressure

ED Level of economic development

EM Episodic memory

GC Global cognition

GWAS-Genome Wide Association Studies

HbA1c-Glycosylated haemoglobin

HDL-high density lipoprotein

HRPI-Health Related Public Infrastructure

HRS-Health and Retirement Study

LATE-Local Average Treatment Effect

MS-Mental health

PGS-Polygenic Genetic Risk Score

SBP-Systolic blood pressure

SES-Socio Economic Status

SNP-single nucleotide polymorphisms

SRH-Self-rated health

Vocab-Vocabulary

WM-Working memory

Chapter 1. Introduction and Outline of the Studies

The determinants of good health in old age is essential for providing insights into our understanding of social inequalities. Though it is common knowledge that health naturally declines with age, there is considerable variation between individuals. Health disparities are multifactorial and reflect socio-economic, environmental, behavioural, biomedical and genetic influences (Belsky, Moffitt, & Caspi, 2013; Hill, Pérez-Stable, Anderson, & Bernard, 2015; Pehkonen et al., 2017). Until now, social scientists have widely examined health-related macro-level contextual factors such as regional income inequality, level of economic development (e.g. Anand & Ravallion, 1993; Beckfield, 2004; Ding, Billari, & Gietel-Basten, 2017), and micro-level socio-demographic factors that include but are not restricted to educational attainment, occupation, access to health care, health behaviours, and marital status (e.g. Creek & Hughes, 2008; Cutler & Lleras-Muney, 2008; Luo, Hawkley, Waite, & Cacioppo, 2012; Robards, Evandrou, Falkingham, & Vlachantoni, 2012; Van Cleave, Gortmaker, & Perrin, 2010).

The mechanisms linking socio-economic factors to health are diverse. At the macro level, a higher level of economic development and healthcare support improve the quality of goods and services, leading to improved health and nutrition among the population (Anand & Ravallion, 1993). Although disputed, scholars have also argued that the distribution of poverty and wealth may influence health via psychological and material pathways (Kawachi & Kennedy, 1999; Pickett & Wilkinson, 2015). At the micro level, more highly educated individuals tend to have better educational, social and labour market outcomes and are subsequently healthier in later life (Chetty et al., 2016; Currie, 2009; Cutler & Lleras-Muney, 2010). People with a higher income tend

to have a higher living standard (e.g. better access to food with higher nutritional content, sanitation and clean water), pay for higher quality health services and advanced health technology, and attain better education, affording them better life opportunities that lead to healthy pathways.

An abundant body of literature that examines health determinants has largely focused on social mechanisms through which health is affected. Little attention has been devoted to causal inference in evaluating associations between health and socio-economic status. Moreover, scientific research has reliably and repeatedly demonstrated that the determinants of health are most accurately conceptualised as biosocial phenomena, in which health and disease emerge through the interplay between biology and the social environment (Krieger & Zierler, 1996; Power & Hertzman, 1997). However, concerns about the plausibility of biological mechanisms are under-represented in the research (Daniel, Moore, & Kestens, 2008). Recent advances in biology and molecular genetics also suggest that genetic heritability may play a role in the transmission of educational attainment and so directly or indirectly affects health (Davies, Dickson, Smith, Windmeijer, & Berg, 2018; Okbay, Beauchamp, Fontana, Lee, & Pers, 2016; Rietveld et al., 2014; Rietveld et al., 2013). Failure to differentiate between the nature (biological and genetic) and nurture (socio-demographic-contextual factors) pathways may lead to over-estimation of the effects of social economic status (SES) as a fundamental factor impacting on health. The association may simply be confounded by a shared genetic predisposition underlying the process, due to their intertwined relationship (Cesarini & Visscher, 2017).

The motivation and scientific contribution of this thesis is to bridge and extend the important but disjointed knowledge on contextual, social and biological influences on

health, and to combine sociological theories with approaches from biology, molecular genetics and medical sciences. The research questions in this dissertation are designed with the aim of testing theories, making causal inferences, and finding evidence using a variety of measures and methods across populations while adopting a biosocial approach integrating the life course perspective and fundamental cause theory.

The overall research questions of this thesis are: 1). *How do macro-level contextual factors and individual socio-economic status influence health?* Examining middle and later life in China I look at both contextual factors (macro) and individual pathways (micro), as they both combine to generate an overall picture of health inequalities. 2). *Is the relationship between socio-economic status and health causal?* Using genetic information as an instrumental variable, I examine the causal link between education and health among American older adults. 3). *How do genetic factors moderate demographic and socio-economic effects on cognitive functions and decline?* The interplay of genetic endowment and age on cognitive performances is analysed.

Overall, this thesis studies whether socio-economic differences in health persist across a variety of contexts, in order to understand the impact of socio-environmental context on these processes and to consider both macro (contextual) and micro (individual) level factors. The study contributes to the literature on biosocial determinants of health by considering SES across both individual and societal levels and examining the changing impact of genetics on cognitive health. Using the life course perspective and fundamental causes theory, this study examines the relationship between SES and physical and cognitive health in both China and the U.S. context.

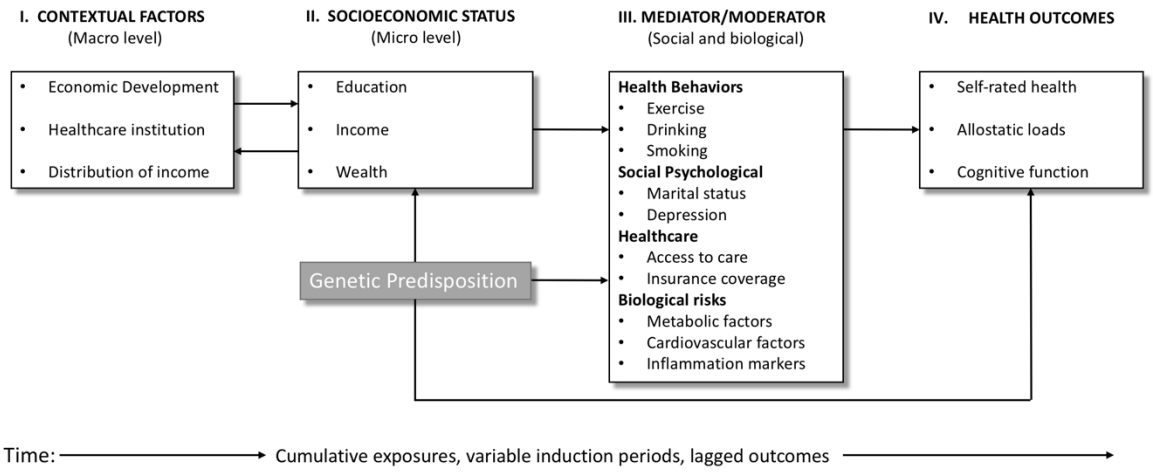
The thesis focuses on the ageing population. In the context of a significant increase in the proportion of older people all over the world (Bloom, Canning, & Fink, 2010), rapid ageing poses significant challenges for healthcare and social security systems to provide adequate elder care. Understanding the determinants of good health is essential for providing insights into both health-related policies and our understanding of social inequalities.

Health is measured using multiple indicators: self-rated health, cognitive abilities, and most importantly, allostatic load (AL). As a comprehensive, multisystem measure of cumulative biological dysregulation, allostatic load takes the cumulative effects of chronic stress into account. By considering the influences of social-demographic factors in tandem with genetic influences, the results described in this dissertation provide new insights into how biological forces and social economic status cumulate over the life span and affect the health of aging populations. In the current chapter, I present a conceptual framework for this study – illustrating the biosocial determinants of health and how they may interact and mediate the mechanism (Figure 1-1).

This introductory chapter has four goals. First, it discusses the overarching biosocial theoretical perspective that informs this research. I start by highlighting the importance of studying health from a life course perspective in that individual experience is shaped by a broader social context, time and history on an individual's life. Fundamental causes theory is then discussed to delineate contextual, social and personal circumstances and their relations with health outcomes. I then provide the rationale for using allostatic load as the main health outcome measuring cumulative biological risks. Since this approach necessitates the introduction of new biosocial techniques that have traditionally been used outside of sociology, I also describe in

more detail Mendelian Randomisation and Gene-Environment Interaction, which are used to understand the complex interplay among socio-environmental and genetic factors. Second, I provide short summaries of the studies conducted in the chapters of the dissertation. Third, I describe the data used in this thesis and, since many of the techniques for integrating genetic information may be new to sociologists, describe in more detail the procedures of constructing genomic measures – polygenic risk score of education (PGS Edu). Finally, I summarise findings, discuss both the contributions and limitations of this dissertation, and propose future promising areas of research.

Figure 1-1: Conceptual framework of the biosocial determinants of health



1.1 A Biosocial Approach to Understanding Health

1.1.1 A life course perspective

The dissertation is guided by an overarching life course perspective in order to link individual biography, structural context, historical timing and health among older adults. The life course approach builds on insights from a wide range of social science disciplines. A central premise of this perspective is the interplay between the macro-level context and micro-level individual behavior and the principles of timing and life-span development (Elder, 1985; Elder & Shanahan, 2006). An individual's life history has been shown to have a strong impact on later life outcomes (Mayer, 2009), with key turning points impacting behavioral and health trajectories (Elder & Shanahan, 2006).

Individual choices and actions through the life course is inextricably linked with the opportunities and constraints of social contexts (Marshall & Mueller, 2003). The likelihood of being adversely affected by individual level health risk factors such as SES is strongly influenced by macro-level determinants such as income distribution and level of economic development (Sauzet & Leyland, 2017). For example, a person with high SES can afford to live in a highly developed region where they are surrounded by others that have a relatively higher status, but also in an environment with lower hazards such as crime, noise, violence and pollution, and more convenient healthcare facilities, gyms, clean restaurants and food stores. For high SES individuals, the health-enhancing circumstances bring benefits in numerous ways regardless of the person's own ability or perception of health; while for the low SES group, even though they may want to live a healthy life, their opportunities can be constrained by a lack of healthy food supplies, gym access, and healthcare institutions

in the neighbourhood. Hence, to understand social inequalities in health, it is important to recognise structural context and the interplay between context and individual outcomes (Bambra et al., 2010; Sacker, Worts, & McDonough, 2010).

Disparities in early life and in utero circumstances can directly or indirectly influence health outcomes in later life (Elder, 1994). The positive impact on health of education achieved in early adulthood varies not only with respect to mechanisms, but also with age. However, scholars are not unanimous in understanding the way which the strength of the education–health gradient changes during the life course (Chen, Yang, & Liu, 2010). The life course perspective provides three hypotheses regarding the extent of health decline across different levels of education in old age: health disparities for high and low levels of education may increase (Ross & Wu, 1996), decrease (Beckett, 2000; House, Lantz, & Herd, 2005), or remain constant (Clark & Maddox, 1992).

The 'age-as-leveler' hypothesis suggests that the protective effect from education in health become smaller in old age, resulting in the convergence of previously differentiated trajectories (House et al., 1994). One explanation for this convergence is a decrease in the rate of health decline among lower educated groups due to improved economic conditions in retirement, such as pension income and access to Medicare in the United States at retirement age (Card, Dobkin, & Maestas, 2008; Herd, 2006). State intervention protects the least economically privileged people by improving their overall financial condition: the strength of the association between education and health thus declines. Another possible mechanism for the convergence is via an accelerated decline among more highly educated groups. Mortality selection related changes to the surviving population may contribute to the convergence

(Beckett, 2000), wherein the most vulnerable and frail individuals in society are more likely to die at a younger age than their counterparts who are better educated and with more resources (Dupre, 2007). In addition, the attenuated association may be the result of reaching a biological limit to the human life span (Kiuila & Mieszkowski, 2007).

Cumulative disadvantage theory, on the other hand, indicates that the impact of education on health increases over the life course (Blane, Netuveli, & Bartley, 2007; Dannefer, 2003; Ferraro & Shippee, 2009). Education is considered a resource established earlier in the life course and leads to the accumulation of desirable experiences, skills, and resources that subsequently improve health status in later life. Health disparities are the result of cumulative experience of disadvantages early in the life course that lead to limited life chances, especially socioeconomically (Palloni, Milesi, White, & Turner, 2009; Wilson et al., 2007). In this sense, health inequalities due to education will increase with age, since a considerable amount of advantages or disadvantages have been accumulated over the life course (Leopold & Engelhartdt, 2012).

The life course approach highlights the dynamic interplay between individual biography, structural context, and timing (Arcaya, Arcaya, & Subramanian, 2015; Ben-Shlomo & Kuh, 2002; Wadsworth, 1997), which is valuable for research on health among older adults. In the next section I discuss the fundamental causes of health in terms of material resources, psychological mechanisms and health behaviors.

1.1.2 Fundamental causes theory

A number of studies have described a link between socio-economic status (SES) and health (Landes, Ardelt, Vaillant, & Waldinger, 2014; Luo & Waite, 2005; Seeman et al., 2008). Lower SES groups have higher rates of mortality (Frank, Cohen, Yen, Balfour, & Smith, 2003), higher incidence of psychiatric conditions (D. R. Williams & Collins, 1995), and higher morbidity in general (Banks, Marmot, Oldfield, & Smith, 2006). Higher income affects nutrition, housing quality, exposure to contextual hazards, stress, schooling, recreation, and access to adequate health care (Hayward, Shapiro, Freeman, & Corey, 1988; House, 2002; Lantz, House, Mero, & Williams, 2005). Education shapes future occupational opportunities and earning potential and provides knowledge and life skills that allow better-educated individuals to adopt healthy behaviours (Ross & Wu, 1995), cope with stress (Lantz et al., 2005), have a sense of personal control (Taylor & Seeman, 1999), and to better self-manage illness and diseases (Goldman & Smith, 2002).

Link and Phelan (1995) developed the theory of fundamental causes to explain why the association between SES and health has persisted in spite of changing medical and social circumstances. SES has a fundamental impact on health for four reasons. First, it affects a variety of health and disease outcomes. Second, it influences health outcomes through multiple risk factors. Third, its relationship with health is replicated over time via different intervening means. Finally, in order to reduce susceptibility to disease, one must have access to resources associated with SES, such as education, money, knowledge, power and social networks (Phelan, Link, & Tehranifar, 2010). While these resources may be used to avoid and/or minimise health risks, they are inequitably distributed among members of society (Olafsdottir, 2007). SES and

fundamental factors on health outcomes operate through various pathways: primarily via their role in obtaining material resources, and their effect on psychosocial and behavioural mechanisms.

SES also has a significant impact on material resources throughout an individual's lifetime. Family origins affect educational attainment and ability, which in turn allow one to obtain the skills to secure a desirable occupation and income (Luo & Waite, 2005; Warren, Sheridan, & Hauser, 2002). Being a member of a higher SES group provides the financial resources to afford health insurance and health care facilities, whereas low SES individuals may be linked to inadequate use and relative ineffectiveness of medical care, particularly in the US context (D. R. Williams & Collins, 1995). Working class patients in the United Kingdom tend to have fewer consultations with general practitioners than their middle-class counterparts, despite universal access to medical care. Middle-class patients also appear to receive higher quality care, insofar as the encounter is more efficient and provides better recommended services than lower SES patients (Asch et al., 2006; Townsend & Davidson, 1982).

Individuals with low SES are likely to be exposed to a more stressful environment, and the cumulative effect can have a significant negative impact on both physical and mental health (Thoits, 2010); conversely, higher SES individuals have been found to have a higher sense of personal control and access to economic resources and social support (Ross & Wu, 1995). Lower SES is related to deleterious health behaviour choices and chronic stressors due to higher rates of crime, unemployment, and marital instability (Jennifer B. Dowd, Palermo, Chyu, Adam, & McDade, 2014). The effect of chronic stressors and stressful life events cumulates over time, builds up psychosocial

stress, and eventually leads to negative health outcomes (Santiago, Kaltman, & Miranda, 2013).

Health behaviours are closely associated with material and psychosocial mechanisms. More highly educated people have better health knowledge enabling them to live healthy lives and efficiently seek healthcare resource and support (Mirowsky & Ross, 2007). Individuals of lower SES more frequently engage in health behaviours that are detrimental to health such as smoking, eating junk food and exercising less than those of higher SES (Pepper & Nettle, 2014).

1.1.3 Allostatic load (AL) as health outcome

The measurement of health is essential to understanding health and its age-associated dynamics. Previous health research within the social sciences often uses specific, narrow domains of health (i.e. activities of daily living (ADL)) or self-reported overall health status (Siegel, Bradley, & Kasl, 2003). While ADL are effective in measuring inability to perform tasks, they cover relatively limited domains and presumably do not provide information about relative differences between individuals who are not disabled. Self-rated general health has been used in a vast amount of research (Latham & Peek, 2013). Researchers have found that self-reported health is generally in line with physician evaluations and accurately predicts mortality (Idler & Benyamini, 1997). Yet self-reported health has been criticised for introducing subjectivity into the measurement process. Individuals may respond differently to this question partially in relation to their age, sex, and ethnicity (Finch, Hummer, & Reindl, 2002). Survey questions may not be consistent across waves, and bias in recalling health-related events may also undermine the validity of the measurements (Dowd & Todd, 2011).

This dissertation overcomes the limitations of traditional health measures by using biomarkers and allostatic load as the main health outcomes (Chapters 2 & 3). Individual biomarkers capture biological changes over time across different body systems. Allostatic load – the merging of multiple biomarkers into a single latent variable – is a more comprehensive, multisystem measure of the cumulative biological dysregulation across major physiological systems resulting from the accumulation of stressful exposures (McEwen & Stellar, 1993).

The concept of AL originates from the idea that "healthy functioning requires on-going adjustments of the internal physiologic milieu, with physiologic systems exhibiting fluctuating levels of activity as they respond and adapt to environmental demands" (Sterling & Eyer, 1988, p. 68). Such a process emphasises that while healthy functioning requires on-going fluctuation in the physiological system, these fluctuations should remain within an optimal operating range. The concept of AL is thus proposed as a measure of the cumulative impact of adaptive physiological responses that chronically exceed optimal operating ranges, resulting ultimately in wear and tear on the body's regulatory systems such that they are no longer able to maintain parameters within normal operating rages. AL is reflected in the cumulative total of physiological dysregulations across multiple physiologic regulatory systems, a total that is likely to impact significantly on health and longevity (Seeman et al., 2004). The coalescing of various measures into a single multifaceted biomarker is useful in health life course research to identify individuals at increased risk of disability and disease. Biomarker and allostatic load produce realistic measurements, and predict mortality and decline in physical functioning more accurately compared to self-reported measure of health (Seeman et al., 2011). These measurements should be able to identify at-risk individuals prior to them developing a disease (Levine, 2013).

Research consistently shows that a lower SES is related to higher risk of physiological dysregulation, and thus increased AL throughout one's lifetime (Dowd et al., 2014; Hawkley, Lavelle, Berntson, & Cacioppo, 2011). People with lower education and income experience greater prevalence of higher-risk values of both biomarker and AL (Crimmins, Kim, & Seeman, 2009; Gruenewald et al., 2012; Seeman et al., 2008). Increasing interest has also focused on how experience of SES adversity at a macro level is linked to biological functioning. Several studies have found that living in an impoverished region or neighbourhood is associated with higher AL (Danese & McEwen, 2012; Gustafsson et al., 2014; Schulz et al., 2012).

Despite the growing body of literature linking the micro- and macro-level of SES to allostatic load, existing studies are limited in two key ways. First, the current evidence on the SES-AL relationship is mostly from the US and other Western countries. Whether the relationship persists in the different socio-political-economic society of China has not been established. In addition, the contextual effect of SES on health is also unclear in China. Chapter 2 thus aims to provide a more comprehensive investigation into the SES-AL association with attention being given to both individual and contextual level factors. It is hypothesised that a higher regional level of economic development is associated with a lower AL, and income inequality is related to higher biological risks to health. Both individual SES and contextual environment are expected to affect health among Chinese older adults.

Second, although the existing largely Western literature has documented strong and persistent evidence linking SES and AL, the estimates seldom examine or make a causal inference. Chapter 3 therefore attempts a deeper examination into the potential

endogeneity in the correlation between education and AL using a novel identification strategy by incorporating genetic variants as instrumental variables.

1.1.4 Integrating genetic risk scores within health research

While the burgeoning literature on the Western world has provided theory and evidence concerning SES as an essential determinant of health (e.g.. Currie, 2012; Marmot, 2005; Wilkinson and Marmot, 2003), the pathways to health are not fully understood, mostly due to analytical challenges. Education level may depend on initial family background and early life health status that can compensate or reinforce its effect on health (Ravesteijn, van Kippersluis, & van Doorslaer, 2013). The effects are further mediated by biological determinants, and vary with age (Herd, 2006). In addition, there is less evidence that shows that the SES-health gradient exerts a substantial causal effect (Lleras-Muncy, 2005; van Kippersluis, O'Donnell, & van Doorslaer, 2011). The correlation may be the result of early childhood endowments and investments, or genetic predisposition (Almond & Currie, 2011; Currie, 2009).

With these issues in mind, recent advances in molecular genetics provide new possibilities for social scientists to bridge the aforementioned gap. Sociologists have increasingly recognised that one of the key social determinants of health – educational attainment – is at least partially due to genetic influences on ability endowments (Krapohl & Plomin, 2016; Todd & Wolpin, 2003; Trzaskowski et al., 2014). Twin and sibling studies have established that around 40 percent of the variation in educational attainment can be attributed to genetic endowments, suggesting that genetic makeup might be an important component of endowed ability (Branigan,

Mccallum, & Freese, 2013). Recent Genome Wide Association Studies (GWAS[1], details discussed in section 1.3) on education have confirmed that there is a genetic basis for educational attainment, by discovering dozens of genetic variants significantly related to years of education (Okbay et al., 2016; Rietveld et al., 2013). Some genes identified by the GWAS are relevant in elevated expression levels in the central nervous system, and may potentially play a role in stages of neural development in cognitive ability, explaining the possible biological mechanisms linking between genes and educational achievement (Okbay et al., 2016).

The genetic risk score has the following application in health studies. First, the score may shed light on the causal pathways between behavioural/social factors and health outcomes (Lehrer & Ding, 2017). This can be achieved by adopting Mendelian Randomisation (MR) – the application of instrumental variable (IV) method with genetic instruments (Davey Smith & Ebrahim, 2003) (Details are discussed in Chapter 3.3). Only a few studies have examined the causal relationship between education and health using the MR method. With the Young Finns Study, Böckerman et al. (2017) used genetic risk score for education as an instrumental variable and found that more years spent in education is causally associated with a lower BMI, but no causal effect has been identified between the education and waist-to-hip ratio association. In contrast, Hagenaars, Gale, Deary, and Harris (2017) found a negative relationship between years of education and a variety of diseases including BMI, blood pressure, coronary artery disease, and diabetes, but the analyses indicated no causal association between educational attainment and physical health within the UK Biobank sample. They argue that the lack of evidence for a causal link may be due to

[1] In genetics, GWAS is an investigation of genome-wide set of genetic variants in populations to detect if any variant is significantly robustly associated with a trait.

weak instrumental bias from the genetic risk score they applied, poorly measured health outcomes, or an insufficient number of disease cases.

Second, genetic risk scores can be used to examine genetic differences between individuals in their responses to certain environments, also known as gene-environment interactions (GxE). The expression of genes can be suppressed or triggered by a particular context. For example, physical activity and diet habits can modify genetic susceptibility to obesity, with physically active individuals appearing to be protected against a genetic burden compared with physically inactive persons (Ahmad et al., 2013; Andreasen et al., 2008; Li, Lai, Tseng, Lin, & Chang, 2010). Domingue, Liu, Okbay, and Belsky (2017) found that although the effect is small, adults with a higher well-being polygenic score have a buffer against increased life stress after experiencing the death of a spouse. Contextual level factors can also trigger or compensate for a genetic vulnerability. In the United States, the genotypic effects of education show a declining association with years of schooling over time (Conley, Laidley, Boardman, & Domingue, 2016; Nielsen & Roos, 2015). The decreasing genetic penetrance is likely due to the educational expansion from the twentieth century that has reduced variation in years of schooling (Conley et al., 2016).

Third, when the predictive power of the score for a health indicator is sufficiently large, the genetic risk score can be used to control for frequently overlooked genetic confounders in social science research. Failing to do so may lead to a bias in the estimates of a predictor in a statistical model due to unobserved heterogeneity (Martschenko, Trejo, & Domingue, 2018; Rietveld et al., 2013).

1.2 Overview of Chapters

This section presents the three research questions in the light of the aforementioned interdisciplinary approach and through which the biosocial gradient in health is analysed. Different perspectives and several aspects of the topic are studied in the research questions. The use of both macro- and micro-level social determinants of health enlightens this less-studied social context, and the inclusion of genetic variants helps to understand the causality between the education-health link. Table 1-1 summarises the three chapters.

1.2.1 Social determinants of health in China

A large number of studies have demonstrated the relationship between SES and a variety of health outcomes (e.g. Cutler, Lleras-Muney, and Vogl, 2008; Kaplan et al., 1987). The persistence of the relationship between SES, assessed at individual or regional levels, and health outcomes has led scholars to suggest that socio-economic status influences health through a broad range of behavioural and physiological mechanisms (House, 2002), with cumulative health effects over the life course. Regional poverty levels influence local social and physical environmental conditions (Schulz, Williams, & Israel, 2002), which influence health-related behaviours (dietary practices, physical activity). Conditions in the social and physical environment may also influence health if they are conducive to stress: exposure to stressful situations may place demands on individuals which could result in a physiological adaptation response, and finally lead to biological dysregulation, reflected in biomarker and allostatic load.

Chapter 2 revisits the SES–health gradient using nationally representative data in China. While macro- and micro-level SES have been shown as positively associated with health outcomes in a variety of settings, evidence of the relationship between inequality and health is less consistent. Three overarching ideas have been proposed to understand health inequalities at the macro level. First, a higher level of economic development is seen as leading to better health outcomes (Preston, 1975), yet it is also disputed that economic growth might also foster the prevalence of chronic diseases, such as obesity, diabetes and their complications. Second, in a thesis that has been widely discussed, greater income inequality is seen to worsen health outcomes, through both psychosocial and material mechanisms (Wilkinson & Pickett, 2010). Third, the provision of health services and infrastructure is considered as a key determinant of health (Anand & Ravallion, 1993), which may even moderate the effect of economic development and income inequality. At the micro level, interpretations of health inequalities have been focused on the lifestyle and living conditions of the lower-SES group, as well as access to and utilisation of medical care, and downward social mobility (Marmot, 2004). The link between inequality and health, on the other hand, is controversial both at the theoretical level and empirically.

While empirical research on the social determinants of health conducted in OECD countries is abundant, research on other parts of the world is scarce. The study in Chapter 2 contributes to the literature on the links between social gradient and health by focusing on Chinese older adults. The income inequality hypothesis has been widely tested in Western societies. As Gerdtham and Johannesson (2004) point out, in order to detect an effect of income inequality on health across geographic areas, it is necessary to have a sufficient level of income inequality and variation income inequality across regions. Most OECD countries are relatively egalitarian, and so may

not be the ideal places to test this hypothesis. China, on the other hand, has reached a relatively high level of income inequality, with a Gini coefficient in the range of 0.53-0.55 (Xie & Zhou, 2014), as well as considerable variation between provinces. This, in addition to the mere size of the population involved, makes China an important test-bed for research.

Using a series of multi-level regression models with baseline data from China Health and Retirement Longitudinal Study (CHARLS), this study contributes to global health policy-making and research in two respects. First, the growth in the older population in China poses challenges not only to Chinese society, but also to the whole world given its magnitude. Older adults have growing healthcare needs, and are more dependent on the support of others, which increases the burden on existing formal and informal institutions (Muramatsu, 2003). The health of elderly people is a growing but still marginalised issue of great policy importance (Feng, Wang, Jones, & Li, 2012). Second, over the past few decades, China has experienced unprecedented economic growth, accompanied by a dramatic increase in income inequality (Li & Zhu, 2006). The ever-increasing share of personal health and medical expenditure poses challenges for the healthcare infrastructure in China. This study provides significant sights into whether the association between economic development, income inequality, health-related public infrastructure, and health outcomes is modified among Chinese adults in midlife and older age.

1.2.2 Can genetic variants help to disentangle the causal relationship between education and health?

The empirical relationship between education and health is strong and persistent. Well-established analyses document overwhelming evidence that higher levels of

educational attainments are correlated with better health outcomes, regardless of what health indicator is used (i.e. self-evaluations of health status, mortality rates, psychological wellbeing, health-related behaviours, etc.) (Brown, Hayward, Montez, & Hummer, 2012; Smith, Anderson, Salinas, Horvatek, & Baker, 2015). These estimates show correlations but seldom represent a causal inference.

Chapter 3 adopts a life course approach and intends to establish whether additional years of education have a causal impact on health, measured by allostatic load. A potential problem in estimating the causality between education and allostatic load is that educational attainment might be confounded by a wide range of environmental factors, including childhood experience, cognitive abilities, family background, and even genetic factors, which are also possible risk factors for health in later life (Kawachi, Adler, & Dow, 2010). An instrumental variable (IV) approach is applied in this study to address the presence of potential unobserved confounders. Specifically, this study uses genetic variants from GWAS, known to be robustly related to educational attainment (Okbay et al., 2016). The counts of each individual's genetic variants are then summarised and weighted by their effect size on educational attainment to construct a polygenic score. The main instrumental variable in this study is the constructed polygenic score. This approach is also referred to as Mendelian Randomisation (MR) (Davey Smith & Ebrahim, 2003), and aims to reduce confounding and reverse causation by using genetic variation in populations. Quarter of birth is used as a second instrumental variable in this study.

Polygenic scores have been shown to serve as powerful instruments for estimating causal effects of observable exposures (Åsvold, Bjørngaard, & Carslake, 2014). The random assortment of genetic variants at conception ensures that variants with effect

on a modifiable exposure of interest are randomly distributed in relation to potential confounders (Davey Smith & Ebrahim, 2003). Compared to the commonly used non-genetic instrumental variables for education such as compulsory schooling laws, a polygenic score has several advantages in meeting the IV assumptions[2] (details are discussed in Chapter 3). First, compulsory schooling laws lead to an increase in educational attainment through the dictated minimum and maximum age of required school attendance (Lleras‐Muney, 2002). In the case of a policy change increasing the mandatory time, those adolescents who would have dropped out of school are forced to stay in school longer than they would have otherwise. Compulsory schooling laws are considered a credible source of exogenous variation in years of education. However, compulsory schooling laws as instruments for education only capture the effect of education on the outcome of interest for individuals who spent an extra year at school because of the law. The instrument has no effect on young people who plan to pursue higher education in the first place (Oreopoulos, 2006). Thus it might violate the monotonicity assumption. Polygenic scores, on the other hand, capture a different local average treatment effect (LATE) estimation. The effect of the polygenic score can be generalised to the entire population of the study. In addition, since genetic variation is determined at conception, it cannot be affected by later outcomes, which is a desirable quality in meeting the exclusion assumption.

With the social-demographic, biometric, and genetic data from the HRS, Chapter 3 applies an instrumental variable approach to identify causality in relation to education

[2] The IV assumptions are: (1) Independence. The instrument is independent of all potential outcomes and potential treatments. (2) Exclusion. The only way in which the instrument affects the potential outcomes is via exposure. (3) Non-zero effect of the instrument on treatment. The instrument must be associated with the risk factor of interest. (4) Monotonicity. The genetic instrument affects the risk factor for every individual in the same direction.

on health as measured by allostatic load. Two sets of instruments are used: a polygenic score associated with years of education and quarter of birth. The analysis finds a causal relation that education reduces the risk of poor health in older adults. This work contributes to the literature in the following ways. First, it documents the less studied causal relation between education and health. Second, it is one of the first to use genetic variations as an instrumental variable. This study provides promising evidence that genetic factors may be useful instruments for studying behavioural effects.

1.3.3 Gene-environment interaction: does genetic predisposition of education moderate age-related cognitive decline?

Cognitive decline affects the quality of life of the elderly population, as it limits their ability to perform instrumental activities of daily living, such as managing money, paying bills or planning sequences of activities (Fillenbaum, Hughes, & Heyman, 1988). Cognitive decline is also a determinant for mortality in an older population (Smits, Deeg, & Kriegsman, 1999). Fundamental causes theory (Link & Phelan, 1995) posits that the educational gradient in cognitive decline exists because those with higher educational attainment have better cultural competency, improving reading, maths and reasoning skills, and promoting more efficient cognitive processing (Ardila, Ostrosky-Solis, & Rosselli, 2000).

The empirical evidence provided by the life course perspective on the relationship between educational level and the rate of cognitive decline is, however, ambiguous. Lee, Kawachi, and Berkman (2003) and Lyketsos, Chen, and Anthony (1999) find that lower educational levels are correlated with a greater risk of poor cognitive performance in old age. Christensen, Hofer, and MacKinnon (2001), Hultsch (1998)

and Leibovici et al. (1996) find that education does not significantly affect the rate of cognitive decline. On the other side of the debate, Ardila, Ostrosky-Solis, and Rosselli (2000), Butler, Ashford, and Snowdon (1996) and Stern et al. (1999) find that educational achievements can lead to a greater rate of decline in cognitive ability in old age. As the evidence is inconclusive, further research is needed to address this inconsistency and to clarify the ways in which education influences cognitive stability and decline.

Both educational attainment and cognitive function have a genetic basis. A recent GWAS on educational attainment found that a linear polygenic score from all measured single nucleotide polymorphisms (SNPs)[3] accounts for about 2-3% of the variance in both educational attainment and cognitive function (Okbay et al., 2016). Many of the genetic variants are associated with educational attainment via mediating pathways related to cognitive process and neuronal development or function (Okbay et al., 2016; Rietveld et al., 2013). The predisposition of more alleles positively associated with education may correlate with higher levels of cognitive function, and decrease in importance with age across cognitive decline.

Recently, an increasing number of social and genetic epidemiology studies have demonstrated how genes and the environment work together with fundamental causes to influence health-related behaviour and outcomes over time (Boardman & Blalock, 2010; Domingue, Conley, Fletcher & Boardman, 2016). While these studies are crucial for understanding health-related gene-environment interactions (GxE) across

[3] At the vast majority of locations in the genome (approximately 99%), there is no variation across individuals in the nucleotide pair on the DNA. Particular SNPs are referred to using its position in the genome (e.g. rs9320913) (Beauchamp et al., 2011; Benjamin et al., 2012). Note that other forms of genetic variation exist, including deletions, insertions and copy-number variations (Feuk, Carson, & Scherer, 2006).

time, no work to date has extended these GxE frameworks to consider how the predisposition of genetic variants in educational attainments may moderate the socio-demographic effect on cognitive function and decline over time. For these reasons, Chapter 4 uses genetic variants for educational attainment as a proxy to assess the relationship between genetic predisposition for education and change across multiple domains of cognitive function among American middle-aged and older adults.

Table 1-1 Summary table of chapters in this thesis

Chapter 2: Micro and macro social determinants of health among Chinese midlife and older adults			
Questions Do individual health outcomes vary across provinces? Do provincial-level economic development, income inequality, and health infrastructure affect health? Controlling for macro social determinants, are micro-level factors still associated with health?	**Outcomes** Self-rated health; single biomarkers; allostatic loads. **Predictors** Micro level: Educational attainment, household income; Macro level: economic level of development, income inequality, health infrastructure	**Data** China Health and Retirement Longitudinal Survey 2011 national baseline **Methods** Principal component analysis; multilevel modelling	**Results** Individual health outcomes differ between provinces; economic growth is associated with better self-rated health, but also with obesity. A better health infrastructure tends to be negatively associated with health outcomes, indicating the likely presence of reverse causality. No evidence is found for the hypothesis that income inequality leads to poorer health outcomes. Micro social determinants are stronger and more persistently associated with health outcomes than macro-level factors.

Chapter 3: Educational attainment and allostatic load in later life: Evidence using genetic markers			
Questions How is educational attainment associated with allostatic loads? Is the association between education and allostatic load causal? Can genetic markers be used as instrumental variable in studying the causal relationship? What are the potential mechanisms between education and allostatic loads?	**Outcomes** Allostatic loads; single biomarkers **Predictors** Years of education **Instrumental variables** Polygenic risk score; quarter of birth	**Data** Health and Retirement Survey wave 9 **Methods** Ordinary Least Squares Regression Two Stage Least Squares Regression	**Results** Using multiple instruments, there was an 18% reduction in allostatic load per year of schooling. Analyses evaluating the plausibility of the IV assumptions indicated that estimates derived from analyses rely on both instruments to provide the best estimates of the causal effect of education. IV analyses were also used to identify potential pathways between education and health. We conclude that IV analyses suggest education is protective against risk of negative biomarker health outcomes in older adulthood.

Chapter 4: Does educational attainment/genetic predisposition of educational attainment affect mental health and decline in cognitive ability in later life?			
Questions How is the polygenic score for education associated with level of cognitive function? How is the polygenic score for education associated with cognitive change? After controlling for genetic effect, how do fundamental social causes associate with the level and slope of cognitive function over age?	**Outcomes** Cognitive function domains **Predictors** Age, sex, polygenic score for education, years of schooling, social integration, health behaviour, and chronic diseases	**Data** Health and Retirement Survey wave 4-11 **Methods** Linear mixed models	Individuals with a higher genetic predisposition to educational attainment perform better in all measures of cognition throughout later life. Genetic effects on cognitive decline change with age and across cognitive domains. For global cognition and episodic memory, the advantages brought by a genetic predisposition to educational attainment gradually disappear with age. For mental status, the PGS Edu effect magnifies from age 70 – 75. No relationship is found between PGS Edu, working memory and vocabulary.

1.3 Data and Methods

This section summarises the data sources used in this thesis. Chapter 2 uses data from the National Baseline Survey of CHARLS 2011 to examine the association between education, income, income inequality and health through multilevel statistical analyses. Chapter 3 & 4 obtained survey and genetic data from the continuous Health and Retirement Study (HRS) for the US. Both CHARLS and HRS are large, nationally representative health surveys that have biomarkers and self-reported measures of health through interviews and physical examinations. Genetic information is currently only available in the HRS.

1.3.1 The CHARLS sample

A large-scale survey on the health of elderly people was rarely available in China before 2000. The CHARLS is an on-going collaborative study of the University of Southern California, University of Oxford, and Peking University. The survey is modelled after the HRS of the University of Michigan, and is related to other ageing surveys such as the English Longitudinal Study of Aging (ELSA) and the Survey of Health, Aging and Retirement in Europe (SHARE). CHARLS is a longitudinal panel study designed to provide a wide range of information, from socio-economic status and social support to health conditions, from a high quality, nationally representative sample of Chinese residents aged 45 and above. The total sample of the baseline national wave comprises 17,596 individuals in 10,257 households, across 28 provinces in China (Appendix 1-1). Three provinces are not sampled: Tibet, Ningxia and Hainan. Among the interviewed subjects, 11,847 individuals (67%) agreed to provide a blood sample, and therefore we have biomarker information such as

Cystatin C and HbA1c. Due to the selectivity in the collection of blood samples, sample weights are used to correct for household and individual non-participation in the blood collection[4].

Despite the CHARLS dataset's public availability, the CHARLS national baseline data has some major advantages over existing Chinese data that has been used to analyse the SES–health gradient. Income and health status measures are more accurate and reliable in CHARLS compared to other available datasets such as the China Health and Nutrition Survey (CHNS) which lacks economic variables such as consumption, income and wealth (Zhao et al., 2014). The CHARLS dataset is also the ideal survey to test hypotheses that refer to the older population across China. Other widely used surveys in China such as CHNS are different from the HRS, in that they are either not strictly an aging survey because the sample is small or merely focused on the oldest aged (over 80 years) (e.g. the Chinese Longitudinal Healthy Longevity Survey (CLHLS)). In addition, the CHARLS dataset has relatively high external validity because the sample is large and heterogeneous and comes from both urban and rural areas across 28 provinces. The estimates from analysing the CHARLS dataset can thus be generalised across the whole country of China. Chapter 2 is the very first analysis using the CHARLS national baseline data to examine the relationships between socio-economic determinants, income inequality, and health. Aggregate-level data for regional income inequality, economic development, and institutional settings are obtained from the Chinese Statistics Yearbook 2012.

[4] The weight for the selectivity of the blood sample collection (Bloodweight) is calculated by the CHARLS team and is included in the dataset. For more information, see Zhao et al., 2014, *China Health and Retirement Longitudinal Study 2011-2012 National Baseline Blood Data Users' Guide*, Peking University.

1.3.2 The HRS sample

The primary dataset for chapters 3 & 4 is from the HRS. The HRS is a nationally representative, longitudinal panel study of over 20,000 American individuals aged 50 and above and their spouses (Ofstedal, Weir, Chen, & Wagner, 2011). The study was launched in 1992 with data collected every two years. The survey contains detailed socio-demographic and health information in addition to a genetic sample. In 2006, HRS initiated an enhanced face-to-face (EFTF) interview. In addition to the core interview, the EFTF interview includes a set of physical performance tests, anthropometric measurements, blood and saliva samples and a self-administered questionnaire on psychosocial topics. The blood sample collected since 2006 provides information on a range of biomarkers as part of the enhanced face-to-face (EFTF) interview. HRS collected blood-based biomarkers on half the sample in 2006; the other half of the sample provided biomarker data in 2008. The first group was asked for another blood sample in 2010 and the second group gave repeated samples in 2012. Chapter 2 uses the 2008 (wave 9) and 2012 (wave 11) biomarkers.

In 2006 and 2008, the HRS genotyped 12,507 respondents who provided DNA samples and signed consent forms. DNA samples were genotyped using the Illumina Human Qmni-2.5 Quad BeadChip, with coverage of approximately 2.5 million genetic variants. Current genetic data available for research also include imputation of approximately 21 million DNA variants from the 1000 Genomes Project. The current HRS genetic data is available under the European Research Council SOCIOGENOME project. Following recommendations from the genotyping centre for quality control, I removed individuals with a genotyping rate less than 95% and SNPs with minor allele frequency (MAF) less than 1% with p-value less than

1×10^{-4} on the test for Hardy-Weinberg equilibrium, and with a missing call rate greater than 5%. Details regarding the quality control procedure can be found in Weir (2012). The resulting genetic sample includes 12,205 individuals and information for 8 million SNPs.

1.3.3 Biomarker measures

Both CHARLS and HRS provide biomarker information, which is used to construct allostatic load in the subsequent chapters. Table 1-2 presents the biomarkers used in this dissertation; the cut-off point used to identify "high risk" disease conditions may vary based on different clinical and literature recommendations for Asian and Caucasian populations (Gijsberts et al., 2016) (Table 1-2).

Body Mass Index (BMI) and waist circumferences are indicators for obesity. Glycosylated haemoglobin (HbA1c) is used as an indicator for type-2 diabetes (Saudek et al., 2008). Compared with self-reported diabetes, the HbA1c test is more accurate in terms of sensitivity and specificity analyses, especially among the Chinese older population (Yuan, Liu, Wu, Zou, & Li, 2015). Hypertension is assessed by mean systolic blood pressure > 140 mm Hg, mean diastolic blood pressure > 90 mmHg, or self-report of currently taking prescribed medication for treating hypertension (Canzanello & Sheps, 1998). Individuals in both CHARLS and HRS have their blood pressure measured three times during the interview. The cholesterol ratio is the ratio of total cholesterol to the amount of high density lipoprotein (HDL)[5],

[5] HDL, often called "good cholesterol", carries cholesterol to the liver when it is eliminated. Maintaining the HDL at a recommended level is desirable, and low levels of HDL is a health risk. On the other hand, low density lipoprotein (LDL) is referred to as "bad cholesterol". An increased amount of LDL cholesterol indicates a higher risk of blocked arteries. The Cholesterol ratio thus measures the amount of desirable HDL cholesterol in the total cholesterol.

and measures risk of blood cholesterol (Kinosian, Glick, & Garland, 1994). Triglycerides is also part of the cholesterol profile and measures the level of blood triglycerides; this measurement is only available in CHARLS. Both the triglycerides level and cholesterol ratio are important indicators for coronary heart diseases, vascular diseases and stroke (Helgadottir et al., 2016). C-reactive protein is an indicator for inflammation system that has been used increasingly in predicting risks for cardiovascular disease (Ridker, 2007). It also reflects chronic inflammation through an auto-immune response and is related to a number of other aging-related diseases including rheumatoid arthritis, diabetes, sarcopenia, and cancer (Licastro et al., 2005). Cystatin C measures renal function in the hematopoietic system. Recent evidence suggests that Cystatin C is useful as a marker for glomerular filtration (Ferguson, Komenda, & Tangri, 2015) and cardiovascular diseases (Angelidis et al., 2013). Handgrip is a physical measure of muscle strength.

Table 1-2 Cut-off points for high risk values of individual biomarkers, Asian and Caucasian Populations

Variable	Cut-off points	
	CHALRS	**HRS**
Body Mass Index (BMI)	≥27.5 or < 18.5 (kg/m^2)	≥30 or < 18.5 (kg/m^2)
Waist circumferences	male > 90; female > 80 (cm)	male > 102; female > 88(cm)
HbA1c	≥ 6.5, or taking medicine (%)	
Systolic blood pressure (SBP)	mean > 140mmHg (three measurements), or taking medicine	
Diastolic blood pressure (DBP)	mean > 90mmHg (three measurements), or taking medicine	
High triglycerides	≥ 50 mg/dl	N/A
High cholesterol ratio	Total to HDL ≥ 5.92	
High C-reactive protein	≥ 10mg/L	
Cystatin C	>1.55 mg/L	
Weak grip strength	<20kg women, 30kg men	

Note: Hba1c = Glycosylated haemoglobin; HDL = high density lipoprotein.

1.3.4 Constructing polygenic score from GWAS with the HRS sample

The GWAS is a hypothesis-free scan of a genome-wide set of SNPs in different individuals to detect if any SNPs are significantly associated with phenotype (trait or outcome) (Belsky & Israel, 2014; Nolte, Mccaffery, & Snieder, 2010). An SNP is a locus of a gene that may vary across individuals. It is a form of mutation that might result in individual differences in phenotypes (e.g. disease or traits) (Beauchamp et al., 2011; Benjamin et al., 2012). Each SNP consists of two nucleotide variations that are called alleles, one from each parent. Thus, under most circumstances an individual can have none, one, or two of a specific allele.

GWAS studies embrace the fact that heritability of most behavioural outcomes is due to multiple genes (polygenic) that are difficult to identify in advance (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015; Martschenko et al., 2018) and thus do not make any prior assumptions about the biological pathway or a specific location. In practice, GWAS regresses an outcome of interest against millions of individual SNPs, corrects the potential statistical artefacts by implementing stringent *p*-value thresholds where the significant level is lower than 5×10^{-8} (genome-wide significant). The GWAS approach overcomes some of the disadvantages imbedded in the candidate genes approach, which presumes genetic variants in the genome that might associate with a phenotype based on elusive knowledge of the relevant biological processes underlying the trait. The early candidate genes studies produce results that are rarely replicable due to the fact that these studies are likely to be underpowered to detect plausible effects of individual SNPs, and thus the detected statistically significant associations are likely to be false positive results (Benjamin et al., 2012). The GWAS approach on the other hand generates more reliable associations and is able to

discover novel genes which could be used in future studies to explain the potential biological pathways (Wray et al., 2013). GWAS research has led to discoveries of a large number of SNPs that predict pathological (e.g. Ganesh et al., 2009), behavioural (e.g. Barban et al., 2016) and socioeconomic outcomes (e.g. Rietveld et al., 2013).

Purcell et al. (2009) suggest that GWAS results can be aggregated into genetic risk scores (also known as polygenic scores) which are linear combinations of the significant SNPs. The genetic risk score can be interpreted as a single quantitative summary of an individual's cumulative genetic predisposition to a specific disease or traits. The scores are constructed by summing the risk alleles of the SNPs associated with the outcome of interest. For each SNP the number of risk alleles is zero to two. The contribution of each SNP is taken into account by applying weights based on the effect size from the ordinary least squared (OLS) regressions of individual SNPs in the GWAS.

Two broad approaches can be used to build the polygenic score from GWAS results; both are used in this thesis. The top-hit approach constructs a polygenic score from SNPs with strong evidence for contributing to the phenotype of interest, i.e. SNPs that is genomic significant. This approach is conservative but has relatively less noise. I use this approach to construct the polygenic score for education as an instrument variable in Chapter 3. Another approach is the whole-genome approach, which assumes that a very large number of SNPs make an "infinitesimal" contribution to the phenotypic variation (Visscher, Hill, & Wray, 2008). This approach constructs the score from the entire number of measured SNPs (Purcell et al., 2008) and thus can serve as proximal phenotypes that describe the biological pathway between genetic markers and outcomes (Belsky & Israel, 2014).

This thesis constructs polygenic scores of educational attainment based on the most recent GWAS, that gave identified associations between specific SNPs and educational attainment (Okbay et al. 2016). Using data from 125,599 individuals with European ancestry, the Social Science Genetics Association Consortium (SSGAC) identified three independent SNPs associated with education outcomes (Rietveld et al., 2013). The study is a landmark discovery, for the paths linking biology to education are weaker than those related to traits such as height or heritable diseases, and the results have been successfully replicated in later studies (Rietveld et al., 2014). In 2016, the SSGAC extended their analyses with a sample of 293,723 individuals with European ancestry and found 74 SNPs genome-wide significantly related to years of education (Okbay et al., 2016). Evidence shows that the associations are heavily reliant on cognitive mechanisms that affect both foetal brain development and development over the life course. At the time of writing this thesis, researchers are currently working on the third iteration of the GWAS on education with over a million individuals (Lee et al., 2017). A polygenic score constructed from the results of this GWAS would improve the predictive power greatly in independent samples.

Research using polygenic scores based on the GWAS education has produced many inspiring interdisciplinary findings. The polygenic score of education robustly predicts educational attainment even after controlling for socioeconomic origin using within-family variation (Conley et al., 2015; Domingue et al., 2016; Rietveld et al., 2014). Moreover, the score has also been shown to be associated with a variety of life course factors including school performance (Selzam et al., 2017), childhood verbal ability (Belsky et al., 2016), and cognitive abilities (Rietveld et al., 2014), and familial/neighbourhood socioeconomic status (Belsky et al., 2016; Conley et al., 2015; Domingue, Belsky, Conley, Harris, & Boardman, 2015). Schmitz and Conley (2017)

find evidence that genetic heterogeneity can moderate the effect of military service during the Vietnam War on subsequent educational attainment. Papageorge and Thom (2016) show that the score not only predicts education, but is also associated with a variety of labour market outcomes.

The polygenic score for education (PGS) is constructed using the top-hit approach (PGS1) in Chapter 3, and the whole-genome approach (PGS2) in Chapter 4. I construct the PGS based on the education GWAS results (Okbay et al., 2016), which identified 74 independent SNPs associated with an individual's total years of schooling. Since the HRS was a part of the GWAS sample, I obtained the list of association results calculated excluding the HRS from the meta-analysis from the SSGAC.

Using these summary statistics, in Chapter 3 I construct PGS1 with SNPs that have a statistical association of $p\text{-}value < 5 \times 10^{-8}$, and excluded the SNPs that has been found to be associated with BMI and cognitive abilities[6] (Okbay et al., 2016). This yields a list of 35 SNPs (Appendix 1-2). PGS1 is used to instrument education in the MR analysis. It is essential that a valid instrumental variable is only correlated with the exposure of interest, influences the outcome via and only via the exposure, and is not associated with any confounder that may influence the outcome (Greenland, 2000; Martens, Pestman, de Boer, Belitser, & Klungel, 2006). MR exploits the random allocation of an individual's genotype at conception, meaning that each child has an equal probability of inheriting either half of their parental genomes. Under the assumption that the PGS1 is specifically associated with the observable exposure of

[6] BMI is used in constructing allostatic load in Chapter 3. Inclusion of genetic variants correlated with BMI and cognitive abilities may violate the exclusion assumption of the instrument variable.

interest, and is randomly assorted in relation to other potential risk factors (Davey Smith & Ebrahim, 2003), it assigns the population into subgroups which systematically differ in the trait of interest, but cannot be affected by reverse causation (Burgess & Thompson, 2013). The MR approach is analogous to randomised controlled trials (RCTs) familiar to social scientists (Lawlor, Harbord, Sterne, Timpson, & Smith, 2008). Furthermore, PGS1 summarises the effects from single risk alleles, has increased predictive power, and can avoid weak instrument bias (Palmer et al., 2012; Pierce, Ahsan, & Vanderweele, 2011).

The PGS2 for Chapter 4 is more liberal: it sums risk alleles across all the genotyped SNPs, thus yields a comprehensive measure of genetic endowment of education. Both scores are weighted for their effect sizes in the meta-analysis using the software PLINK and PRSice (Euesden, Lewis, & O'Reilly, 2015; Purcell et al., 2007).

To recap, the two scores polygenic scores for individual i are calculated as the sum of the allele counts a_{ij} (0, 1, or 2) for each SNP $j = 1, \dots M$, weighted by association strength p_j:

$$Polygenic\ score = \sum_{j=1}^{M} p_j a_{ij} \qquad (1)$$

To illustrate the relationship between the constructed PGS1, PGS2 and educational attainment, I create an analytical sample that includes all genotyped individuals with European ancestry born before 1955 with non-missing education data. Only white and non-Hispanic Americans are included because the SNPs I used to construct PGS1 and PGS2 are based on the GWAS discovery in a sample of genetic Europeans. This analytical sample consists of 8,195 individuals. To address potential confounding by population stratification, I include the first ten principal components (PCs) from the

entire sample of genotyped HRS based on variance-standardised relationship matrix. The PCs measure the uncorrelated variation in the data, accounting for any systematic ancestry differences in genetic structures within populations that could bias estimates (Price, Patterson, & Plenge, 2006).

Table 1-3 provides descriptive statistics on socio-demographic variables and PGS. PGS1 and PGS2 are moderately correlated (corr. = 0.27, $p<0.001$). The mean number years of education for respondents is around 13 years, with women attaining significantly fewer years than men. Men are more likely to attain General Education Development (GED) and finish college, while females are more likely to finish high school and drop out of college. The pattern also extends to female respondents' parents. Both female respondents' parents achieve fewer years of education compared to male respondents' parents. Turning to PGS, the mean of PGS2 for men is higher than PGS1 for men, and the mean of PGS2 for women is lower than PGS1 for women. Yet PGS2 also have a much larger standard deviation. The differences between male and female for both PGS are not significant. Figure 1-2 presents a plot of the standardised PGS constructed from each observation, showing a bell-shaped distribution. The linear prediction of years of education, obtained from a regression on the genetic variant of education, is represented by the straight line. One standard deviation increases in PGS1 and PGS2 increases the years of education by one month and four months, respectively ($\beta_{\text{top-hit}} = 0.08$, $SE_{\text{top-hit}} = 0.03$; $\beta_{\text{genome-wide}} = 0.143$, $SE_{\text{genome-wide}} = 0.012$). There is, however, a considerable amount of unexplained variation in educational attainment ($R^2_{\text{top-hit}} = 0.001$; $R^2_{\text{genome-wide}} = 0.026$), as shown in Figure 3.2, where the linear prediction is represented by the same straight line.

Table 1-3 Summary Statistics of the HRS Sample

	Male			Female		
Variable	**Mean/Proportion**	**Std.**	**N**	**Mean/Proportion**	**Std.**	**N**
Birth Cohort						
<1934	0.395	0.489	3448	0.398	0.488	4684
1935 - 1944	0.360	0.480	3448	0.352	0.478	4684
1945 - 1955	0.245	0.430	3448	0.258	0.438	4684
PGS1	0.002	0.001	3460	0.002	0.001	4735
PGS2	0.038	1.005	3460	-0.004	0.986	4735
Years of Education						
Respondent	13.365	2.778	3460	12.993***	2.358	4735
Father	10.074	3.466	3149	9.834**	3.425	4217
Mother	10.515	2.960	3209	10.218***	2.948	4441
Qualification						
Left High School	0.130	0.337	3460	0.131	0.338	4735
GED	0.050	0.217	3460	0.038*	0.192	4735
High School	0.287	0.452	3460	0.378***	0.485	4735
Some College	0.224	0.417	3460	0.251**	0.343	4735
College and Above	0.310	0.462	3460	0.201***	0.401	4735
Childhood Health						
Excellent	0.492	0.500	2260	0.483	0.500	3165
Very Good	0.329	0.470	2260	0.312	0.463	3165
Good	0.127	0.333	2260	0.150*	0.358	3165
Fair	0.037	0.188	2260	0.040	0.196	3165
Poor	0.014	0.118	2260	0.015	0.120	3165

Note: T-test significance level: $^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$

Figure 1-2 Distribution of the PGS

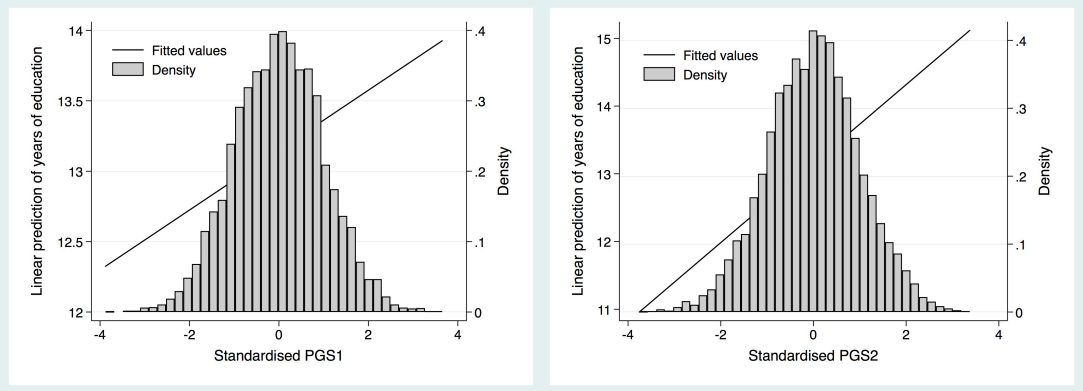
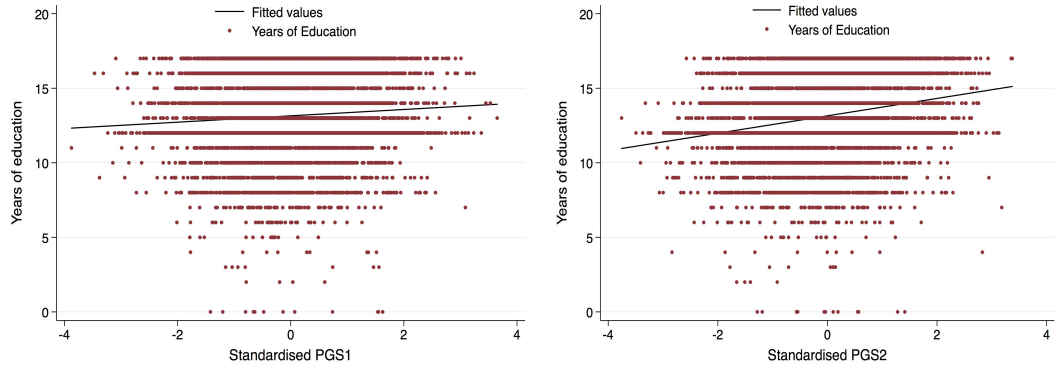


Figure 1-3 Educational Attainment by PGS



1.4 Summary

To recapitulate, the thesis integrates social, contextual, psychological, biological and genetic influences in order to gain further insight on variations in health among older adults. The aim of this introductory chapter was to review the current state of knowledge and put the contribution of this thesis into context within the SES-health link literature. I first provided a theoretical framework that highlights the importance of studying health from a life course perspective. An individual's later life health outcomes are strongly affected by his or her life history, and the interplay between micro-level individual behaviours and macro-level social context. After touching upon the preview of chapters, I turned to the methodologies of the biosocial approach that included both social, biological, and genetic determinants of health. The integration of genetic and social factors may reduce the estimation bias of the past sociological research that excludes biological and genetic influences. Moreover, the biosocial approach helps to facilitate the examination of how the expression of the genes changes with age.

Chapter 2. Health of midlife and older adults in China: the role of regional economic development, inequality, and institutional setting[7]

Abstract

The aim of this chapter is to document the association between economic development, income inequality, and health-related public infrastructure, and health outcomes among Chinese adults in midlife and older age. A series of multi-level regression models with individual-level baseline data from the China Health and Retirement Longitudinal Survey (CHARLS) are used. Provincial-level data are obtained both from official statistics and from CHARLS itself. Multi-level models are estimated with different subjective and objective health outcomes. This study finds that economic growth is associated with better self-rated health, but also with obesity. Better health infrastructure tends to be negatively associated with health outcomes, indicating the likely presence of reverse causality. No supportive evidence is found for the hypothesis that income inequality leads to worse health outcomes. The result shows that on top of individual characteristics, provincial variations in economic development, income inequality, and health infrastructure are associated with a range of health outcomes for Chinese midlife and older adults. Economic development in China might also bring adverse health outcomes for this age group; as such specific policy responses need to be developed.

[7] This chapter is based on Ding, X., Billari, F. C., & Gietel-Basten, S. (2017). Health of midlife and older adults in China: the role of regional economic development, inequality, and institutional setting. *International journal of public health*, 62(8), 857-867.

2.1 Introduction

Three overarching ideas have been proposed to understand health inequality across time and place. First, a higher level of economic development is seen as leading to better health outcomes (Preston, 1975). Second, in a thesis that has been widely discussed, greater income inequality is seen to worsen health outcomes, through both psychosocial and material mechanisms (Wilkinson & Pickett, 2010). Third, the provision of health services and infrastructure is considered a key determinant of health (Anand & Ravallion, 1993), which may even moderate the effect of economic development and income inequality.

It is widely acknowledged that economic development allows to improve the quality of goods and services such as food, health care, medical services, etc., which in turn leads to improved health and nutrition among the population (Anand & Ravallion, 1993). However, recent research shows that economic growth might also foster the prevalence of chronic diseases, such as obesity, diabetes and their complications. Evidence shows that the urbanisation and economic progress in China have led to a radical reduction in overall and occupational physical activity (Ng, Norton, & Popkin, 2009; Sherif & Sumpio, 2015), as well as an increase in fat consumption.

The link between income inequality and health is also controversial, both at the theoretical level and empirically. Wilkinson and Pickett (2010) suggest that individuals who live in a more equal society have on average better health outcomes than their counterparts living in less equal societies. This idea, formulated with specific reference to developed societies, is hypothesised to work through both psychosocial and material mechanisms. More specifically, income inequality would

influence health through relative deprivation. For individuals with relatively low incomes, inequality generates negative emotions such as shame and stress that harm health through "psycho-neuro-endocrine" mechanisms, and induces unhealthy behaviours such as smoking and alcohol abuse. Relative deprivation also impairs health for the whole population, through a reduction of social capital and social cohesion: in more unequal societies, participation in community activities is reduced, and trust and efficacy within a community are weakened, with potential effects on the health of the entire population, including those higher up the income range (Kawachi & Kennedy 1999). The evidence from the large body of empirical work testing the income inequality hypothesis is however mixed. While Pickett and Wilkinson (2015) insist on the relationship between inequality and population health being causal, methodological concerns and empirical evidence have cast doubts on the causal nature of this relationship. Studies using large and high-quality data sets found that the effects of income inequality, which are significant in OLS regression models, tend to disappear or become markedly weaker when more appropriate fixed-effect or multi-level regression models are used (Beckfield, 2004). Mellor and Milyo (2003), in a study on the US, added a variety of controls to their analysis and found that income inequality has no significant effect on health. Biggs et al. (2010) and Rajan, Kennedy, and King (2013) revisited the income inequality hypothesis in Latin America and India and found no evidence supporting the claim that income inequality is detrimental to health in these less developed global settings.

The provision of health-related public infrastructure (HRPI) has been shown to make a difference to health outcomes through its link to economic development and income inequality. Higher levels of economic development allow greater public investments in HRPI at the aggregate-level, and make out-of-pocket expenditures in medicines

and services at the individual-level more affordable (Dollar & Kraay, 2002). Societies with higher levels of income inequality, with the US as a textbook case, tend to spend less on improving public health or human capital development. This lower level of public investment weakens the opportunities that individuals have to improve their living standards and health (Kentikelenis, Stubbs, & King 2015). Improved health services and infrastructures make healthcare more affordable and accessible, with the potential to buffer the negative effects arising from income inequality (Ellwardt et al. 2014).

In summary, the literature emphasizes three interdependent aggregate-level determinants of health: economic development, income inequality and investment in health infrastructure. Although it has been widely recognised that individual characteristics explain most of the variation in health disparity, this study aims to understand the effects of these contextual factors for a specific group: Chinese midlife and older adults (age 45 and above). In China, the rapidly growing elderly population poses great challenges for global health. Over the past few decades, the country has experienced unprecedented economic growth, accompanied by dramatic increase in income inequality (Li & Zhu, 2006). Although a high rate of improvement in HRPI has occurred in China since the 1990s (Liu, 2004), the ever-increasing share of personal health and medical expenditure still poses a challenge for the government (Zhang & Kanbur, 2005). It is hence paramount to examine whether the effects of economic development on health are modified by inequality or health infrastructure.

We specifically focus on midlife and older adults. Midlife is a period in life in which limited physical functioning and manifest chronic diseases start to become widespread. Furthermore, this period of life is linked to growing healthcare needs,

which increase burdens on existing formal and informal health infrastructures (Muramatsu, 2003). Midlife and older adults are therefore vulnerable to socio-economic disadvantages and changes in their living environment, and are particularly relevant to understanding the relationship between economic growth, inequality and medical infrastructure on health (Mosquera et al., 2016).

Previous studies of the link between wealth/inequality and health link have relied on survey data, or hospital records. While our study also uses self-rated health (SRH), we additionally employ biomarker data to measure health risks. The utilisation of a series of biomarkers provides some attractive features. Biomarkers are measured objectively, minimising systematic reporting errors caused by bias and preferences. They provide an identification of pre-disease pathways, since physiological processes are often below the individual's threshold of perception. We also include allostatic load (AL) – a comprehensive index that incorporates multiple biomarker risk factors, which is expected to better predict future health risks than any single risk factor by itself. However, the mechanisms underlying the links between income inequality and specific biomarkers are not yet clear. Any (or all) of the aforementioned mechanisms could mediate the possible relation between income inequality and biomarkers in cardiovascular diseases and physical functions. "Psycho-neuro-endocrine" factors could potentially affect diet choice and rates of physical activity, consequently affecting blood pressure, inflammation and grip strength. In addition, less egalitarian provinces may invest less resources in promoting and maintaining healthy behaviours, and may also invest less in health education and preventive care. The exposure to economic underdevelopment and income inequality accumulates throughout the life course, and places demands on the biological system (e.g., cardiovascular and metabolic system), ultimately leading to greater system dysregulation, subsequently

enhancing risk for poor health and functioning (Gruenewald et al., 2012). The prevention, diagnosis, and long-term treatment of non-communicable and chronic diseases, as well as physical functioning indicated by biomarkers, are heavily relying on health infrastructures (Blankart, 2012). Some recent studies focusing on the United States found that risk factors for cardiovascular diseases, including hypertension, diabetes, and grip strength, show variation at regional levels and are associated with state-level income inequality (Cushman, McClure, & Howard, 2009; de Vries, Blane, & Netuveli, 2014; Diez-Roux, 2000). To our knowledge, this paper is the first to study the associations between income inequality, economic development, health infrastructure and health as measured through biomarkers among Chinese midlife and older adults.

2.2 Methods

2.2.1 Data

Given our multi-level framework, we need data both at the individual and aggregate (provincial) level. Individual-level SRH and physical measures of girth, blood pressure, handgrip strength, and covariates comes from the 2011 national baseline survey of the Chinese Health and Retirement Longitudinal Study (CHARLS). CHARLS, modelled after the US Health and Retirement Study, provides a wide range of information, from socio-economic status and social support to health conditions for a randomly-selected and nationally-representative sample of Chinese residents age 45 and above, living in households. The total analytical sample of the baseline national wave comprises 17,368 individuals across 28 provinces. Among the interviewed subjects, 11,635 individuals (67%) accepted to provide a blood sample, and therefore allow us to have biomarker information on glycosylated haemoglobin, triglycerides,

cholesterol ratio and C-reactive protein. Since women had a slight higher blood response rate than men (69% versus 65%), we use the sample weights that the CHARLS team has calculated to correct for household and individual non-response as well as non-participation in the blood collection (for details, see Zhao et al. 2014).

2.2.2 Outcome variables

We study SRH, seven single biomarkers, and AL as outcomes. SRH and single biomarkers are coded as dichotomous indicators. AL is treated as continuous variable. The seven single biomarkers are: girth, glycosylated hemoglobin, blood pressure, triglycerides, cholesterol ratio, C-reactive protein, and grip strength. These biomarkers are good predictors of diseases. For instance, Ridker (2003) found that C-reactive protein helps predict risk of heart attack and stroke. Abdominal girth (Alberti & Zimmet, 1998), glycosylated hemoglobin (an indicator for diabetes) (Seccareccia et al., 2001), triglycerides, cholesterol ratio, and blood pressure (Chobanian et al., 2003) are risk factors of cardiovascular disease (CVD). For each of the single biomarkers, a binary indicator of bad health is created. A score of "1" is assigned to those with "high-risk" values and a score of "0" is assigned to those with "lower risk" values. Values assigning high and low risk are based on cut-off values commonly accepted in clinical practice and the literature for Chinese or Asians. However, each of these biomarkers only measures the potential for a specific type of disease, their effects on general health could be fairly small and a type II error may present. Hence, we also include AL as a summary measure representing the number of biomarkers falling within high-risk values. The AL in this study refers to the group allostatic load index (Juster, McEwen, & Lupien, 2010), which is equal to the sum of "high-risk" conditions weighted by the number of non-missing values. Respondents missing more

than three biomarkers are excluded (15%). AL is standardised for ease of interpretation of results. A number of variables has missing or unknown values, the highest level being reached for household income (5.8%). After deleting these cases we are left with 16,249 respondents for SRH models; the sample size for biomarker models varies from 10,802 to 12,827.

2.2.3 Provincial-level independent variables

Most provincial-level information is obtained from the 2012 Chinese Statistics Yearbook. Nine variables are selected from available official statistics to reflect the economic situation and healthcare organisation of each province, including GDP per capita, urban/rural median income, level of urbanisation (measured by the proportion of a province's population living in urban areas), government expenditure for health care, number of hospitals, primary care institutes and doctors weighted by provincial population, and the ratio of government expenditure for health care to total government expenditure. Four variables – GDP per capita, urban median income, rural median income, and level of urbanisation - transformed statistically using natural logarithm. In order to limit the number of provincial-level variables and to avoid multicollinearity problems, Principal Component Analysis is carried out, with two components extracted, which we interpret as representing a general economic development dimension and a health infrastructure dimension.

Consistent with the literature regarding income inequalities, we use the Gini coefficient. However, given that there are no official published data on Gini coefficients at the provincial level, we constructed Gini coefficients using CHARLS. More specifically, we use equivalised household income using the square root scale and calculate the Gini coefficients for each of the 28 provinces using the package

INEQDECO in Stata 12.0, taking the design-weights into account. The Gini coefficient for the *j*-th province is computed as (Jenkins, 2010):

$$G_j = 1 + \frac{1}{n_j} - \left(\frac{2}{n_j^2 \cdot \mu_j}\right)\sum_{i=1}^{n_j}(n_j + 1 - i)y_{ij}\ , \qquad j = 1,2,.,\cdots,k \qquad (2)$$

In (1) n_j represents the number of households in the province, μ_j is the average equivalised household income, and y_{ij} denotes the equivalised household income for household *i* in province *j* (with households sorted by their income).

2.2.4 Individual-level control variables

At the individual level, we use three SES-related control variables: urban/rural residency, education, and equivalised household income. Other socio-demographic covariates include: age, age squared, gender, marital status, and living arrangement.

2.2.5 Analytical strategy

We use a set of two-level logit regression models using the same specification for different outcomes variables, with individuals nested in provinces. The multilevel modelling provides a potential solution of ecological fallacy – i.e. attributing characteristics of social aggregates to individuals. It is able to incorporate both explanatory processes and random variation at several levels, improve estimation of individual effects, and formulate and test hypotheses about how variables measured at one level affect the relations occurring at another. In health research, a multilevel modelling framework is a practical and robust analytical strategy because it allows (1) the simultaneous investigation of the attributes that describe the individuals and attributes that describe the social groups; (2) the assumption of non-independence of

observation within groups; (3) treating groups as related in a larger population of groups (Duncan & Yeung, 1998); (4) examination of both within-group and between-group variation; and (5) examination of the contributions of individual-level and group-level variables to these variations (Snijders & Bosker, 1993). This is especially useful because of the prevalence of data that follow multi-level or nested structures confronted by sociologists. The generic equation for a binary health outcome variable y_{ij} for the individual *i* living in province *j* has the following form:

$$log\frac{Pr(y_{ij}=1)}{1-Pr(y_{ij}=1)} = \gamma_{01}X_{ij} + \gamma_{02}W_j + \mu_{0j} \quad (3)$$

where: X_{ij} is a vector of individual-level independent variables; W_j is a vector of provincial-level variables; $\gamma_{01}$and γ_{02} are vectors of parameters related respectively to individual- and provincial-level covariates; μ_{0j} is a random intercept at the provincial level (with the usual assumptions of normal distribution, independence from observed variables, expected value of zero and variance $\sigma^2_{\mu_0}$).

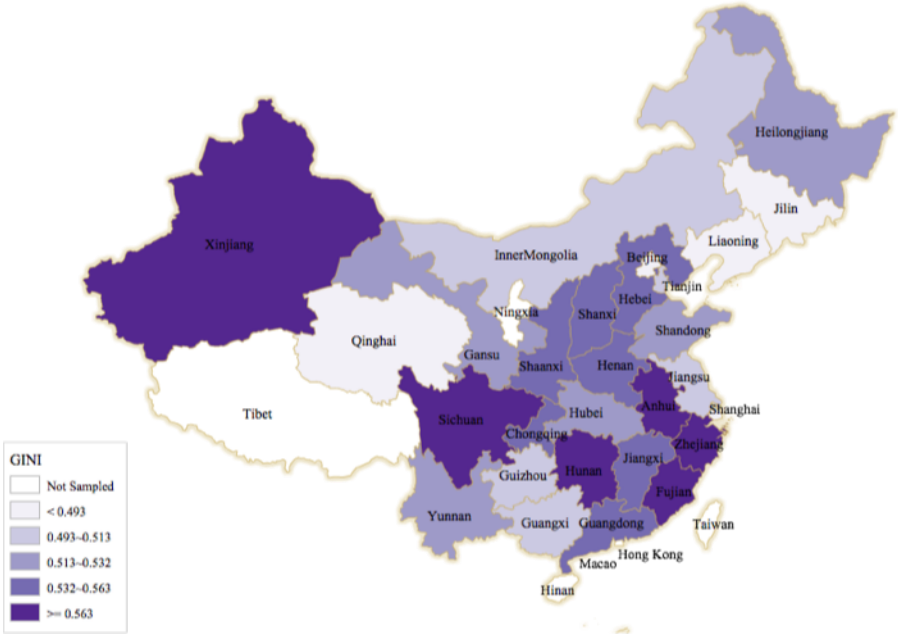
2.3 Results

2.3.1 Descriptive statistics

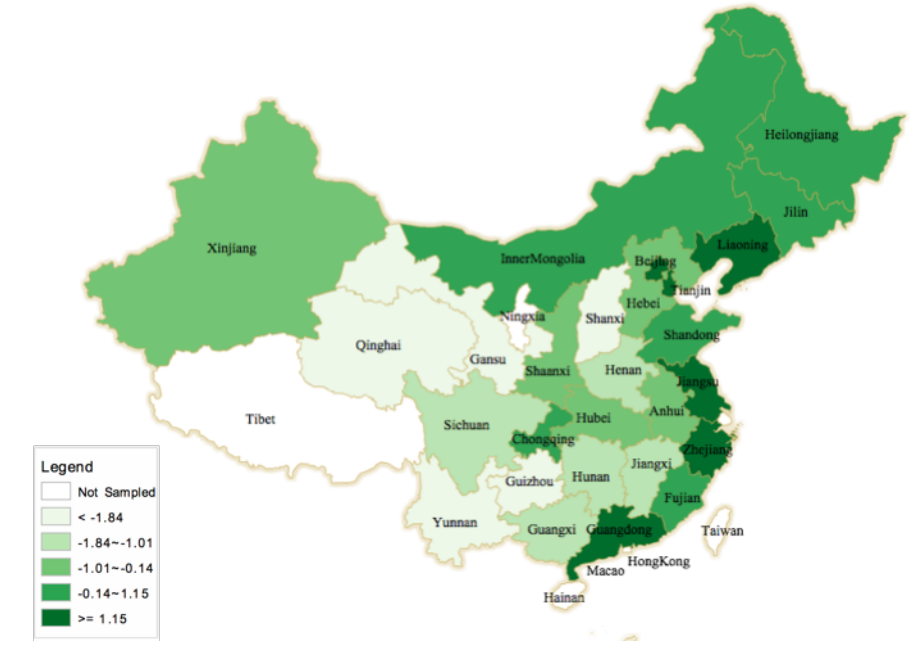
Table 2-1 shows descriptive statistics for health outcome variables by gender and age. Except for high cholesterol ratio, health outcomes show the expected gender and age gradient. The most prevalent negative outcomes are poor self-rated health, abdominal girth, high triglycerides, weak grip strength, and AL. Weak grip strength in particular has a strong age gradient, and abdominal girth has an exceptionally substantial gender effect. Abdominal girth and high triglycerides have an inverse relationship with age, indicating the possible presence of cohort effects or changes in the composition of the

population with aging in a selection in frailty process (Rosero-Bixby & Dow, 2009). Figure 2-1 maps the values for provincial-level independent variables (for actual values, see Appendix 2-1). The average Gini coefficient over the 28 provinces in China is 0.54, with Fujian as the most unequal and Shanghai as the most equal (Figure 2-1a). These figures are in line with the recent study of Xie and Zhou (2014), who use multiple data sources in 2010 and 2011 and also find that China's income inequality has reached very high levels with the overall Gini coefficient in the range of 0.53-0.55.

Figure 2-1:
(a) Gini Coefficients by province (estimated using CHARLS), China Health and Retirement Survey 2011



(b) Economic Development (PC_1) by province, Chinese Statistical Year Book 2012



(c) Health-Related Public Infrastructure (PC_2) by province, Chinese Statistical Year Book 2012

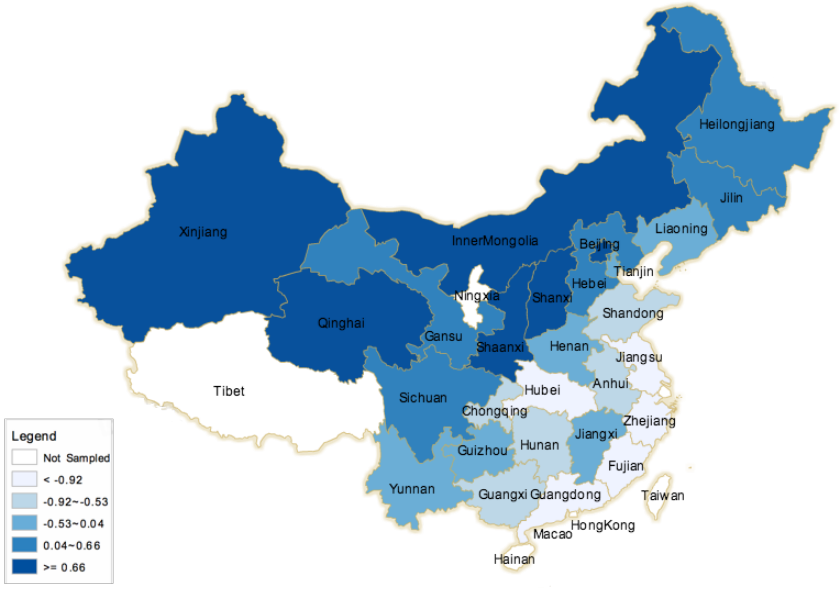


Table 2-1: Descriptive statistics for health outcomes, China Health and Retirement Survey 2011

Health Outcome	Sample Size	% of Negative Outcomes	% of negative outcomes by gender			% of negative outcomes by age		
			Male	Female	$\chi 2$	45-64	65+	$\chi 2$
Poor self-rated health	16,249	23.8	20.2	27.2	108.8^{***}	20.5	30.5	193.6^{***}
Abdominal girth	12,827	48.0	28.02	66.12	1900^{***}	49.1	45.6	13.87^{***}
Diabetes	10,893	5.4	5.0	5.8	2.9^{***}	5.0	6.2	6.77^{**}
High blood pressure	10,319	13.0	14.0	12.3	7.0^{**}	12.5	14.3	6.5^{*}
High triglycerides	10,808	27.3	24.6	29.6	34.0^{***}	28.8	24.1	26.4^{***}
High cholesterol ratio	10,802	10.0	10.0	10.1	0.1	10.1	9.7	0.6
High C-reactive protein concentrations	10,815	10.3	5.2	3.7	13.6^{***}	3.7	6.0	31.5^{***}
Weak grip strength	12,477	26.1	25.3	26.9	4.1^{*}	16.9	45.0	1100^{***}
		Mean (SD)	Mean by gender (SD)		T-test	Mean by age (SD)		T-test
Allostatic load[a]	10,902	0.7 (0.5)	0.6 (0.5)	0.8 (0.5)	20.1^{***}	0.7 (0.5)	0.8 (0.5)	-8.4^{***}

Note: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; [a]Allostatic load reported here is log transformed.

The Principal Components Analysis produced two principal components with eigenvalues greater than one, which explain 75% of the total variance. The first principal component (PC_1), which accounts for 58% of the total variance, is highly and positively correlated with GDP per capita, urban and rural median income, and level of urbanisation (loadings are 0.41, 0.41, 0.39 and 0.39, respectively). We therefore consider PC_1 as a measure of overall provincial-level economic circumstances and call it "Economic Development" (ED). The second principal component, PC_2, is highly and positively correlated with the number of hospitals, government expenditure on health care, and doctors (loadings are 0.64, 0.53, 0.34, respectively), and for this reason we call it "Health-Related Public Infrastructures" (HRPI). Beijing and Shanghai are the most economically developed provinces, whereas Guizhou is the least economically developed province. As one could expect from Chinese economic geography, there is a clear pattern showing that southern-east coastal regions are the most economically developed area, followed by the north and northeast regions. Central and western regions are the least economically developed areas (Figure 2-1b).

However, economically well-developed coastal provinces in the south-east – such as Shanghai – lag behind in terms of HRPI. While the less developed middle and west parts have higher scores on HRPI. This finding in line with previous literature, in particular, Li and Wei (2010) and Evandrou et al. (2014) find that the healthcare level of the prosperous coastal provinces is below the national average.

Table 2-2 provides descriptive statistics on individual-level covariates. The mean age of respondents is 61 years. Approximately 48% of the respondents are male and 88% are married. Average family size is four, and 40% live in urban areas. 27% have never

received formal education, 39% have attended or finished primary school, 21% received middle school education, and 13% have finished high school and above. The average equivalized household income in 2011 was about 25,100 yuan (approximately 3,860 USD).

Table 2-2: Descriptive statistics for individual-level independent variables, China Health and Retirement Survey 2011

Variables	Mean/Proportion	SD	Min	Max
Age	61.01	9.81	45	103
Male	0.48	0.50	0	1
Marital Status (Married=1)	0.88	0.33	0	1
Family Size	3.65	1.79	1	16
Urban Residents	0.40	0.49	0	1
Illiterate	0.27	0.46	0	1
Low Education	0.39	0.49	0	1
Intermediate Education	0.21	0.41	0	1
High Education	0.13	0.33	0	1
Household Income (1,000 yuan)	25.10	46.46	0	2700
Quintile: 1st (1,000 yuan)	1.16	0.87	0	3
Quintile: 2nd (1,000 yuan)	6.36	2.20	30.11	30.30
Quintile: 3rd (1,000 yuan)	15.12	3.17	10.32	20.91
Quintile: 4th (1,000 yuan)	28.68	5.10	20.92	38.40
Quintile: 5th (1,000 yuan)	74.47	85.45	38.40	2700

Source: 2011 CHARLS Wave 1 (Baseline)

2.3.2 Results – self-rated health (SRH)

Our regression models show that ED is negatively associated with poor SRH (Table 2-3, Model 1&5). One unit increase in ED related to GDP per capita, urban and rural median income, and level of urbanisation decreases the odds of poor self-rated health by 4% (OR=0.96) after adjusting for covariates. Income inequality is not significantly associated with SRH, even when we include individual-level controls (Models 2&6). On the contrary, HRPI is positively associated with poor health outcomes (Model 3&7). The HRPI effect remains significant even after controlling

for provincial ED and individual covariates (Models 4&8). One unit increase in HRPI that related to the number of hospitals, primary care institutions, and doctors is associated with a 14% increase in the odds of reporting poor health.

Individual-level covariates show expected and consistent effects, with being older, a man, and of lower SES associated with poor SRH. Consistent with current literature and common knowledge, health declines as age increases. The odds of poor health outcome increase by 5% with every year of age. In line with most studies in the Western societies, women are at significantly higher health risks than men. Being male decreases the odds of poor health by 28% compared with that of females in China. Living in an urban area also decreases the odds of poor health outcomes by 28% over living in a rural area. As expected, higher educational attainment and household income are negatively related to poor health. Those with high educational attainment are associated with a 47% decrease in the odds of poor health condition, and the odds of poor health decrease by 29% and 11% for intermediate and low educational attainment, respectively, compared to the illiterate population. Household income is substantially negatively associated with poor health status, and the relationship is also consistent. The odds of reporting poor health for those in the second highest income quintile are 0.79 times as high as the bottom quintile, and those on the top income quintile's odds ratio is 0.51 times as high as the reference group. In other words, advantaged economic conditions play a salient role in promoting self-reported health.

2.3.3 Results – biomarkers and allostatic load

Table 2-4 shows the results of a series of parallel models, each with a different outcome variable and containing the same covariates as Model 8 in Table 2-3. Compared to the results on SRH, results using biomarkers tend to have a weaker statistical significance, possibly because for the seven single-biomarker models, false negative errors may occur due to an insufficient sample size. At the provincial level, a higher level of income inequality is associated with low risks of hypertension and high triglycerides. One standard deviation increases in Gini coefficient (SD = 0.04) reduces the odds of hypertension by 4% (OR = 0.03) and the odds of high triglycerides by 3% (OR = 0.13). Provincial-level ED is positively associated with high risks of abdominal girth and high cholesterol ratio. HRPI is significantly associated with outcomes in 4 out of 8 cases—however with opposing effects. Higher levels of HRPI are associated with abdominal girth, high blood pressure, high C-reactive protein concentrations and allostatic load. One unit increase in HRPI is associated with 12%, 11%, 7% increase, respectively, in the odds of abdominal girth, high blood pressure, and high C-reactive protein concentrations, and increases allostatic load by around half of a standard deviation ($\beta = 0.03$).

Individual-level SES is not statistically significantly associated with all biomarkers, in contrast to its consistent effect on self-rated health and allostatic load. SES is associated with grip strength, with higher educational attainment and income level associated with stronger grip strength. For other biomarkers, higher income only matters for lower risk of high blood pressure in the low and highest quintile income group. Education also loses its significance in predicting most of these outcomes. In three of the eight of the health indicators in the table, there is no significant joint SES

effect ($p > .05$). For the others, the SES gradient sometimes behaves as expected with below-one odds ratio for the high-SES categories and above one for the low SES. We observe a reversal for abdominal girth, with higher level of income linked to higher risk.

Table 2-3: Two-level logit models for self-reported health (poor health=1, odds ratios, N = 16,249), China Health and Retirement Survey 2011

	Covariates Unadjusted				Covariates Adjusted			
Estimates	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**
Provincial-level Explanatory Variables								
ED	0.91*** (0.02)			0.92** (0.02)	0.95* (0.02)			0.96* (0.02)
Gini Coefficient		1.94 (2.06)		1.63 (1.51)		0.95 (0.91)		1.48 (1.29)
HRPI			1.09*** (0.05)	1.10*** (0.05)			1.13**(0.05)	1.14** (0.05)
Individual-level Covariates								
Socio-demographic								
Age					1.05*(0.02)	1.05*(0.02)	1.05*(0.02)	1.05*(0.02)
Male					0.71*** (0.03)	0.72*** (0.03)	0.72*** (0.03)	0.72*** (0.03)
Married					1.05 (0.06)	1.04 (0.06)	1.04 (0.06)	1.05 (0.06)
Household Size					1.02*(0.01)	1.03* (0.01)	1.03* (0.01)	1.02*(0.01)
Socio-economic Status								
Urban Resident					0.73***(0.03)	0.72***(0.03)	0.72***(0.03)	0.72***(0.03)
Education (Ref.=Illiterate)								
Low Education					0.89* (0.04)	0.89* (0.04)	0.89* (0.04)	0.89* (0.04)
Intermediate Education					0.72*** (0.05)	0.71*** (0.05)	0.71*** (0.05)	0.71*** (0.05)
High Education					0.53*** (0.04)	0.53*** (0.04)	0.52*** (0.04)	0.53*** (0.04)
Income Quintile (Ref. = 1st)								
2nd					0.97 (0.05)	0.97 (0.05)	0.97 (0.05)	0.97 (0.05)
3rd					0.79*** (0.05)	0.79*** (0.05)	0.79*** (0.05)	0.79*** (0.05)
4th					0.65*** (0.04)	0.65*** (0.04)	0.65*** (0.04)	0.65*** (0.04)
5th					0.51***(0.04)	0.51***(0.04)	0.51***(0.04)	0.51***(0.04)
ICC	*0.012*	*0.014*	*0.014*	*0.012*	*0.012*	*0.012*	*0.012*	*0.012*
Level 2 variance	*0.23***(0.04)*	*0.28***(0.05)*	*0.26***(0.05)*	*0.19*** (0.04)*	*0.22***(0.04)*	*0.24***(0.04)*	*0.20*** (0.04)*	*0.18***(0.04)*
BIC	*17697.46*	*17707.18*	*17705.15*	*17713.28*	*17010.4*	*17013.88*	*17006.69*	*17022.37*

Note: Robust standard errors are reported in parentheses. Significance levels: † 10%, * 5%, ** 1%, *** 0.1%.

Table 2-4: Two-level logit models for single biomarkers (poor health=1, odds ratios), and two-level linear model for allostatic load (Coefficient), China Health and Retirement Suvey 2011

Estimates	Abdominal Girth	Diabetes	Hypertension	High Triglycerides	High Cholesterol ratio	High C-reactive Protein concentration	Weak grip strength	Allostatic Load
Provincial-level Explanatory Variables								
Gini Coefficient	0.63 (0.94)	0.32 (0.48)	0.03** (0.04)	0.13* (0.14)	1.46 (1.87)	1.82 (2.61)	1.40 (2.13)	-0.66 (0.44)
ED	1.08* (0.04)	1.02 (0.04)	0.96 (0.03)	0.99 (0.03)	1.06* (0.04)	1.05 (0.04)	1.02 (0.04)	0.01 (0.01)
HRPI	1.12* (0.08)	1.05 (0.08)	1.11* (0.06)	1.03 (0.06)	1.02 (0.07)	1.07* (0.05)	1.08(0.05)	0.03*** (0.01)
Individual-level Covariates								
Socio-demographic								
Age	1.05*(0.02)	1.28*** (0.07)	1.01* (0.01)	0.99** (0.01)	1.00 (0.01)	1.03***(0.01)	1.08***(0.01)	0.01***(0.01)
Male	0.17*** (0.01)	0.77** (0.07)	1.20** (0.08)	0.77*** (0.04)	0.99*** (0.07)	1.40** (0.14)	0.94 (0.05)	-0.34*** (0.02)
Married	1.22** (0.08)	1.41* (0.21)	0.74** (0.07)	1.06 (0.08)	1.18 (0.13)	1.09 (0.16)	0.77*** (0.05)	-0.01 (0.03)
Household Size	0.97** (0.01)	0.98 (0.03)	1.00 (0.02)	1.00 (0.01)	1.05* (0.02)	0.99 (0.83)	1.03* (0.01)	-0.01 (0.01)
Socio-economic Status								
Urban Resident	1.72*** (0.08)	1.74*** (1.06)	1.19** (0.08)	1.32*** (0.06)	1.46***(0.10)	1.07 (0.11)	0.93 (0.05)	0.15***(0.02)
Education (Ref.=Illiterate)								
Low Education	1.10† (0.06)	0.97 (0.11)	0.98 (0.08)	0.98 (0.06)	1.12 (0.10)	0.88 (0.10)	0.77*** (0.04)	-0.01 (0.02)
Intermediate Education	1.21** (0.08)	1.27† (0.18)	0.97 (0.10)	1.04 (0.08)	1.13 (0.12)	0.89 (0.14)	0.61*** (0.05)	-0.02 (0.03)
High Education	1.17* (0.10)	1.14 (0.19)	0.88 (0.11)	0.97 (0.09)	1.17 (0.15)	0.62* (0.13)	0.56*** (0.06)	-0.07* (0.03)
Income Quintile (Ref. = 1st)								
2nd	0.98 (0.06)	0.93 (0.13)	0.89 (0.08)	0.96 (0.07)	0.94 (0.10)	0.85 (0.12)	0.77*** (0.05)	-0.05† (0.03)
3rd	1.01 (0.07)	0.99 (0.14)	0.93 (0.09)	0.95 (0.07)	1.03† (0.07)	0.73* (0.11)	0.69*** (0.05)	-0.07* (0.03)
4th	1.10 (0.07)	0.14 (0.16)	0.81* (0.08)	1.01 (0.07)	1.09* (0.04)	0.83 (0.13)	0.62*** (0.05)	-0.05† (0.03)
5th	1.15 (0.08)	1.09 (0.16)	0.88 (0.09)	1.13 (0.09)	1.10 (0.10)	0.85 (0.14)	0.53***(0.04)	-0.05 (0.03)
Intercept								*-0.25* (0.19)*
ICC	*0.017*	*0.02*	*0.015*	*0.012*	*0.017*	*0.019*	*0.019*	*0.005*
Sample Size	*12827*	*10893*	*10319*	*10808*	*10802*	*10815*	*12477*	*10902*

Note: Robust standard errors are reported in parentheses. Significance levels: † 10%, * 5%, ** 1%, *** 0.1%

2.4 Discussion

This study uses multi-level data to investigate the association between economic development (ED), income inequality, and health-related public infrastructure (HRPI), and various health outcomes for Chinese midlife and older adults. Consistently with previous research, the three contextual factors vary greatly between provinces (Evandrou et al. 2014). Coastal areas are more economically developed than inland areas, but the level of HRPI of these wealthy areas is below the national average. Income inequality has reached very high levels in China, and is negatively associated with ED (corr = -0.41; $p < 0.01$), indicating that the large increase in economic inequality may constrain the potential for rapid econoimc growth (Xie & Zhou, 2014).

We show that a higher level of provincial ED is positively correlated with SRH, but is not significantly associated with most of the biomarker outcomes. ED is positively associated with high risks of abdominal girth and high cholesterol ratio. The results are consistent with research in less developed countries, i.e. higher average income can be a marker of risk for obesity and obesity-induced heart diseases (Sayeed et al., 1997). Individual-level covariates further confirm that abdominal girth and high cholesterol ratio are more prevalent among urban residents with higher SES. Dietary pattern and physical activity behaviours are likely to be relevant explanations. People from wealthier provinces tend to consume unhealthier food, and exercise less. People from less developed province, and with lowest SES tend to reside in the rural area, consuming less total food, less fat and oil, and more vegetables(Xu et al., 2006). Rural residents also tend to actively engage in agricultural activities, thus are less likely to be overweight or obese.

Consistent with recent research on less developed countries (Biggs et al., 2010; Rajan et al., 2013), we find no supportive evidence in favour the income inequality hypothesis. In fact, regional income distribution is not correlated with health conditions for most of our health outcomes, and the only statistically significant relationship runs in a direction that is in contradiction to the income inequality hypothesis. More specifically, we find that greater inequality is correlated with better health outcomes in blood pressure and triglycerides. This positive association between income inequality and health may reflect the impact of income inequality on economic growth. Apart from observing a moderate negative relationship between income inequality and ED, economists have also argued that income inequality affects the economy negatively, by depriving the poor of the ability to accumulate human capital, generating political and economic instability that reduces investment, and impedes the social consensus required to adjust to shocks and sustain growth (Ostry, Berg, & Tsangarides, 2014). Provinces with relatively equal income distribution, thus tend to have higher level of economic development, and as we explained before, may have a negative impact on diseases related to over-nutrition.

Our result seems to corroborate a materialist pathway, i.e. that societal economic level of development is more important than inequality in determining individual health status (Preston, 1975). However, it would be premature to conclude that income inequality does not matter for the health of midlife and older adults in China. Pickett and Wilkinson (2015) suggest that income inequality may not be an independent determinant of health, but it might strengthen the many known and unknown causal process through which social class imprints itself on people throughout life. Moreover, Subramanian and Kawachi (2004) provide evidence that income inequality may have a lagged effect on health, possibly of up to 15 years. Our study thus suffers

from the time-frame limitation that the effects of income inequality on health may operate over many years.

Throughout our models, higher levels of health-related public infrastructures are robustly associated with poor health. The association indicates the likely presence of reversed causality. The Chinese government's efforts to increase investment as well as effectiveness in areas with lower level of public health (Zhu, 2013). Another explanation is that the current settings of health infrastructure may not be efficient in treating the chronic diseases measured in our study. We recognise that future research is required to illuminate these puzzling relations.

Our results are suggestive, albeit not conclusive, regarding the effects of aggregate-level socioeconomic factors on subjective health outcomes and biomarkers. It is indeed likely that the causal mechanisms and pathways linking aggregate-level socioeconomic factors to each biomarker are different. Additional research is needed to generate theories and evidence on the specific mechanisms.

The results of this study further confirmed huge health gap between rural and urban areas. Regional income inequality in China not only comes from between-province, but also from within-province rural/urban differences. Whether the huge disparity between rural and urban areas within province has an impact on individual health remains unclear to theoretical mechanisms of income inequality. Official data on rural and urban Gini coefficients is not publicly available, and it is difficult for research institutes to estimate due to the lack of reliable and proper economy data. This study is thus not able to test the relationship between income inequality on health with separate rural and urban analyses. Future studies on income inequality and health link in China should try to control for the rural/urban income gap if data permits.

To summarise, this study helps to extend our knowledge of how provincial variations in ED, income inequality, and HRPI, on top of individual characteristics, can affect individual health status according to a range of health indicators. These findings point to significant policy implications. First, interventions to alleviate the effects of poverty on health in China are likely to be of greatest benefit if targeted at the poorest regions. Second, we speculate that policy makers should also focus on dietary and life style issues, as the availability of unhealthy food and sedentary behaviours may have become a by-product of economic growth. While inequality cannot predict most of the health outcomes, it is moderately negatively connected to economic growth, and thus may undermine the effect of economy on health. Economic policies narrowly focused on growth, are likely to be insufficient in improving Chinese midlife and older adults' health.

Chapter 3. Educational attainment and allostatic load in later life: Evidence using genetic markers[8]

Abstract

Education is strongly correlated with health outcomes in older adulthood. Yet whether the impact of education expansion improves health remains unclear due to a lack of clarity over the causal relationship. This paper applies an instrumental variable (IV) approach to identify causality in relation to education on health as measured by allostatic load. Using the Health and Retirement Study (2008), we adopt two sets of IV: (1) a polygenic score built from single-nucleotide polymorphisms (SNPs) associated with years of education; and, (2) quarter of birth. Using multiple instruments, we find a 15% reduction in allostatic load per year of schooling. IV analyses were also used to identify potential pathways between education and health. If our main and sensitivity analyses are valid, the results suggest that a higher level of education is causally related to better health in older adulthood.

[8] A revised version of this chapter is published as Ding, X., Barban, N., & Mills, M. C. (2019). Educational attainment and allostatic load in later life: Evidence using genetic markers. *Preventive medicine*, *129*, 105866.

3.1 Introduction

The empirical relationship between education and health over the life course is well-established. Using large population representative data sources, Brown et al. (2012) found that education was strongly related to increased longevity and lower mortality for both US men and women. Smith et al.'s (2015) meta-analysis of 40 studies across 17 countries found a 16% reduction in the likelihood of developing a chronic disease among the more educated compared to those with less education. The measurement of health also remains crucial to understanding health and its determinants. Previous health research within the social sciences has tended to use specific activities of daily living (ADL) or self-reported overall health status (Siegel et al., 2003). Both measures have limitations. ADL are effective in measuring the inability to perform tasks, but they cover relatively narrow domains and presumably do not provide information about relative differences between individuals who are not disabled. Self-rated general health corresponds with physician evaluations and accurately predicts mortality (Idler & Benyamini, 1997), but has been criticised for introducing subjectivity into the measurement process thereby undermining the validity of the measurements (Ferraro, 1980). This study uses a broader and objective health measure – allostatic load – to take into consideration the experiences and exposures that accumulate throughout the life course. Allostatic load is a comprehensive, multisystem measure of the cumulative biological dysregulation across major physiological systems resulting from the accumulation of stressful exposures (McEwen & Stellar, 1993). Such stressful exposures place more demands on the biological system (e.g., immune, cardiovascular and metabolic systems), ultimately

leading to greater system dysregulation, and subsequently enhance the risk for poor health and functioning (Gruenewald et al., 2012).

A few researches investigate the relationship between socioeconomic gradient and allostatic load, but the results remain inconclusive. Analysing a nationally representative sample of the US, Seeman et al. (2010) provide evidence of an inverse association between allostatic load and level of education across all age groups. A review of the literature by Dowd, Simanek, and Aiello (2009) finds weak evidence that lower socioeconomic status is associated with higher levels of allostatic load. Despite the growing body of replications across different time periods and socio-political and economic contexts, evidence for a causal effect of education on biomarkers and allostatic load remains limited. To our knowledge, the only study attempting to explore the association between education and allostatic load using a twin study design failed to find a causal relationship (Hamdi, South, & Krueger, 2016).

The purpose of this paper is to establish whether additional years of education have a causal impact on allostatic load. This is particularly relevant for older individuals, since they have not only have been exposed to stressors imposed by the current environment, but also by their own survival and the ever-changing environments they have experienced. One challenge in the estimation of the causal relationship between education and allostatic load is that educational attainment is potentially confounded by a broad range of confounders, including childhood health status, cognitive abilities, and familial socioeconomic status, which are also possible risk factors for health in later life (Kawachi et al., 2010). We employ an instrumental variable (IV) approach to address the presence of unobserved confounders. Specifically, this study

uses information on a variety of genes known to be related to educational attainment as an instrumental variable. Such an approach is also referred to as Mendelian Randomisation (MR) (Davey Smith & Ebrahim, 2003). MR is designed to avoid spurious link and reverse causality bias by using genetic variation in populations. Genetic variants are randomly allocated at conception, their effect on the observable exposure of interest, i.e., educational attainment, are randomly assorted in relation to potential confounders (Davey Smith & Ebrahim, 2003). For this reason, genetic information is considered strong instruments for estimating causation of modifiable exposures (Åsvold et al., 2014). Based on the findings from the largest scale genome-wide association study (GWAS) of educational attainment (Okbay et al. 2016), a genetic risk score is constructed for this study to predict educational attainment with data from the Health and Retirement Study (HRS).

In addition, we use quarter of birth as a second set of instrument. Quarter of birth has previously been used as an instrument to estimate the effects of education on health. The argument is that laws regulates students to start school in September and continue to attend school until a particular age. Some students can thus drop out of school as soon as they're above the age that the law requires, resulting in a few months less education for students who are older in their grade (Angrist & Keueger, 1991).

Previous studies examining the education – health causality link have heavily relied on survey data or medical records (Amin, Behrman, & Kohler, 2014). Utilisation of a series of biomarkers provides a variety of attractive features over self-assessed or other self-reported measures such as functional limitations or chronic conditions (Domingue et al., 2015; Levine, 2013). The use of self-rated health cannot rule out heterogeneity due to reporting. Reported illness also suffers from potential biases

resulting from differential access to care and probability of diagnoses (Cantu, Sheehan & Domingue, 2016). Respondents' answers may be subject to normative bias and preferences, blur past medical history and present symptomatology and future prognosis. Biomarkers, in contrast, such as those related to cholesterol, BMI or blood pressure, are objective measures from the laboratory and circumvent systematic reporting error. Because the physiological processes are often below the individual's threshold of perception, biometric measures can capture early onset of diseases. Since it is a comprehensive measure that incorporates multiple biomarker risk factors, allostatic load is expected to serve as a better predictor of future health risks than any single risk factor by itself. In this study, allostatic load is defined as an overall summary of multi-system risk that combines nine biomarkers. Moreover, this study provides a new identification strategy to estimate the causal effects of education on health. No previous studies have used a MR design on the education to allostatic load causation. The paper is the first to exploit genetic variants for education in attempt to estimate the causal effect of schooling on allostatic loads in later life.

3.2. Literature Review

Allostatic load is a good predictor of morbidity and mortality and of the risk of a decline in cognitive and physical functioning in older men and women (Seeman, 1997). Only a few studies on the education to health association have focused on allostatic load specifically. For more appropriate coverage of this research area, we do not restrict the literature review to allostatic load alone.

3.2.1 Mechanisms between education and health in later life

There are three theories regarding the observed association between educational attainment and health (Cutler & Lleras-Muney, 2006; Eide & Showalter, 2011). The first supposes that education causes better health. The second argues a reversed direction of causality and holds that poorer health leads to lower educational attainment. The third suggests that both schooling and health are affected by unobserved factors such as family background, parental investment to children, non-cognitive ability, and genetic factors (Boardman et al., 2015). Several studies investigate the association between socioeconomic gradient and allostatic load, but the results remain inconclusive.

Several pathways through which education can causally affect health are discussed in the literature. Grossman (2006) points out two types of effects – productive and allocative efficiency, which may generate differences in health between individuals with different education levels. In particular, education may affect direct knowledge about health and health behaviours. Increased productive efficiency suggests that more educated individuals may possess and utilise advanced health technologies, and thereby improve health more efficiently. Education could also shift the allocation of health inputs. The well-educated improve health outcomes by using a more effective combination of inputs when given the same resources. However, in countries such as the US, the inequality of health care provision and access to health technologies this mechanism may be difficult to discern. The reason is that the higher educated have higher income and better health knowledge, in turn have better access to healthcare services, this effect may cancel out the effect from productive/allocative efficiency.

The indirect effects of education on health are multi-faceted. The most frequently mentioned factor is the effect of education on economic resources – more education increases both employment levels and income. These additional economic resources could impact health by making general health-improving investments, such as gym membership and access to health care, more affordable, or by reducing income volatility and hence stress. Moreover, the health effects of economic resources are not one-directional. For example, increased resources may also increase the consumption for goods/activities that reduce health, such as increased smoking and drinking, less walking and other factors (Cutler & Lleras-Muney, 2012). Moreover, higher education can lead to well paid jobs providing secure and healthy work environment and better access to health insurance and care.

It is also possible that higher education provides individuals with better interpersonal skills and improves both spouses' level of marital satisfaction (Faulkner, Davey, & Davey, 2005). Recent meta-analysis shows that marriage was a key predictor of longevity. Married individuals have a 9% to 15% reduction in mortality risk compared to non-married individuals (Manzoli, Villari, Pirone, & Boccia, 2007). Education could also affect health via changing one's relative position or rank in society. The perceptions concerning one's position in the lower end of social hierarchy could produce negative emotions such as shame and distrust, causing increases in stress and subsequently resulting in stress-related diseases (Gallo & Matthews, 2003). However, whether status differentiation and comparison is the mechanism that links education and social stratification to health remains unclear. Prag, Mills, and Wittek (2013) shows that individuals who are more likely to engage in social comparison of income have no negative effects on health nor health

differences by relative income. Their results challenges Wilkinson and Pickett's (2010) argument about the mechanism of status comparison as the link between income and health.

As opposed to a causal effect, there may be omitted variables that relate to both educational attainment and health outcomes driving the association. The unobserved variables potentially bias the estimate of the effect of education on health. One important potential omitted variable is childhood health or more broadly, health endowments shaped before the highest educational attainment obtained (also known as reversed causality). Children with poor health conditions may be more likely to miss schooling than healthy children, the absence from school in turn may affect their educational outcomes. Likewise, Redline et al. (1999) found that obesity are associated with sleep apnoea and sleep disorders, which are negatively related to children's cognitive functioning. Children with obesity and other disability may also be treated differently by teachers, peers and parents. Their educational development may be affected by experiencing bullying or other self-esteem harming incidents (Schwartz & Puhl, 2003).

Other potential confounders include genetic make-up of both educational attainment and health. This may be especially relevant in this context. Given that both education (Boardman et al., 2015) and health (Sullivan, Neale, & Kendler, 2000) have genetic basis, it is likely that the association between education and health is partly due to common genetic factors. The observed link between education and health can still be spurious.

3.2.2 Previous research exploring causal link

A larger body of research has sought to causally estimate and untangle the education-health gradient. This is not an easy task given that it is not possible to directly assess the counter-factual, and since estimated effects are likely to be arbitrary when there are aforementioned omitted characteristics relevant to both educational attainment and health. IV is one of the most popular approach is to treat the endogeneity of schooling. Recent studies have used policy changes caused schooling variation (e.g., compulsory schooling laws) as instrumental variables to estimate the causal effects of education. The set of laws is meant to induce an increase in educational attainment through the dictated minimum and maximum age of required school attendance, a minimum period of attendance, and penalties for non-compliance of the laws (Lleras-Muney, 2002). In the case of a policy change increasing the mandatory time adolescents must stay in school, particularly those who would have dropped out of school are forced to stay in school longer than they would have otherwise. Since the amendments decision are made by policy makers at the state or federal level, changes in the compulsory schooling laws only capture the exogenous variation in years of completed schooling.

Studies using compulsory schooling laws, again, have found mixed results. Lleras-Muncy (2005) is one of the very first studies to use changes in compulsory schooling laws across states and over time to examine schooling effects on mortality. Their study presented relatively large effects of education on mortality in the U.S. – one more year of schooling would lower the mortality rate over a ten-year period by nearly 60 percent. Lleras-Muney's original methods have been re-examined by other researchers using a broader sample and by performing a number of sensitivity checks

(see e.g., Lillard & Molloy, 2010), the replication results, however, are mixed and often null. Fletcher (2015) revisited the literature using a large, novel survey to overcome the small samples and lack of mortality information that proved to be an obstacle in previously used datasets. His finding suggests that higher education improves several outcomes of health, such as self-reported health, cardiovascular and weight. Yet the result of other dimensions of health appear underpowered, which suggests that further applications of this methodology may requires a much larger, and potentially unattainable sample sizes.

Another similar instrument that has been wildly used in examining the return to schooling is the quarter of birth. Angrist and Keueger (1991) found significant associations between quarter of birth, educational attainment, and earnings for cohorts of men born during the first quarter of the year in that they obtained less education and had lower earnings than those born during the rest of the year. The intuition is that the typical compulsory school attendance law requires students to start first grade in the autumn of the calendar year in which they turn 6 and to stay in school until their 16^{th} birthday. Individuals born in the early months of the year will usually enter first grade when they are near seven years of age and will turn 16 in the middle of tenth grade. Individuals born the third or fourth quarter will typically start school either just before or just after their sixth birthday and will finish tenth grade before they turn 16. Hence, adolescents born in later quarter, especially those who would have dropped out of school, would stay in school longer than they would have otherwise. One's quarter of birth can thus be used in an instrumental variable approach aimed at purging estimates of biases resulting from individual-specific error

components correlated with education (Angrist & Keueger, 1991; Lleras-Muney, 2002).

Using the quarter of birth as instrumental variables for education, Adams (2002) explores the first wave of Health and Retirement Survey (HRS) and provides evidence of an education-health relationship among older adults, even after accounting for biases in the estimates resulting from omitted variables. Braakmann, (2011) improves the quarter of birth identification strategy by using a dummy for being born in either January or February. He argues that this instrument is stronger, and can avoid some of the potential endogeneity problems (discussed below) associated with quarter of birth instruments. Using data on individuals born in these two months from two British surveys, the results indicate neither an effect of education on various health related measures nor an effect on health-related behaviour.

Results using instrumental variables to exploit the causal effect of education on health are thus inconclusive. The main problem has been to locate a valid instrument that meets the IV assumptions. Both compulsory schooling laws and quarter of birth instruments may violate the monotonicity assumption, for the reason that estimates of research using such instruments capture only the effects of education on the outcome of interest for individuals who spent an extra year at school because of the law or the change in laws. Compulsory schooling and school age starting laws has no effect on young people who plan to pursue higher education in the first place (Oreopoulos, 2006). Under a more realistic context, the only effect one can be sure that this method estimates is the local average treatment effect (LATE) among those who have no intention to stay in school that long, and that is typically fewer than ten percent of the

population. Therefore, such an effect may not be generalised to the entire population or to the effects of education at other points in the education distribution.

3.2.3 Prior studies using genetic IV

We first introduce some of the genetic terms that will be used in this study. The most common type of genetic variation among people is called a single nucleotide polymorphism (SNP). Each SNP consists of two nucleotide variations that are called alleles. An individual inherits two alleles, one from each parent, for each SNP. Thus an individual can have none, one, or two of a specific allele. SNPs occur once every 100 to 300 DNA building block, also referred to as a nucleotide. There are around ten million SNPs in the human genome. A large number of recent genetic studies identify the role of SNPs and their relationship to different phenotypes – ranging from diseases (e.g. Ganesh et al. 2009) to socioeconomic outcomes (e.g. Rietveld et al. 2013) and fertility (Barban et al. 2016). Such studies are called a genome-wide association study (GWAS) (Visscher, Brown, McCarthy, & Yang, 2012). It is from the results of these studies that we derive a single genetic indicator in the form of polygenic score, discussed in more detail shortly.

There is a growing interest in using genes as instrumental variables to infer the causal effect of (non-genetic) behaviour on (non-genetic) outcomes using observational data (Benjamin et al., 2012). MR is conceptually related to Randomised Controlled Trials, where the allocation of a treatment is randomised over all eligible individuals, as alleles are randomly allocated from parents to offspring. The treatment effect of genetic IV is carrying specific genetic variants. Compared to other IV used in traditional sociological studies, such as the previously mentioned compulsory

schooling laws and quarter of birth, which only capture LATE — the estimated return to education for whose behaviour is affected by the policy, the genetic IV works across the whole distribution of education leaving ages. Thus, the use of MR has the advantage over compulsory schooling laws and quarter of birth in the sense that it captures effects closer to an ATE and estimates "intention to treat" or "genetic endowment of education". Previous studies have also demonstrated that at a population level, genetic variants are generally unrelated to the potential confounding socioeconomic and behavioural characteristics (Lawlor et al., 2008). Genetic variable cannot be affected by later outcomes. Under certain assumptions that we discuss in the next section, genetic variants will allow us to explain away the confounding.

Most existing statistics and epidemiological literature in this area exploit genetic variation to identify the effects of health indicators on socioeconomic outcomes using genetic variants, also often reaching conflicting conclusions. (Ding, Lehrer, Rosenquist, & Audrain-McGovern, 2009) examine the effects of attention deficit hyperactivity disorder (ADHD), depression, and obesity, on adolescent's academic achievement. They use the four SNPs as instrumental variables. Their IV results show large and significant negative effects on schooling performance for females. Fletcher and Lehrer (2009) take a similar approach with a different dataset. They use within-sibling genetic inheritance with slightly different genetic variants from Ding et al. (2009) as a natural experiment. They find that obesity does not affect academic achievement. Using two genetic markers as instrumental variables for BMI, Norton and Han (2008) find no evidence of a causal association between obesity and labour market outcomes.

A valid choice of genetic variants in MR needs to meet several requirements. The three studies cited above use a set of variants generally associated with neurotransmitters based on the literature, and their choice of instruments are unlikely to satisfy the valid IV conditions that need to be met for using genetic markers. In fact, both Ding et al. (2009) and Fletcher and Lehrer (2009) acknowledge that their evidence of the association between genetic variants and health and health related outcomes is weak and inconsistent in the medical literature, based on inadequate unrepresentative samples. Norton and Han (2008) selected their SNPs based on a candidate gene study by Guo et al. (2006), which states that there is a negative association between these candidate gene and obesity. This association is not evident in other replications.

With the increasing number of complete genome-wide association results, the validity of genetic instruments of choice has improved in recent studies. von Hinke et al. (2012) use two genetic markers that have been consistently shown to relate to BMI and adiposity and has been confirmed with a genome-wide association study with 38,759 individuals with European ancestry (Frayling et al., 2007). While their instruments are not weak in a statistical sense, they find no evidence that adiposity affects academic performance. von Hinke et al. (2013) used a set of nine variants that have been robustly associated with height among individuals of European ancestry to examine the effect of child height on a wide range of outcomes, including academic performance, IQ, self-esteem, depression symptoms and behavioural problems. Results show that height is associated with better cognitive performance for girls and increased behavioural problems. A more recent study by Nguyen et al. (2016) conducted IV analyses with three genetic variants and compulsory schooling laws of

the association between education and dementia risk. Their analyses did not find evidence suggesting a causal association between education and risk of dementia via MR. Instead, IV analyses relying on compulsory schooling laws provide better estimates of the causal effect of education. Other studies using MR has studied the effect of cigarette smoking on BMI (Wehby, Murray, Wilcox, & Lie, 2012); the effects of alcohol exposure in utero on child academic achievement (Von Hinke Kessler Scholder, Wehby, Lewis, & Zuccolo, 2014); and the effects of quitting smoking during pregnancy on different health behaviours (Wehby, Wilcox, & Lie, 2013).

One general question lingering from these studies is whether genetic variants are weak instrument to identify causal effects in studies examining outcomes. In most cases, even if the genetic instruments are not weak in a statistical sense, their power may be too small to impact on the possible pathways to the outcome of interest. For example, in the study of von Hinke et al. (2010), a two-kilogram increase in adiposity may not have a substantial effect on a large drop in self-esteem, and it is therefore not surprising that a significant effect on academic achievement is not observed.

On possible solution to this problem is to combine more variants into one or more instrumental variables, such as a count of the number of risk alleles or polygenic score, as we will be using in this present study. This increases the explained phenotypic variation and the precision of the estimates. Quintana-Domeque et al. (2016) construct a polygenic score that measures genetic predisposition to higher educational attainment using a large proportion of the information in the DNA to assess assortative mating in the marriage market. They found that female socioeconomic attractiveness in the marriage market is driven only by education, but

male socioeconomic attractiveness is driven by education and other correlated variables. A recent MR study using genetic predisposition for health as instrumental variable found that low education is causally related to the development of coronary heart disease, smoking, BMI and blood lipid profiles (Tillmann et al., 2017). Their research sheds light on using polygenic score as instruments to increase the effect size on phenotypic variation and to achieve more precise estimates.

In the next section, we demonstrate the assumptions underlying valid genetic IV and explain how the polygenic score is constructed and meets these assumptions of a valid IV in the present study.

3.3. Methods

3.3.1 Polygenic scores as genetic IV

The growth in GWAS has identified SNPs associated to particular traits and offered an opportunity to use SNPs as genetic instrumental variables. Nevertheless, given the polygenic nature of human diseases and traits, most variants identified by GWAS confer relatively small increments in risk, and explain only a small proportion of heritability (weak instrument). A common solution is to combine the results from a GWAS and compile a polygenic score for a phenotype aggregating multiple SNPs and weighting them by the strength of their association (Plomin, Haworth, & Davis, 2009).

A polygenic score is a single quantitative summary of an individual's cumulative genetic predisposition to a specific disease or traits, weighted by effect size on the trait of interest. In the present study, we use the results from a recent GWAS of

educational attainment (Okbay et al. 2016), and include SNPs that are genome-wide significant (e.g., $p< 5 \times 10^{-8}$) (Also referred to as PGS1 in Chapter 1, constructed using the top-hit approach).

The polygenic score outperforms single SNPs for several reasons. First, genetic variants show a cumulative effect on biological (Hohenadel et al., 2016) and socioeconomic outcomes (de Zeeuw et al., 2014), implying that the outcomes are highly polygenic (Visscher et al., 2008). Polygenic score assumes that individuals fall somewhere on a continuum of genetic predisposition resulting from small contributions from many genetic variants (Quintana-Domeque et al., 2016). Second, polygenic scores are pathway non-specific, or "hypothesis-free" measures that do not require knowledge about the biological processes involved. This is particularly important when the trait of interest is influenced by a large number of genes, or when its biological pathways are not yet fully understood (Belsky & Israel, 2014). Third, a single SNP has too small of an effect in explaining complex traits. A polygenic score aggregates the genotypic score for SNPs known to be associated with a trait and thereby increases predictive accuracy. For example, the top genome-wide significant SNP from the recent GWAS on educational attainment (Okbay et al. 2016) explains around 0.035% of the variation in the years of schooling. A polygenic score from all measured SNPs explains 3.2% of the same variable.

3.3.2 Assumption for a valid genetic IV

The credibility of genetic IV analysis depends on whether four assumptions – independence, exclusion, non-zero effect of the instrument on treatment, and

monotonicity – are satisfied (for a detailed review of the assumptions, see von Hinke (2016)).

Assumption 1. (Independence) The independence assumption implies that the instrument is independent of all potential outcomes and potential treatments. In other words, the instrument ought to be randomly assigned. Although MR implies that genotypes are randomly allocated at conception, the genetic distribution may differ for different population (e.g., ethic groups). If there is a systematic relationship between the genetic variants and the outcome of interest in different population subgroups (also known as population stratification), this could lead to an association between the two subgroups at the population level without an actual causal relationship (von Hinke et al., 2016), and thus violates the independence assumption. Genetic similarity is often correlated with geographical proximity. Spouses are more genotypically similar than randomly matched individuals even within ethnically homogeneous samples (Christakis & Fowler, 2014; Domingue et al., 2014). The presence of assortative mating based on genes can also violate independence.

To deal with the population stratification, our IV analyses is based on ethnic homogenous population, that is, we only focus on white/Caucasian and non-Hispanic subgroups with European ancestry. We also adjust for the first ten principal components from genome-wide data that capture ancestry markers and geographical differences in the sample (Price et al., 2006). In a sensitivity test we control for region of birth, and cluster our sample by households.

Assumption 2. (Exclusion) The exclusion assumption requires that the only way through which the instrument affects the potential outcomes is via exposure. In our

case, the genetic instrument affects allostatic loads only through educational attainment. One can never directly test whether exclusion holds, and there are various situations where the exclusion assumption is violated, invalidating the instruments. The first situation is that behaviours may be affected by the genotype. Since individuals inherit their genes from their parents, it may be important to consider whether parents' behaviours are affected by their genotype (and hence are related to their children's genotype). In the presence of strong "dynastic effects", genetic instruments may be invalid if they are related to parental behaviours that in turn affect the outcome of interest (Fletcher, 2011). For example, parents who carry more 'high' educational attainment genetic variants may be treated different because of their good school performance. If this affects their preferences for their children's health outcomes until later life, the exclusion assumption may be violated. The extent of this potential violation, however, will depend on the effect sizes of the variants. In our case, the genetic variants increase the average years of schooling by a relatively modest amount. In addition, since individuals do not know their genotype, parents are unlikely to notice the subtle difference in children's size that is related to their genotype. Since our study focus on health status in later life, it is far less likely that a genotypic effect on parent's behaviour or preference on children's health will last such a long period. Empirically, Conley et al. (2015) found no effect from parental genotype to children's educational attainment. The parental genetic endowment did not transmit social advantages to their offspring. We argue that it is thus unlikely that we will observe any strong parental responses.

Second, if the mechanisms through which genetic variants affect the exposure variable imply changes in behaviours or preferences that directly affect the outcome,

the exclusion assumption is violated. For example, if the education-related genetic variants that we use below influence educational attainment because they are related to pathways associated with cognitive abilities, and if cognitive abilities affect health in later life, the exclusion assumption would be violated. In order to meet the exclusion assumption to a greater extent, we exclude the genetic variants that have been found to be associated with cognitive abilities or biomarkers used to construct allostatic load.

Assumption 3. (Non-zero effect of the instrument on treatment) A valid instrument must be associated with the risk factor of interest. MR can only be used with genetic variants that have been robustly shown to affect the risk factor (Colhoun, McKeigue, & Smith, 2003). This study uses genetic markers that replicate in a large number of independent samples and has been shown to robustly affect education (Rietveld et al., 2013 Okbay et al. 2016). Thus we are confident that the genetic instrument in our study meets this assumption. However, even if a suitable genetic instrument is available, it may explain little of the variation in the observed risk factor, and could result in a biased estimate and has implications for statistical power. We dealt with the weak instrument problem by using the polygenic risk score as an instrumental variable. The combination of multiple variants in an allele score can increase the explained phenotypic variation and the precision of the estimates.

Assumption 4. (Monotonicity) This assumption requires that the genetic instrument affects the risk factor for every individual in the same direction. In other words, given random allocation of genetic variants and the fact that individuals do not know their genotypes, we assume that an individual who carries a genetic variant that is positively related to education is at least as educated as the same individual, had the

individual not carried the genetic variant. Whether monotonicity is satisfied thus relies on knowing each individual's counterfactual and always remains an assumption. The assumption may be violated in the presence of gene-environment interaction; i.e., when the effect of the environment on education differs depending on an individual's genetic predisposition, or when an individual's genetic predisposition is expressed differently in different environments. For example, if the expression of a genetic variant that increases educational attainment depends on the social resource an individual was provided, monotonicity may be violated when the potential education level of an individual with the genetic variant in a poorer neighbourhood is less than the potential educational attainment for the same individual in that neighbourhood without the genetic variant. However, if the expression of the variant is simply reduced in a less well-off environment, monotonicity would not be violated, as the potential education level of an individual with the genetic variant remains at least as high as the same individual's counterfactual. After an extensive literature search, we are not aware of any evidence of such a situation for the genetic variants used in our study.

3.3.3 Data

The data used in this paper comes from the Health and Retirement Study (HRS), a national representative study of individuals 50 years of age or older and their spouses in the United States (Ofstedal et al., 2011). The survey contains detailed socio-demographic information in addition to a genetic sample. The first survey wave was collected in 1992, with biennial interviews available through 2010. New cohorts were added in 1993, 1998, 2004, 2010 and 2012.

In 2006, HRS initiated an enhanced face-to-face (EFTF) interview that collects biological and genetic information from respondents. Between 2006 and 2008, the HRS genotyped 12,507 respondents using the Illumina Human Qmni-2.5 Quad BeadChip. Our study also uses the 2008 (wave 9) and 2012 (wave 11) biomarkers. We built two cross-sections with Wave 9 and Wave 11. We focus on individuals for whom the genetic data and biomarker data are available after the quality control. The 2008 blood sample has been assayed for five biomarkers and the physical measures and biomarkers in the year of 2008 and 2012 yields a sample of 6,329 and 8,541 participants, respectively (the 2012 sample also include a random half of the new cohort enrolled in 2010). Domingue et al. (2016) discussed how selection into a genomic dataset can influence results from genomic analyses. Since the HRS only collected genomic data for those who lived until 2006, only the subset of birth cohort members who have survived to the time of data collection are sampled. To correct the mortality selection, we include inverse probability weights based on the procedure that Domingue and colleagues used in their study. We also restrict the sample to only white respondents, excluding non-Caucasian or Hispanic respondents. Since we focus on the health outcomes of American older adults, we drop respondents who are younger than 45 years old. This yields a final analytic sample of 3,919 respondents for wave 9 and 3,077 for wave 11.

3.3.4 Measures

Exposure

The main exposure of interest was educational attainment, operationalised as the number of completed years of schooling (ranging from 0 to 17). Since our genetic

instrument for educational attainment is extracted from the GWAS of Okbay et al. (2016), the same measures of educational attainment are used as in the GWAS.

Outcomes

Health outcome is measured by an overall summary index of multi-system risk ("allostatic load") based on nine biomarkers, to reflect the cumulative effect of physiological dysregulation across multiple systems. The nine biomarkers are subsets of five physiological systems (Table 3-1): the inflammation system includes C-reactive protein; Hba1c, cholesterol ratio, BMI, and waist circumference are subsets of metabolic system; diastolic/systolic blood pressure are indicators of cardiovascular system function; cystatin C belongs to hematopoietic system, and handgrip is a measure of muscle stress. Note that the biomarkers can overlap with each other and predict diseases from different systems. For example, Ridker (2003) concluded that C-reactive protein helps predict risk of heart attack and stroke. BMI, glycosylated hemoglobin, cholesterol ratio, and blood pressure are indicators of cardiovascular disease (CVD).

For each of the nine biomarkers, a dichotomous indicator was created, reflecting those with "high risk" values (assigned a score of "1") and "low risk" of values (assigned a score of "0"). Values assigning high and low risk are based on cut-off values commonly accepted in clinical practice and the literature. Respondents who reported taking medication for hypertension and diabetes are also categorised as "high risk" for blood pressure and Hba1c. The indicators are then summed to create allostatic load. Allostatic load is equal to the sum of "high risk" conditions scaled by the ratio of "number of items in the index" to "number of non-missing values". Missing values do

not pose a problem for this study since only 2% of the respondents are missing more than three biomarkers. Descriptive statistics for biomarkers are reported in Table 3-2. The average allostatic load value was 2.14 (SD = 1.57, range = 0 - 9). For ease of interpretation, we subsequently standardised the allostatic load (Mean = 0, SD = 1).

AL is a reliable predictor of mortality. To illustrate, I predicted survival using both self-rated health and AL with Cox proportional hazard models. The Cox model describes the association between AL, self-rated health, age, age at first interview, and the hazard of mortality. Duration time is measured by the number of years between the year of the first interview and the year of the most recent interview. Sample is restricted to white and non-Hispanic American aged over 50, to be consistent with the rest of the thesis (N = 4,250). Appendix 3-2 contains estimates for the main Cox survival models. Holding all other covariates constant, each standard deviation increases in AL increases the yearly hazard of death by 18%, even after controlling for self-rated health.

Table 3-1: Description of each physiological system contributing to the allostatic load index

Biomarkers	Physiological System
Diastolic blood pressure (DBP)	Cardiovascular
Systolic blood pressure (SBP)	Cardiovascular
Glycosylated haemoglobin (hba1c)	Metabolism
Cholesterol ratio	Metabolism
BMI	Metabolism
Waist Circumference	Metabolism
C-reactive protein	Inflammation
Cystatin C	Hematopoietic
Handgrip	Muscle

Source: Seeman et al. (2010)

Table 3-2: Descriptive statistics and cut-off points for high risk values of individual biomarkers

Biomarkers	N	M	SD
BMI (kg/m^2)	3903	0.31	0.46
Waist Circumferences (cm)	3826	0.64	0.48
HbA1c (%)	3891	0.11	0.31
Cholesterol ratio	2336	0.09	0.28
SBP (mmHg)	3739	0.20	0.40
DBP (mmHg)	3739	0.08	0.26
High Cystatin C (mg/L)	2572	0.04	0.20
C-reactive protein (µg/mL)	3484	0.18	0.38
Handgrip (kg)	3717	0.32	0.46
Allostatic load (unstandardised)	3930	1.85	1.39

Note: N=sample size; M=mean; SD=standard deviation; HDL=high density **lipoprotein.**

Instrumental variables

We compare two sets of instruments. First, we use the quarter of birth. HRS contains respondents' birth month information. We divided the 12 months into 4 quarters (quarter 1 = Jan – Mar; quarter 2 = Apr – Jun; quarter 3 = Jul – Sep; quarter 4 = Oct – Dec).

Second, we construct a polygenic score derived from a recent GWAS of educational attainment conducted in a sample of 293,723 individuals Okbay et al. (2016), which identified 74 independent SNPs associated with an individual's total years of schooling. This study is an extension of earlier work (Rietveld et al. 2013). Since the HRS was a part of the GWAS sample, we obtained the list of association results calculated excluding the HRS from the meta-analysis from the Social Science Genetic Association Consortium. Using these summary statistics, we selected SNPs that have a statistical association of $p\text{-}value < 5 \times 10^{-8}$, and excluded the SNPs that has been found to be associated with BMI and cognitive abilities (Okbay et al. 2016). 35 SNPs are used to a linear polygenic score weighted for their effect sizes in the meta-analysis using the software PLINK and PRSice.

Covariates

We present the main findings both with and without adjustment for covariates. All models control for age, age squared, gender and the first ten genetic principal components for each individual using genome-wide principal components that function as ancestry markers (Price et al., 2006). Controlling for population stratification and focusing on the white non-Hispanic population would further ensure that the independence assumption is not violated.

In the analysis that adjusts for covariates, we additionally control for the respondent's childhood health conditions (count of negative childhood conditions), area of birth, and parental years of education.

3.4 Results

3.4.1 Descriptive statistics

Columns 1, 2 and 3 in Table 3-3 present the descriptive statistics (sample size, mean, standard deviation) of the key variables in this study. These individuals were born between 1908 and 1963, with 13 years of average schooling. 42% of the respondents were male. Column 4-6 show the raw association between these measures, the covariates and the genetic variants, obtained from a regression of years of schooling or each covariate on the polygenic allele score. The top row of these columns presents the relationship between years of education and the instrument, showing a strong positive relationship for educational attainment (β = 0.210, p < 0.001). This significant and substantial effect suggests that there is a non-zero effect of the genetic IV on education, supporting *Assumption 3*. The remaining rows show no clear patterns or statistically significant associations in the relationship between the contextual variables and the genetic instrument, with the exception of the negative childhood health condition. The association with negative childhood health implies potentially reversed causation. These non-significant associations provide suggestive evidence that the genetic IV meets the exclusion assumption *(Assumption 2).*

Table 3-3: Descriptive statistics of education and the covariates: column 1, 2 and 3 show their mean and standard deviation. Columns 4-6 present the coefficients, standard error and p-value of the variables shown in the first column regressed on the genetic instrument (polygenic allele score of educational attainment).

	(1) N	(2) Mean	(3) Std. dev.	(4) Coeff.	(5) Std.err.	(6) P-value
Years of Education	4,029	13.2	2.5	0.210	0.039	<0.001
Age	4,029	70.4	9.9	0.228	0.150	0.128
Male	4,029	0.4	0.5	0.008	0.008	0.271
Married = 1	4,029	0.6	0.5	0.004	0.007	0.621
Childhood health condition	2,762	0.6	1.0	0.005	0.019	0.775
Mother years of education	3,617	10.3	3.0	0.091	0.047	0.051
Father years of education	3,763	9.9	3.5	0.137	0.057	0.017

Table 3-4: OLS estimates of years of education on standardised allostatic loads.

	(1) Covariate Unadjusted	(2) Covariate Adjusted
Years of Education	-0.050^{***} (0.006)	-0.030^{**} (0.009)
Observations	3919	2401
R^2	0.022	0.024

Note: Bootstrapped standard errors in parentheses.
$^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$
Allostatic load is standardised. All regressions include respondent's age, age square, gender, and top 10 principal components for their respective population stratification. The covariates adjusted model additionally includes mother's year of education, father's years of education, negative childhood health conditions, and area of birth.

3.4.2 OLS versus IV estimates

Table 3-4 presents OLS estimates of the regression of individuals' years of education on health in the later life. Using 3,919 individuals, we found that a higher level of education was strongly correlated with individuals with lower allostatic loads, indicating better health. Column (1) shows unadjusted results and column (2) present the results adjusted for covariates. Column (1) shows that years of education is negatively correlated with allostatic load: the point estimate of the coefficient for years of education is -0.05 and is statistically significant at the 0.001% level. This estimate indicates that an additional year of schooling reduces allostatic load by 5% of a standard deviation. Given the likelihood that unobserved characteristics are positively associated with both years of schooling and health outcomes, this OLS estimate is likely to be biased. After controlling for covariates, the point estimate became -0.03.

Table 3-5 presents the instrumental variable analysis. The table contains four sets of regressions, with column (1) and (2) using the single instrument of polygenic score for education and quarter of birth, respectively. Column (3) applies both instruments, and column (4) is adjusted for additional covariates. Genetic IV analyses provided evidence that the association between education and allostatic load was partly causal. Each additional year of schooling predicted a better health probability by 40% (larger than 5%, the one obtained using OLS in Table 3-3) when applying the polygenic score of education as instrument alone. The IV estimate in column (2) using quarter of birth as an instrument also indicated the protective effect of years of schooling on negative health outcomes, but the estimate is statistically insignificant, and quarter of birth is a weak instrument as the F statistics is less than 10. Using both instruments in

column (3), the IV point estimate of the coefficient is -0.227 (SE = 0.079), revealing a 9% reduction in negative health probability. Covariate adjustment estimates indicate similar results showing that years of schooling has a protective effect on allostatic load. Overall, our results consistently suggest that the actual impact of education on health is underestimated.

In Table 3-6 we present OLS and 2SLS estimated effects of education on each of the nine biomarkers that constitute our overall allostatic loads. The OLS findings in Table 3-3 are replicated using disaggregated health biomarkers. With the exception of diastolic blood pressure, the OLS estimate is negative for each high-risk biomarker, the most for waist circumference, and the least for Cystatin C (indicator for kidney inflammation) and Cholesterol ratio. The BMI estimate of -0.235 implies that an additional year of schooling decreases the risk of having abnormal BMI by 9%. The IV analyses implied that educational attainment is causally related to BMI and diabetes. However, for the model of diabetes (Hba1c), the F statistic is lower than 10, indicating that the polygenic score is a weak instrument for this model, and thus the causal relation is inconclusive.

Table 3-5: First Stage and 2SLS estimates of years of education on allostatic loads

	(1) IV = Polygenic Score (PGS)		(2) IV = Quarter of birth	
	First Stage	2SLS	First Stage	2SLS
Years of Education		-0.399* (0.187)		-0.588† (0.325)
Polygenic Score	0.200*** (0.039)			
Quarter (Ref = 1)				
2			0.152 (0.116)	
3			0.093 (0.111)	
4			0.231* (0.114)	
Observations	3919	3919	3919	3919
F statistics	26.19***	-	7.79***	-
P-value DWH test	-	0.1102	-	0.0097
	(3) IV = PGS, quarter of birth		(4) IV = PGS, quarter of birth; covariates adjusted	
	First Stage	2SLS	First Stage	2SLS
Years of Education		-0.227** (0.079)		-0.243* (0.126)
Polygenic Score	0.199*** (0.039)		0.065 (0.045)	
Quarter (Ref = 1)				
2	0.141 (0.115)		0.049 (0.124)	
3	0.087 (0.110)		0.070 (0.125)	
4	0.221† (0.113)		0.289*(0.130)	
Observations	3919	3919	2401	2401
F statistics	18.47***	-	16.32***	-
P-value DWH test	-	0.0154	-	0.2325

Note: Bootstrapped standard errors in parentheses.
$^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$
Allostatic load and year of education are standardised. All Regressions include respondent's age, age square, gender, and top 10 principal component for their respective population stratification. Column (4) were adjusted for parental education (mother's and father's years of education) and childhood number of negative health conditions.

Table 3-6: OLS and 2SLS estimates of years of education on single health biomarker.

	(1) BMI		(2) Hba1c	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	-0.037*** (0.003)	-0.235* (0.095)	-0.008*** (0.002)	-0.060* (0.025)
Observations	3884	3884	3879	3879
R^2	0.049		0.017	
First stage F statistics		14.23		8.89
P-value DWH test		0.0248		0.0174
	(3) Systolic blood pressure		(4) Diastolic blood pressure	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	-0.006*(0.003)	-0.027 (0.031)	-0.001 (0.002)	-0.008 (0.020)
Observations	3739	3739	3739	3739
R^2	0.033		0.006	
First stage F statistics		6.65		7.44
P-value DWH test		0.4884		0.7204
	(5) Cholesterol ratio		(6) Cystatin C	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	-0.006* (0.002)	0.001 (0.034)	-0.004* (0.002)	-0.021 (0.21)
Observations	2336	2336	2572	2572
R^2	0.020		0.014	
First stage F statistics		6.70		8.08
P-value DWH test		0.8148		0.4038
	(7) C-reactive Protein		(8) Waist circumferences	
	(a) OLS	(b) 2SLS, both IVs	(a)OLS	(b) 2SLS, both IVs
Years of Education	-0.007** (0.003)	-0.018 (0.03)	-0.016***(0.003)	-0.056 (0.036)
Observations	3848	3848	3826	3826
R^2	0.009		0.025	
First stage F statistics		8.34		7.50
P-value DWH test		0.6935		0.2583

	(9) Handgrip	
	(a) OLS	(b) 2SLS, both IVs
Years of Education	-0.013*** (0.003)	-0.030 (0.032)
Observations	3717	3717
R^2	0.264	
First stage F statistics		7.14
P-value DWH test		0.6095

Note: Bootstrapped standard errors in parentheses.
$^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$
Standardised coefficients are reported. All regressions include respondent's age, age square, gender, and top 10 principal component for their respective population stratification.

3.4.3 Potential pathways

As discussed previously, the pathways through which education affect health are multi-faceted. With better health knowledge, the well-educated may improve health by adopting a healthier life style. Education also increases income and wealth since additional economic resources improve health by investing in health care. More education also provides individuals with better interpersonal skills is liked with higher marital satisfaction, and lower levels of stress-related diseases. Thus we performed additional analyses to investigate whether the factors suggested in health literature can serve of a pathway for the effect of education on allostatic load. The factors we tested include participants' health behaviour (smoking, drinking and daily exercise[9]), wealth and health insurance, life satisfaction, and marriage (marital stability and spousal educational level). We repeated the same procedure as in Table 3-6. The results are displayed in Table 3-7.

Health behaviour

Higher levels of education have also been shown to be significantly associated with better knowledge of health and a decrease in smoking. Education, however, also brings additional economic resources which may increase the consumption for alcohol and lower levels of exercise (Cutler & Lleras-Muney, 2012). Our IV analyses found that education causally decreased the probability of smoking – each additional year of schooling reduced the probability of smoking by 2%. No causal evidence is found between education and drinking and daily exercise, however, since the F-

[9] Participants walk for 20 minutes as exercise daily.

statistics for drinking and exercise models are less than 10, the IV for education may not be valid for the causation.

Wealth and health insurance

Using 3,920 participants, we found that higher education is associated with more wealth and health insurance. An additional year of schooling increased household wealth by 10%, and increased the level of health insurance by 1%. IV analyses show that the association between education and wealth is causal. No causal evidence is found between education and health insurance. But the F-statistics for both models are less than 10, indicating that the IV is not relevant for these models.

Marriage

More education is associated with more stable marriages and a higher educated spouse. Each additional year of education causally increased the length of the respondent's longest marriage by 10%. One's own education level is also causally related to the spouse's educational attainment.

Table 3-7: OLS and 2SLS estimates of years of education on potential mechanisms

	(1) Smoking		(2) Drinking	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	-0.018*** (0.002)	-0.047* (0.023)	0.085*** (0.002)	-0.126 (0.455)
Observations	3912	3912	2136	2136
R^2	0.052		0.045	
First stage F statistics		17.75		8.73
P-value DWH test		0.1917		0.9771
	(3) Exercise		(4) Marital Stability	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	-0.095***(0.002)	-0.510 (0.347)	0.237** (0.091)	0.25† (0.05)
Observations	3565	3565	3930	3930
R^2	0.024		0.256	
First stage F statistics		4.18		5.51
P-value DWH test		0.1758		0.0407
	(5) Spouse's education level		(6) Life satisfaction	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	0.505***(0.017)	0.602* (0.264)	0.069*** (0.002)	-0.076 (0.049)
Observations	2554	2554	3629	3629
R^2	0.266		0.027	
First stage F statistics		12.88		5.44
P-value DWH test		0.0712		0.4159
	(7) Household wealth		(8) Health Insurance	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	0.251***(0.021)	0.605* (0.252)	0.028*** (0.003)	0.038 (0.041)
Observations	3926	3926	3920	3920
R^2	0.046		0.058	
First stage F statistics		7.36		6.84
P-value DWH test		0.1449		0.7881

Note: Bootstrapped standard errors in parentheses.

†p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001.

Years of education is standardised. All regressions include respondent's age, age squared, gender, and top 10 principal components for their respective population stratification. Smoking is measured by whether the respondent smokes at wave 9 (yes = 1, M=0.12 SD=0.33); drinking is measured by number of days per week the respondent drinks alcohol (M=2.44 SD=2.59); exercise is measured by how often the respondent walks for 20 mins (daily 1 – not in last month 6, M=3.46 SD=1.94); Marital stability is measure by length of longest marriage in years (M=35.86, SD=16.53);Spousal educational attainment is measure by current spouse's years of education completed (M=13.25, SD=2.56); life satisfaction is measure by "I am satisfied with my life" (strongly disagree 1 = strongly agree 7, M=5.47, SD=1.68); household wealth is measure by natural log transformed household total wealth (M=11.41, SD=3.35); health insurance is measured by the level of health insurance the respondent has (M= 0.72, SD=0.58)

Health change

Because allostatic load is a measure of accumulated biological burden, we also ran follow-up analyses for health changes between 2008 and 2012. We first constructed allostatic load for 2012 using the same method we did with the 2008 sample. The analyses using 2012 sample replicated the 2008 results. We then created a new variable to measure health change during the four years. For the purpose of accounting for selection mortality (Domingue et al., 2017), we added an item in addition to the nine biomarkers which indicates whether the respondent died after completing the 2008 survey but before the 2012 collection. 2SLS estimates implied no significant evidence that education is causally linked to changes in allostatic load (Table 3-8).

Table 3-8: OLS and 2SLS estimates of years of education on allostatic load for 2012 sample and health change between 2008 -2012

	(1) Allostatic load 2012		(2) Health change 2008-2012	
	(a) OLS	(b) 2SLS, both IVs	(a) OLS	(b) 2SLS, both IVs
Years of Education	-0.061*** (0.007)	-0.153* (0.076)	-0.019** (0.010)	-0.056 (0.070)
Observations	3077	3077	2987	2987
R^2	0.057		0.010	
First stage F statistics		15.39		12.21
P-value DWH test		0.2160		0.3175

Note: Bootstrapped standard errors in parentheses.
$^{\dagger}p < 0.10$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$
Allostatic load is standardised. Health change is standardised. All Regressions include respondent's age, age squared, gender, and top 10 principal components for their respective population stratification.

3.5. Discussion

The existing literature indicates that education is positively associated with health, but was inconclusive as to whether this relationship is causal. Several studies (e.g. Ding et al., 2009; Norton & Han, 2008; Tillmann et al., 2017; Von Hinke et al. 2012) used sophisticated methodologies, such as instrumental variables or twin designs, to try to untangle causality. They produced rather conflicting findings, with some supporting a causal relationship and other failing to do so. A few studies have found that education may result in better self-rated global health (Amin et al., 2014; Fujiwara & Kawachi, 2009), but the evidence for a causal effect on more specific measures of health and health behaviours remains limited.

The current study made use of both genetic and season of birth instrumental variables to control for confounders in examining the association between education and a direct, biologically-based measure of allostatic load that captures physiological dysregulation across multiple, major regulatory systems. Our IV analysis with the polygenic score of educational attainment showed a significant, negative relationship between education and allostatic load, meaning that a higher level of education leads to better health. Moreover, we use a second instrument of quarter of birth to compare the results. IV analysis using quarter of birth as an instrument does not show any significantly negative association between education and health. This difference may be due to the identification of different Local Average Treatment Effects (LATE), but may also be caused by a violation of one or more of the assumptions. Bound and Jaeger (1996) and Bound, Jaeger, and Baker (1995) have questioned the validity of quarter-of-birth instruments used in Angrist and Krueger's (1990) since quarter of birth is weakly associated with education. In our analyses, quarter of birth also turns

out to be a weak instrument. Moreover, quarter of birth is likely to be correlated with unobserved ability, due to seasonal effects. Such correlation, even a weak one, may bias the IV estimates with large inconsistency. Even though not observed in our analyses, some researchers cast doubt on the exogeneity of quarter of birth and suggested that other factors like socioeconomic status of the mother may influence the season of birth. Using data of all live birth registered in Czech Republic for 1989-1991, Bobak and Gjonca (2001) found that mothers with higher socioeconomic status tend to give birth during the warmer seasons. Buckles & Hungerman (2013) indicates that teenage, single, and less educated women are more likely to give birth to children in winter in the U.S. The potential association between quarter of birth and socio-economic status gives rises to another concern – violation of the exclusion restriction assumptions. Students from low SES backgrounds tend to have fewer health resources and lower nutrition, which contribute to poorer health conditions. If lower SES students tend to be born in the winter, quarter of birth will be directly associated with later life health instead of only through the effect of compulsory schooling laws. A recent study by Rietveld and Webbink (2016) provides new evidence that genetic factors for schooling are not randomly allocated over the year. Individuals born in the second quarter of the year are less likely to have three specific genetic markers related to educational attainment. This variation may affect the relationship between quarter of birth and education, and thus bias the estimation.

Overall, our results consistently suggest that the actual degree of higher education on health is underestimated. The IV estimate is substantially larger than the estimate from the OLS regression. One explanation is that the instrumental variable is estimating the local average treatment effect, while OLS tries to estimate the average

treatment effect over the entire population. Genetic predisposition of education may shift the behaviour of a subgroup of individuals for whom the effect of education on health are larger than average. Then IV estimates will be larger than OLS estimates because of heterogeneity in the population. The F-statistics are consistently larger than 10 for main models, indicating that the instruments are relevant. The differences between the estimates suggest that OLS may underestimate the true effect of education on health due to omitted variables that are positively related to education but negatively related to health, or vice versa. Nevertheless, both IV and conventional analyses' estimates are generally small compared to the standard deviation of years of education. The greater magnitude of 2SLS compared to the OLS estimates is not a rare case among MR studies (Sanderson, Smith, & Munafò, 2018; Schmitz & Conley, 2017; Willage, 2018).

This study uses a multisystem measure of allostatic load as the outcome since a comprehensive indicator of health is preferred. Nevertheless, since allostatic load is a composite variable, we ran additional follow-up analyses for each of the nine physiological indices that contribute to allostatic load. Our analyses showed that years of education was significantly associated with reduced risk for BMI and Hba1c, which are indicators for metabolic dysregulation (2SLS $p < 0.05$), after accounting for the effects of age, sex, and population stratification. This finding aligns with previous research that education has a protective effect on BMI (Brunello, Fabbri, & Fort, 2013; Kemptner, Jürges, & Reinhold, 2011). We found no consistent evidence of a causal relation between higher education and a lower value of biomarkers. One possibility is that the effect size of a single physiological measure is too small to

detect, making the genetic IV a weak instrument in these analyses. Research with larger sample sizes on separate biomarker may provide a more accurate estimation.

As a robustness test we rerun the analyses with the HRS 2012 sample. The analyses replicated the results as in 2008 sample. But there is no evidence that educational attainment is associated with health change. This result suggests that educational differences seem to lead to diverging health outcomes in late life, supporting the idea of a social gradient in health across the full length of the life course. Exploring possible pathways suggests that education may affect allostatic load via smoking, marital stability, spousal educational level and household wealth.

3.6. Conclusion

Using genetic variants as an instrumental variable for education, our study provides evidence that a higher level of education has a causal effect on better health, measured by allostatic loads. The study adds causal evidence to a large number of observational studies. Our paper contributes to both the substantive and methodological literature of health research, but also has several limitations. First, while previous studies employing neurotransmitter genes often suffer from unconvincing exclusion restrictions, the polygenic score employed here appears to alleviate the threat of weak instrument, and satisfy the exclusion assumption based on the current knowledge of the gene's function. However, there is still a possibility that the genetic instrument we used may be correlated with other socioeconomic and behavioural factors or health conditions besides education that may also affect allostatic loads. There is no gold-standard to test the fulfilment of the exclusion assumption. One source of violation is pleiotropy, which means the genetic IV may have direct effects on both educational

attainment and health, as their biological pathways of effect are unclear. To minimise the likelihood of this violation, I removed genetic variants that are found to be related to BMI and cognitive functions in other GWAS studies. To further test whether the results could be explained by pleiotropic effect, I applied MR-Egger, weighted median and weighted mode approaches (Bowden, Davey Smith, Haycock, & Burgess, 2016; Hartwig, Smith, & Bowden, 2017). These tests allow to test for causality even when the genetic IV is invalid. The sensitivity analyses found no evidence for pleotropic effect in our models (Appendix 3-3). Moreover, there is currently no consistent evidence from the literature about a pathway between the genes we used to construct polygenic score and allostatic load other than education.

Another concern on the validity of this study comes from the dynastic effects or bias due to assortative mating. The moderate association found between parental education and genetic IV may reflect either direct effects of the participants' educational attainment, assortative mating between their parents, or dynastic effects of their parents' education. The last two scenarios represent assumption violation. Tests of such violation requires parental genotype, or via sibling designs, which is unfortunately not available in HRS genotypic data. However, Okbay et al. (2016) found little evidence that the effects of the polygenic score for education attenuated after controlling for family structure. Conley (2015) found no effect from parental genotype to children's educational attainment, indicating genetic endowment didn't transmit social advantages to their offspring. After controlling for parental education and childhood health status, our IV results are still robust. These findings all suggests that parental education have little contribution to the causal pathway between participants' education and health in old age.

Nevertheless, this current study does not have sufficient power to test the dynastic effects. Using parent-offspring sample from Iceland, Kong et al. (2018) detects dynastic effects that non-inherited genetic variants for education are also associated with offspring's education. These non-transmitted genes contribute to 29% of the size of the association with the inherited polygenic score for education. It is thus possible that the effects identified in this study reflect a mix of the effect of the participants education and their parents' education. The contribution of parental education to health in older age is likely to be much smaller than 29%. To further investigate the dynastic effects will require larger sample data with parental-offspring genotypic information.

Furthermore, the genetic variants may not be powerful enough to identify causal effects. While the IVs are not weak in a statistical sense, the IV's effect may be too small to impact the biomarkers and on the possible pathways to health. In other words, a 1-2 year increase in education may not lead to a large drop in morbidity. Hence, it is not surprising that we find no significant effect on most of the biomarkers and some potential pathways. Future research needs to use larger samples to test the relationship between education and a specific pathway or disease.

In summary, our findings support the hypothesis that education reduces the risk of poor health in older adults. This would support potential preventive interventions based on educational attainment. Policy makers should also bear in mind that this recommendation has the assumption that the education induced by genes have the same biological and psychological effects as the education induced by policy intervention, which is not necessarily true. Future research on genetic variants as IVs needs to be used and interpreted with care. This paper is the first to exploit genetic

variation in education to examine the causal effects of education on allostatic loads. We instrument education with educational polygenic score and season of birth, and find that education has a protective effect on health. This study also provides promising evidence that genetic factors may be useful instruments for studying behavioural effects.

Chapter 4. Genetic Predisposition to Educational Attainment and its relationship with Cognitive Decline[10]

Abstract

Studies of cognitive decline in older age likely account for the potential effects of a genetic risk score of education, since recent studies have demonstrated a common genetic basis of educational attainment and cognitive abilities. Whether the effect from genes on individual differences in cognition becomes more or less prominent over the life course remains largely unknown. In this analysis of over 5,000 older adults from the Health and Retirement Study (HRS) in the U.S., I measured change in performance on global cognition, episodic memory, working memory, mental status and vocabulary over a 14 year period. Linear mixed effect models are used to evaluate the association between a polygenic risk score on education (PGS Edu) and cognitive change, where models incorporate an inverse probability of mortality attrition weighting. Individuals with a higher genetic predisposition to educational attainment perform better across all measures of cognition throughout later life. Genetic effects on cognitive decline change with age and across cognitive domains. For global cognition and episodic memory, the advantages brought by a genetic predisposition to educational attainment gradually disappear with age. For mental status, the PGS Edu effect intensifies from age 70 – 75. No relationship is found between PGS Edu, working memory and vocabulary.

[10] A revised version of this chapter is published as Ding, X., Barban, N., Tropf, F. C., & Mills, M. C. (2019). The relationship between cognitive decline and a genetic predictor of educational attainment. *Social Science & Medicine*, *239*, 112549.

4.1 Introduction

Throughout our lives, our body and brain ages. Cognitive competences tend to decline with age and the prevalence of cognitive impairment rises, even among healthy and disease-free individuals (Salthouse, 2004). Cognitive decline threatens independence and quality of life for older adults and brings challenges to healthcare systems (Williams & Kemper, 2010). A better cognitive status has been associated with a decreased risk of mortality (Batty & Deary, 2004; Deary & Batty, 2007), decreased risk of dementia and Alzheimer's disease (Scarmeas & Stern, 2004; Stern et al., 1999), and a better quality of life (Callahan, Hendrie, & Tierney, 1995; Deary et al., 2009; Moritz, Kasl, & Berkman, 1995; Tucker-Drob, 2011). The U.S. is anticipated to experience a twofold increase in its population aged 65 years and above by 2050 (Ortman, Velkoff, & Hogan, 2014). With a growing aging population, both in the U.S. and worldwide, cognitive decline is an emerging health and social issue, especially since older individuals are increasingly taking on additional responsibility for financial and medical decisions. This means that memory, reasoning, and other cognition-related skills are more important now than ever before.

Biologically, an aging-related shrinkage of brain size (e.g., prefrontal cortex) and the disturbance of structural and functional connectivity are responsible for cognitive decline in domains such as speed, reasoning, and short-term memory (Dixon, Bäckman, & Nilsson, 2004). Yet this does not explain the interpersonal variability in either age-related (non-pathological) or pathological cognitive decline: while some

people experience substantial deterioration in cognitive function, others maintain better cognitive status despite the presence of considerable brain deterioration (Stern, 2009). The mismatch between examined brain damage and observed cognitive function indicates the existence of factors that protect cognitive abilities from the effects of aging or pathology.

Variation in cognitive status and change is influenced by both socioeconomic and genetic factors. Among the social indicators that may allow individuals to cope more effectively with age-related brain changes, education is the most consistent indicator, showing a significant positive relationship with the level of cognitive performance in old age (Albert et al., 1995; Lee, Kawachi, Berkman, & Grodstein, 2003). Research has documented that individuals with higher levels of educational attainment in early adulthood perform better on cognitive tasks in later life (Scarmeas & Stern, 2004; Lenehan et al., 2015). Through the acquisition of knowledge and skills, education improves problem-solving and stress-coping abilities (Ross & Wu, 1995) and increases one's effectiveness in using brain networks or cognitive paradigms (Stern, 2009). Evidence on whether educational level influences the trajectory of age-related cognitive decline is inconsistent, however (Anstey & Christensen, 2000). Some studies linking education with cognitive change in old age find that lower levels of education are associated with a faster decline of cognitive abilities (e.g. Albert et al., 1995; Jacqmin-Gadda, Fabrigoule, Commenges, & Dartigues, 1997; Lyketsos et al., 1999). Other studies contradict this evidence, suggesting that higher levels of education do not attenuate the rate of cognitive decline (e.g. Bosma, van Boxtel, Ponds, Houx, & Jolles, 2003; Christensen, 2001; Karlamangla et al., 2009; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008; Zahodne et al., 2011), and are

even associated with a faster rate of deterioration (e.g. Alley, Suthers, & Crimmins, 2007; Alfredo Ardila, Ostrosky-Solis, Rosselli, & Gómez, 2000; Proust-Lima et al., 2008). The relationship also varies by cognitive subdomains, age, race, and educational group (Alley et al., 2007; Lipnicki et al., 2017).

The effect of education on cognitive level and change is difficult to separate from genetic influences. Genetic endowments may affect individual heterogeneity in cognitive abilities and aging (Tucker-Drob, Reynolds, Finkel, & Pedersen, 2014) both independently and through interplay with the environment (Domingue, Liu, Okbay, & Belsky, 2017). For example, education and cognitive ability have been shown to share a common genetic basis (Marioni et al., 2014; Okbay et al., 2016; Rietveld et al., 2014). Hence, even when the protective effect of education on cognitive differences and decline in old age is identified, the relationship is still questionable: both education and cognitive change can be influenced by genetics (Deary, Johnson, & Houlihan, 2009). Recent twin and family studies, as well as Genome Wide Association Studies (GWAS) found that cognitive function is about 40-60% heritable (Deary & Brett, 2015). Until now, research on the education-cognitive decline gradient has not been able to account for genetic markers and the potential heterogeneity they bring in terms of the rate of cognitive decline. A biosocial approach could help sociologists distinguish both social and genetic pathways illuminating educational influences in cognitive change in old age. The integration of genetic effects not only establishes new channels and novel findings, but also reduces the bias of past sociological research and facilitates the examination of factors that shape cognitive decline.

Furthermore, whether the effect from genes on individual differences in cognition becomes more or less prominent with age remains largely unknown. Existing research predominantly focuses on quantifying genetic and environmental components of variance in cross-sectional cognitive data and has provided evidence of genetic influences on cognitive ability (Davies et al., 2016; Rietveld & Webbink, 2016), yet few researchers have examined longitudinal cognitive change and genetic predisposition. Genes are inherited pre-birth and remain the same over a lifespan, but genetic effects on phenotypes can vary over age as a function of gene expression associated with developmental timing or environmental circumstances (Lee, Gatz, Pedersen, & Prescott, 2016). Research to date has not offered information on changes in the genetic contribution to individual heterogeneity in cognitive performance in older age.

The objective of this study is thus to investigate whether the polygenic risk score of educational attainment (PGS Education)[11] is associated with later life cognitive function and cognitive decline among middle-aged and older adults in the United States. The PGS Education summarises an individual's cumulative genetic predisposition to educational attainment, and is constructed by adding the risk alleles across the genome associated with education based on Okbay et al. (2016)'s GWAS results, weighted for their effect sizes in the meta-analysis. The score can be interpreted as a proxy measure of endowed ability, or genetic predisposition to educational attainment. I am focusing on genetic predisposition to educational attainment and its interaction with age, as these traits have been shown to be

[11] In this chapter, since this is the only polygenic score I use, the terms "PGS Education", "EA score", "polygenic score" and "genetic risk score" are used interchangeably.

associated with domains of cognitive ability and change (Deary et al., 2009). I am also re-examining the effects of sociodemographic and behavioural factors, after accounting for genetic markers. Using longitudinal data from the Health and Retirement Survey (HRS) covering 1998 to 2012 in the U.S., I have tracked individual changes in cognitive ability using a mixed effects method. This paper, to my knowledge, is the first study to estimate the age-dependent genetic effect on cognitive heterogeneity in later life. The goal of this study is to provide a better understanding and insight into the underlying mechanism between education and cognition over a lifespan.

4.2 Conceptual Framework

4.2.1 Types of Cognitive Abilities

Cognitive ability varies between individuals and over the life course. Moreover, a within-person's sub-dimensions of cognition decline at different rates. Verbal, numerical and knowledge-based abilities remain relatively stable in later life and may even improve with age, while other mental abilities such as memory and processing speed start to deteriorate from middle age or even earlier, and at a faster rate (Harada et al., 2013; Mustafa et al., 2012; Nisbett et al., 2012; Whitley et al., 2016).

Concepts of *crystallised intelligence* and *fluid intelligence* are introduced to categorise patterns of cognitive change over time. Crystallised intelligence represents knowledge that is learned and practiced, and remains fairly intact or gradually improves with age. Vocabulary and generally learned knowledge are examples of crystallised intelligence. Crystallised intelligence is formed through accumulating knowledge and experience, thus older adults tend to perform better at tasks requiring

this form of intelligence compared to their younger counterparts (Salthouse, 2012). As a channel to gain knowledge and skills, education is expected to have a strong effect on crystallised abilities.

Fluid intelligence, on the other hand, refers to the ability to perceive, recall, problem-solve and apply reasoning to things that are less familiar and independent to what one has learned (Baltes, 1993). Fluid intelligence is influenced by a person's innate ability to process new information and solve problems, thus is expected to be more sensitive to genetic endowment. Memory and processing speed are examples of fluid cognition. Compared to crystallised intelligence, fluid abilities have an earlier onset of deterioration and this occurs at a faster rate (Salthouse, 2012). In this study, I break down these two types of cognition further into specific sub-domains, including episodic memory, working memory, mental status, and vocabulary. Table 4-1 provides a summary of these subdomains according to crystallised/fluid and type. Their hypothesised relationships with higher levels of genetic risk scores are discussed in detail in Section 4.2.2.

Working memory (WM) and *episodic memory* (EM) are two types of memory greatly influenced by aging (Daselaar & Cabeza, 2013). WM represents the short-term memory that maintains and manipulates information, essential for reasoning and decision-making processes. EM is memory that encodes and retrieves personally experienced events that occurred at a specific place and time (Gabrieli, 1998). WM and EM are both forms of fluid intelligence. *Mental status* (MS) is a complex measure that covers orientation, attention, language, and knowledge of current affairs. These tasks measure the most basic crystallised cognitive functions (Farmer, Kittner, Rae,

Bartko, & Regier, 1995; Lyketsos et al., 1999). Finally, a large *vocabulary* (Vocab) learned over a lifetime is clearly an indicator of crystallised ability.

Table 4-1 Summary of Cognitive Sub-domains' Changes with Age and Education

	Crystallised vs. Fluid	Hypothesised Association with Higher PGS
Episodic Memory	Fluid	Compensation Hypothesis: Faster Decline
Working Memory	Fluid	Compensation Hypothesis: Faster Decline
Mental Status	Crystallised	Active Cognitive Reserve Hypothesis: Slower Decline
Vocabulary	Crystallised	Negative Cognitive Reserve Hypothesis: No Associations

4.2.2 Education, PGS Education, and Cognitive Ability

Cognitive reserve theory explains the variation in the brain's resilience to the effect of aging. The theory suggests that structural or functional characteristics of the brain allow individuals to maintain optimal performance over a longer period of time and to cope more effectively with most age-related brain changes (Stern, 2002, 2009). These features are also called cognitive reserve, which accumulates throughout the course of one's life and can be modified with intervention (Fratiglioni & Wang, 2007; Stern, 2012). Older individuals with greater experiential resources exhibit better cognitive functioning and are more resilient to brain pathology. The widely recognised determinants of cognitive reserve include childhood intelligence ability, education, occupation, and an active lifestyle (Opdebeeck, Martyr, & Clare, 2016; Reed et al., 2011).

Among the cognitive reserve proxies, education is the most well-established. In line with the cognitive reserve theory, many studies have identified that educational level in early life is associated with better cognitive status in later life (Gatz et al., 2001; Seeman et al., 2005; Tucker-Drob, Johnson, & Jones, 2009; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008; Zahodne et al., 2011). Education can improve cultural competence and skills in reading and mathematics as well as

reasoning, which reflects a more effective use of brain function and cognitive processing (Chen, Anthony, & Crum, 1999). Education also plays an indirect role in maintaining cognitive function later in life through its association with occupation and lifestyle, which are also commonly studied cognitive reserves that may result in greater mental activity in career and leisure pursuits throughout life (Andel, Vigen, Mack, Clark, & Gatz, 2006; Kramer, Bherer, Colcombe, Dong, & Greenough, 2004).

Although common genetic variants have been identified for educational and cognitive performance, it is unclear whether the educational-attainment associated genetic variants are also associated with the rate of cognitive change at an older age. This study adopts a biosocial approach to examine the relationship between the genetic predisposition to educational attainment and the rate of cognitive decline. Variation in cognition is substantially influenced by genetic factors. A genetic predisposition to higher educational attainment is associated with higher cognitive performance (Ward et al., 2014). A recent GWAS study of cognitive function using the UK Biobank estimates that up to 5% of the variance in cognitive test scores can be predicted by the polygenic score of cognitive function in an independent cohort (Davies et al., 2016). Using the proxy phenotype method, common genetic variants related to cognitive traits such as memory and mental status are detected (Conley et al., 2015; Okbay et al., 2016). Unlike studying the association of observed years of education, or highest educational achievement and cognition, evaluating this relationship with the genetic component captured through the polygenic risk score offers a novel approach to understanding the extent to which cognitive decline is influenced by educational attainment via biological mechanisms or by unobservable confounders related to environmental factors.

A genetic predisposition to educational attainment can affect cognitive decline directly via a shared genetic basis, and indirectly through its association with childhood intelligence, education and occupation. PGS education is shown to be robustly associated with years of education. Papageorge and Thom (2016) used the polygenic score based on the whole genome's genetic variants from Okbay et al.'s study to predict education in HRS. They reported 3-6% of the variation in years of schooling explained by the genetic risk score and replicated the strong relationship between the genetic score and educational attainment found in Okbay et al. (2016). Additionally, they found that the polygenic score is also associated with better childhood socioeconomic status and labour market outcomes. These findings are consistent with previous studies using the polygenic score constructed from Rietveld et al.'s (2016) results (Conley et al., 2015; Domingue et al., 2015). Drawing from the recent advances in socio-genomic studies and the theoretical relationship between education and cognitive performance, I hypothesise that both genetic predisposition to educational attainment (PGS education) and actual years of education predict a higher level of baseline cognitive abilities in old age (Hypothesis 1).

Results based on longitudinal data have shown conflicting results with respect to the relationship between educational attainment and cognitive change in old age. Some longitudinal studies have reported that educational attainment moderates cognitive or specific cognitive domain decline in samples of older adults (Alley, Suthers, & Crimmins, 2007; Alvarado, Zunzunegui, Del Ser, & Béland, 2002; Anstey & Christensen, 2000; Proust-Lima et al., 2008; Zahodne et al., 2011). Other studies report a lack of evidence of a relationship between educational level and rate of cognitive decline (Hans Bosma et al., 2003; Helen Christensen, 2001; van der Donk,

Hiemstra-Beernink, Tjeenk-Kalff, van der Leij, & Lindauer, 2015). Cognitive reserve theory thus provides three competing models that pose contrasting hypotheses.

First, the *active cognitive reserve hypothesis* postulates that individuals with a higher level of education use brain networks or cognitive paradigms more efficiently or flexibly, and the same amount of organic cognitive disruption would result in a smaller decline in cognitive function relative to those with a lower level of education. Well-educated individuals use knowledge to enhance memory via richer elaborative encoding and more effective ways to organise received information. Easier access to relevant information and better organised representations of the problem in turn facilitates problem-solving skills. Knowledge of prior solutions to familiar problems reduces processing time (Salthouse, Atkinson, & Berish, 2003). These mechanisms again reflect that individuals with a higher level of education enjoy a higher level of cognitive performance throughout their lifespan, and suggest that education attenuates the rate of cognitive decline in older ages. Thus, based on the active cognitive reserve hypothesis, the study postulates that genetic predisposition to educational attainment is associated with a lower rate of decline in crystallised cognitive abilities among older adults (Hypothesis 2).

On the other hand, (Tucker-Drob et al., 2009) argue that if the abovementioned mechanisms between education and cognition are increasingly relied upon with increasing neurobiological deterioration, a higher level of education would result in a shallower rate of cognitive decline. Otherwise, the active cognitive reserve model does not necessarily lead to the hypothesis of a flatter cognitive decline among those with a higher educational background. The argument thus emphasises the discussion as to whether the effect of education on cognition magnifies in later life.

Research on the effects of cognitive reserve on cognitive performance in old age shows that young adults with high levels of brain resources require little environmental support to improve their cognitive performance. By contrast, when older adults eventually reach exceedingly low levels of brain resources, both education and knowledge have minimal impact. Cognitive reserve is most effective for individuals with intermediate brain resources during normal aging – i.e. mid-life to early old age (Shing, Werkle-Bergner, Li, & Lindenberger, 2008). The hypothesis that educational effects are amplified at an intermediate level of brain resource extends to the genetic models of cognition (Lindenberger et al., 2008). Research using candidate genes [12] shows that genetic effect on cognitive performance in early adulthood and later stages of life is weak, but manifest during mid-life to early old age (Lindenberger et al., 2008; Rawle et al., 2018). This could be explained by the ceiling and floor effects. Cognitive-enhancing genetic variants are translated into increasingly larger performance inequalities for middle-age and old age adults, and have a smaller effect over the young and the very old. As this study focuses on the effects of genetic endowment on cognitive performance in middle-aged and older adults, I expect the effect of PGS education on cognitive abilities to diminish over age by observing a negative gene-age interaction term.

This proposition is in line with the second hypothesis of cognitive reserve theory. The *compensation hypothesis* (Christensen et al., 1997; Stern, 2002) suggests that if older individuals rely on crystallised cognitive domains to compensate for declines in fluid

[12] For example, Apolipoprotein E (APOE) is involved in clearing beta amyloid from the brain; carrying the ε4 allele may be less efficient at this task and thus the individual is at a higher risk of Alzheimer's disease.

cognitive domains, this compensatory mechanism would slow the decline in fluid cognitive abilities until crystallised cognitive domains also start to deteriorate (Alley et al., 2007). Older adults with higher educational attainment may overcompensate for their decline in fluid abilities by focusing on their crystallised abilities via the gaining of knowledge and experience (Compton, 2003). When age eventually interferes with the compensation scheme, deteriorating crystallised abilities, fluid abilities decline faster among a better-educated older population. Hence, Hypothesis 3 suggests that older adults with a higher PGS of education may have a faster rate of decline in fluid functions, which in this study is measured by episodic and working memory.

The third hypothesis, unlike the active model which is based on differences in how individuals process tasks, is based on physiological differences. The *passive cognitive reserve hypothesis* indicates that the number of neurons and synaptic density determines our brain's ability to cope with damage (brain reserve capacity). Individuals with a larger brain reserve with more neurons and synapses are likely to sustain more cognitive damage before clinical impairments arise (Stern, 2002). A higher level of education in this sense does not help slow the rate of cognitive decline in normal aging brains, such as a decline in processing speed, but the well-educated would continue to perform at a higher level at any age due to a greater baseline brain reserve (Salthouse, Atkinson, & Berish, 2003; Tucker-Drob, 2011). Vocabulary ability is practiced and accumulated with experience and remains relatively intact over age; drawing from the passive model, genetic endowment of educational attainment would be unrelated to the rate of vocabulary decline. The PGS-age interaction term would be insignificant (Hypothesis 4). The hypotheses are summarised in Table 4-1.

4.2.3 Lifestyle, Behavioral and Health Predictors

The sociodemographic predictors that I also include in the models are gender, years of education, social engagement, smoking, drinking, and health status. The life-cognition hypothesis suggests that maintaining a healthy lifestyle and actively engaging in activities may help prevent age-related cognitive decline (Baumgart et al., 2015). Social engagement has been found to be a protective indicator for cognitive aging (James, Wilson, Barnes, & Bennett, 2011; Krueger et al., 2009; Small, Dixon, McArdle, & Grimm, 2012). A recent study from the HRS shows that the social engagement index, taking into account marital status, participation in volunteering work and social interaction is significantly associated with better mental status and self-rated health in later life. However, the same analysis did not find evidence of any impact of the level of social engagement on patterns of cognitive decline over time (Nelson, Noonan, Goldberg, & Buchwald, 2013). Being married or cohabiting with someone and frequently interacting with other people may stimulate cognitive functions and protect the brain from deterioration (van Gelder et al., 2006). The loss of a partner could result in changes in health behaviour such as stress-induced smoking and drinking, and eventually cause adverse health and cognitive outcomes (Vidarsdottir et al., 2014). Krueger et al (2009) found that a higher level of social interaction in old age is associated with better cognitive performance in general, but this association varies across subdomains. Social engagement has a significant effect on fluid intelligence, but not on crystallised abilities. This body of research underlines the potentially vital importance of social engagement for good cognitive functioning in later years (Ertel, Glymour, & Berkman, 2008). After taking into consideration the genetic effect on cognitive abilities, the study thus expects a protective relationship

between the level of social engagement and cognitive performance and decline (Hypothesis 5a).

Behavioural factors include physical activity, smoking status, and alcohol intake. Physical activity increases production of growth hormone and neurotrophic factors that have a protective effect on cognitive functioning (Lytle, Vander Bilt, Pandav, Dodge, & Ganguli, 2004) Research has shown that even mild physical activity such as walking is associated with decreased risk of cognitive impairment and improved cognitive functions among older individuals (Blondell, Hammersley-Mather, & Veerman, 2014; Sofi et al., 2011). A large body of research on older adults has documented that smoking increases the risk of cognitive decline (Hebert et al., 1993; Ott et al., 2004; Plassman, Newman, Welsh, Helms, & Breitner, 1994). Small or moderate alcohol consumption by older individuals is associated with better cognitive outcomes (Baumgart et al., 2015). In addition, a higher level of genetic predisposition to educational attainment is associated with higher parental social economic status (Domingue et al., 2015), which may bring a positive influence on children's health behaviours and lifestyles. As a result, this study explores whether a healthy lifestyle is associated with a better cognitive performance and a slower rate of cognitive decline, after accounting for the genetic effect of educational attainment (Hypothesis 5b).

Several chronic health conditions have been identified as predictors of adverse cognitive performance, including heart disease, stroke, hypertension, and diabetes. Changes in cognitive functions as a result of chronic disease are increasingly receiving more attention. Chronic diseases related to physiological change affecting brain function may explain the association. Cardiovascular diseases are related to cognitive deterioration in vocabulary, working memory and mental status (Qiu &

Fratiglioni, 2015). Thus, having a chronic health condition is expected to be associated with poorer cognitive performance and a faster rate of cognitive decline (Hypothesis 5c).

Gender differences in cognitive abilities have been observed throughout the population. On average, older men have a better spatial ability than older women, while older women outperform men on reasoning and vocabulary abilities (Denis Gerstorf, Ram, Hoppmann, Willis, & Schaie, 2011). Finkel et al. (2003) demonstrate that women also perform better on episodic memory performance. The rate of decline is similar for both sexes, but after adjusting for the effect of education, women outperform men in processing speed, episodic memory, fluency and knowledge (D. Gerstorf, Herlitz, & Smith, 2006). This result suggests that women's lack of access to education earlier in life suppresses their advantage with cognitive tasks. Thus, I hypothesise that women outperform men in cognitive functions (as spatial ability is not analysed), and experience a slower rate of decline (Hypothesis 5d).

4.3 Data and Methods

4.3.1 Data

The Health and Retirement Survey (HRS) began in 1992, and is a biennial, longitudinal survey of a nationally-representative sample of individuals and their spouses aged 50 and above. In 2006 and 2008, the HRS collected genetic (saliva) samples from approximately 84% of participants undergoing face-to-face interviews (12,507 individuals). These DNA samples were genotyped for about 2 million SNPs. This study exploits the longitudinal nature of the HRS to explore the cognitive performance trajectories among older adults in the U.S. The mental status index in

HRS is only available from wave 3 (1996) onwards[13]. Measurement for social engagement is available from wave 4 (1998) onwards. In order to be consistent, I use eight waves of the HRS data (from 1998 to 2012). Pre-processed datasets included the user-friendly RAND HRS data files (version P)[14] and 1998-2012 HRS Core Files. 19,341 respondents participated in the 1998 HRS survey and had at least one measure of cognitive ability in the baseline, and among these participants, 6,984 were genotyped.

4.3.2 Sample

Mixed models typically require at least three measures per individual (Curran, Obeidat, & Losardo, 2010) in order to be able to identify a linear trajectory. 1,925 respondents whose cognitive performance was measured fewer than four times were removed. Since this study only focuses on age-related cognitive decline, I have differentiated normal cognitive functioning from impaired functioning. A composite score measuring memory and mental status has been constructed (ranging from 0 - 27). 36 respondents with a score of less than 7 at the baseline (1998) indicated the presence of Dementia, and were not included in the study. The cut-off points have been validated clinically and empirically (Crimmins, Kim, Langa, & Weir, 2011). Finally, for the main analysis, only individuals from European and non-Hispanic backgrounds were included. The 5,704 remaining respondents had at least four cognitive interviews: 4% had four or five interviews, 20% had six or seven

[13] For recall tasks, the word list in the cognitive test contains 20 words in wave 1 and 2 (1992 and 1994), and 10 words for the rest waves.

[14] More information is available at https://www.rand.org/labor/aging/dataprod/hrs-data.html

interviews, and 77% had completed eight waves of interview, providing 38,037 person-wave observations. Note that vocabulary was not measured in 2000 and 2004, resulting in fewer observations.

Dependent variables – cognitive measures

In HRS, assessment of cognitive function is based on a reduced version of the telephone interview for the assessment of cognitive status (Desmond, Tatemichi, & Hanzawa, 1994), which was derived from the Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975). The assessment has been validated for use as a screening instrument for cognitive performance. The same cognitive tests were administered during all the included waves of data collection and were used to construct cognitive trajectories for individuals on each test (Herzog & Wallace, 1997). This study includes four specific cognitive tasks (three fluid and one crystallised ability tasks), and a summary measure of global cognition (GC).

Episodic Memory (EM) was measured by immediate and delayed word recall. Respondents were read a list of ten common words (e.g. hotel, sky, water) and were then asked to recall as many of them as possible both immediately after the list was read and also several minutes later. The score records the total number of words the respondent correctly recalled at each instance.

Working Memory (WM) was assessed with the serial 7s subtraction test. The respondents were asked to subtract 7 from 100, and continue subtracting 7 from each subsequent number for a total of five trials. The scores record the correct number of

trials (ranging from 0-5). The serial 7s subtraction test assessed mixed abilities of WM, attention, and calculation.

Mental Status (MS) was assessed by naming the date, month, year and day of the week, backwards counting from 20, object naming, and naming the current president and vice president of the U.S.

The crystallised ability measured in the study was vocabulary (Vocab) and mental status (MS), which represents established knowledge. Respondents were asked to define five words from one of two sets: a) repair, fabric, domestic, remorse, plagiarise, and 2) conceal, enormous, perimeter, compassion, audacious. Respondents were randomly assigned one set of words in the first wave and the sets were alternated in each wave thereafter.

Global Cognition (GC) is a summary measure of the abovementioned cognitive domains. Although the MMSE is the most widely applied cognitive test in epidemiological research for picturing cognitive decline that occurs with age (Ganguli, Du, Dodge, Ratcliff, & Chang, 2006), it has been criticised for floor and ceiling effects (Tombaugh & McIntyre, 1992). The floor effect occurs when having a disadvantaged social background adversely affects the cognitive performance for respondents, thus reducing test specificity. The ceiling effect occurs when an advantaged social background positively influences respondents' cognitive abilities, and reduces test sensitivity (Franco-Marina et al., 2010). To minimise floor and ceiling effects, cognitive sub-domain scores can be incorporated into a global cognitive score (Rosselli, Tappen, Williams, & Salvatierra, 2006). Summary measures of EM, WM, MS and Vocab are formed along with a measure of global

cognition (ranging from 0-35). The global measurement has been validated (Herzog & Wallace, 1997) with a normal distribution and is sensitive to sociodemographic factors. To provide comparability across all measurements, I rescaled individual and global cognitive variables into a corrected percentage score – based on a division by the maximum score and multiplication by 100.

Independent variable - genetic predisposition of education (PGS Edu)

This study uses the polygenic risk score based on the most recent GWAS that did not include HRS GWAS data for educational attainment (Okbay et al., 2016), from which SNP effects on years of education are obtained. A weighted mean for each individual across all available SNPs was generated (also referred to as PGS2 in Chapter 1 constructed using the whole-genome approach). The weighted mean was based on the SNP effect in the GWAS (excluding HRS) so that the SNPs most relevant to the phenotype were weighted most heavily following standard approaches for polygenic score calculation (Cardon & Palmer, 2003; Domingue et al., 2015). Larger scores predict higher years of education and serve as indicators for a genetic predisposition to educational attainment. The polygenic risk score was standardised for the full HRS GWAS sample, so that effects can be interpreted as a 1 SD change relative to the full HRS sample (equivalent to an increase in the raw polygenic risk score by 0.99, relative to the sample mean of 0.048).

The research method using genetic data may suffer from potential selection bias, as respondents had to live until the 2006-2008 genotyping period. Of the original 37,495 respondents, 28,136 (75%) lived until at least 2006. Such selective attrition may introduce bias into analyses of the determinants of cognitive functions (Domingue,

Belsky, et al., 2017). I have therefore used inverse probability weighting to avoid mortality selection bias on the estimated association between genetic predisposition to educational attainment and cognitive decline.

Covariates

Basic demographic characteristics of the respondents included gender and observed years of education. Age is centred at 67 (mean age at baseline, SD = 6.90, range from 55-91).

Social engagement is measured by an index similar to the one used by Ertel et al. (2008) and Nelson, Noonan, Goldberg, and Buchwald (2013). It consists of measures for marital status, volunteering activities, and contact with family and neighbours. Respondents received one point each for: 1) being married; 2) volunteering for religious, educational, health-related, or other charitable organisations at least one hour in the past year; 3) contacting parents weekly or more frequently; 4) contacting offspring weekly or more frequently; and 5) meeting with neighbours weekly or more frequently. The index score ranges from 0 to 5. The sample was categorised into low (scores 0-1), moderate (scores 2-3), and high (scores 4-5) levels of social engagement.

Behavioural risk factors are measured by a binary variable of the respondents' current smoking status, and alcohol consumption (number of drinks per day). Alcohol consumption is divided into non-drinkers (0 drinks per day), moderate drinkers (1-3 drinks per day), and heavy drinkers (4 or more drinks per day).

Health risk indicators are measured by determining whether the respondent had ever had heart disease, diabetes, stroke or hypertension. The summarising scores were then

divided into three groups: no condition (count = 0), few conditions (count = 1, 2); many conditions (count = 3, 4).

I have introduced a control for population stratification, as the frequencies of certain genetic variants vary by ancestral background. Ignoring genetic variation due to ancestry may result in population stratification bias when genetic effects are confounded by ancestry. The standard practice to account for population stratification using GWAS data is to include as covariates the first few principal components of SNPs that capture most of the genetic variation due to ancestry. I have adjusted the first 10 principal components for population stratification (Price et al., 2006).

4.3.3 Analytical Strategy

Linear mixed models were used to examine the individual cognitive trajectories of the respondents, which enabled us to study the effect of genetic predisposition to educational attainment on the baseline level of cognitive ability and on its rate of change. The use of cognitive measurement at multiple time points has several advantages. First, repeated measurements provide a more reliable assessment of long-term cognitive change relative to the use of change scores. Second, the linear mixed model accounts for the correlation of multiple measurements within subjects and minimises the underestimation of standard errors typical of analyses predicting change (Glymour, Tzourio, & Dufouil, 2012). Third, the coefficient of age is allowed to randomly vary between subjects and is optimal to examine random and fixed effects for age (Rabe-Hesketh & Skrondal, 2008). Finally, the sample in this study is unbalanced and the models were able to accommodate participants for whom the observation is missing at some time points.

Firstly, I have reported descriptive statistics for key variables (Table 4-2). Sub-domain and global cognitive measures are visualised (Figure 4-1) to examine the trajectory of age-specific mean cognitive tasks scores for all participants. Random components of the model are built by systematically adding the linear and quadratic intercept and slope of age. A comparison of model fits between different specifications of fixed and random components suggest that a linear, age-related decline random effect model is the most appropriate option (Appendix 4-1).

Separate linear mixed models were estimated with each cognitive measure as a dependent variable. In the case of global cognition, the initial model includes a fixed effect of current age, PGS edu, age × PGS edu (Model 1), testing the genetic effects of education on cognition and cognitive decline. Gender, observed years of education, and their relationship with age are added to examine sociodemographic effect. Social engagement, behavioural risks, and chronic conditions are systematically introduced to fit Models 3, 4 & 5. Random effects for the linear mixed model included intercept and linear age, with the conventional unstructured covariance. Models were evaluated with likelihood ratio tests (-2LL), the Akaike Information Criterion (AIC; Akaike, 1974) and the Bayesian Information Criterion (BIC; Schwarz, 1978), for which smaller values indicate a better fit.

A general specification of the model is

$$Cognition_{ij} = \beta_0 + \beta_1 * Age_j + \beta_2 * PGSedu_i + \beta_3 * PGSedu_i * Age_j + \beta_4 * X_{ij} + \beta_5 * X_{ij} * Age_j + \mu_{ij} + \mu_{ij} * Age_j + \varepsilon_\iota \quad (4)$$

where $Cognition_{ij}$ represents the cognitive score for person i at age j, β_0 is the population mean of cognitive ability at baseline, β_1 represents the linear fixed effect of age, β_2 represents the effect of PGS edu on the baseline cognitive ability (age = 67), β_3 is the linear effect of PGS on the change rate of cognitive skills, and β_4 and β_5 are the effects of X – a vector including individual covariates – on the initial cognitive abilities and the growth rate of change. σ_1 and σ_2 are the random intercept and slope. X is a vector including individual covariates. μ_{ij} and μ_{ij} are intercept and age variance.

The same procedure is applied to build models for EM, WM, MS and Vocab; only full models for individual measures are reported. All models applied the inverse probability weight for mortality selection, and controlled for the first 10 principal components if not indicated otherwise. The fixed effect of age squared, interaction of age squared and predictors were also tested, but there are no significant findings, thus results are not reported.

4.4 Results

Descriptive statistics of the sample (Table 4-2) show that mean age at the sample's baseline was 67 and on average, older adults had received 13 years of education. 58% of the sample were female, and 19% of the sample smoked at the 1998 interview. Only 17% of older adults were engaged in two or more social interactions. 63% of older adults did not consume alcohol at the baseline and only 1% of the sample reported four or more drinks per day. Two thirds of the sample did not have heart disease, stroke, hypertension, or diabetes at the baseline. 1% of the sample had three of these, or all of them. The descriptive statistics are in line with previous studies

using HRS samples (e.g. Alley et al., 2007; Karlamangla et al., 2009; Nelson et al., 2013).

The rescaled cognitive scores represent the percentage of correctly completed tasks, and thus are comparable. WM and MS tasks were relatively easier compared to Vocab and EM tasks. Older adults on average competed 90% and 80% of the WM and MS tests respectively, while EM and Vocab have only a mean score around 60, dragging GC towards 70. The trend in cognitive change over age (Figure 4-1) reflects that EM and MS decline faster during later life, while WM and Vocab are relatively stable. Vocab even appears to increase with age until 65 and stabilises. Further variance analyses (results not represented) show that for MS, most variance comes from within-person deviation (SD = 25); between-person variation only accounts for a small proportion (SD = 9). On the contrary, for Vocab, between person variance (SD = 15) is larger than within person variance (SD = 10). Other measures have similar between- and within- person variances.

Tables 4-3 and 4-4 include results from linear mixed models. For GC, the inclusion of demographic, socioeconomic, lifestyle and health factors (Model 5) improved the model fit substantially compared to Model 1. These covariates are thus retained in the cognitive sub-domains' models. The intercept in each model shows the mean score for the cognitive measure at age 67. For example, the average GC score at age 67 for any individuals is 50 (Model 5), meaning the population on average correctly completed half of the cognitive tasks. Older age is significantly related to a lower level of baseline GC, WM, EM, and MS, but has no significant effect on Vocab, suggesting that vocabulary, as a crystallised ability, remains intact later in life.

Figure 4-1 Mean cognitive measures trajectories among HRS participants over age

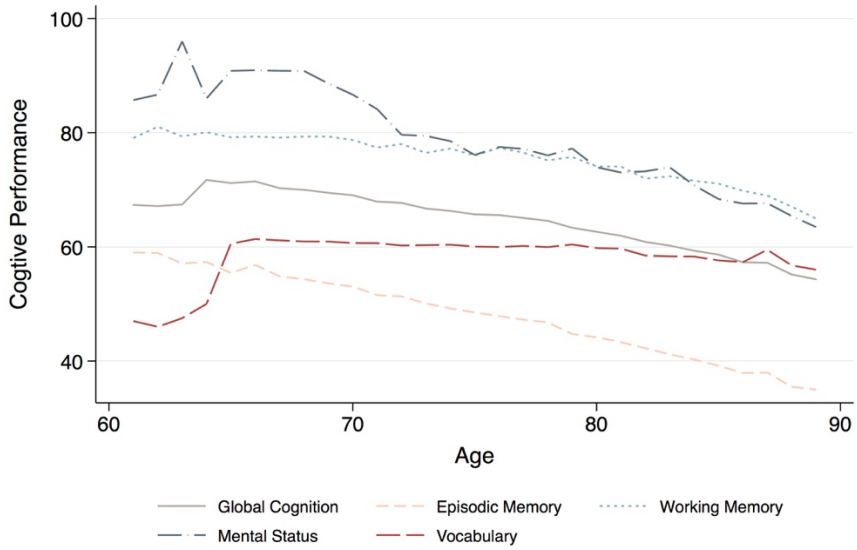


Table 4-2. Baseline Characteristics of the HRS sample (n=5,005)

Variables	Mean (SD) or Percentage
Cognitive Functions (rescaled)	
EM	56.13 (16.62)
WM	79.60 (27.30)
MS	90.85 (10.85)
Vocab	61.81 (17.97)
Global Cognition	69.46 (11.15)
PGS edu (Unstandardised)	0.04 (0.99)
Age	66.73 (6.90)
Gender (female)	58.26%
Years of Education	12.96 (2.51)
Social engagement	
Low	83.12%
Moderate	15.18%
High	1.7%
Current Smoker	18.84%
Drinking	
Non-Drinker	63.49%
Moderate-Drinker	35.37%
Heavy-Drinker	1.14%
Chronic Conditions	
No Condition	68.31%
Few Conditions	30.55%
Many Conditions	1.14%

4.4.1 Higher Education Polygenic Score is Associated with Better Cognitive Performance

HRS respondents with higher PGS Edu scored higher in cognitive tasks across all measures at age 67. The effect size of one standard deviation increase in PGS Edu on cognitive abilities ranges from 0.8 (Table 4-4, EM) to 2.4 (Table 4-4, WM). One standard deviation increase in PGS Edu is associated with 2.4 point higher initial WM score (Table 4-4, WM). After taking PGS Edu into account, years of education are still positively related to all initial cognitive tasks, with the largest effect size found in WM and Vocab. For each additional year of education, baseline scores on each of the cognitive tasks is about 1.4 to 2.6 point higher. Substantively, this translates into an

effect such that an older adult with four years of college education scores about 5.6 to 10.4 percent higher at baseline than a respondent with only high school education.

4.4.2 The Effect of Education Polygenic Score on Cognitive Ability Varies Over Age

The polygenic risk score of education is related to the rate of longitudinal decline in cognitive performance, but the direction of the relationship varies by cognitive subdomains. HRS respondents with higher polygenic scores experienced steeper trajectories of GC and EM decline in older ages compared to their counterparts with lower polygenic scores. For the two cognitive measures, the significant negative coefficient representing the interaction of age and PGS of education indicates that the protective effect of PGS on these tasks diminishes over age (Table 4-3, Table 4-4), endorsing the compensation hypothesis (H3). In contrast, the lack of significance of age and the PGS interaction coefficient on the WM and Vocab tasks suggest that genetic predisposition to educational attainment has no effect on the rate of cognitive decline (negative cognitive reserve hypothesis, H4). Finally, the positive sign on this interaction term in the MS model indicates moderate protective PGS Edu effects on MS decline. Higher level of PGS is related to an attenuated rate of decline on this task, which is evident for the active cognitive reserve hypothesis (H2). These PGS estimates are robust controlling for demographic, socio-economic, lifestyle, health and population stratification covariates.

To illustrate these trajectories, Figure 4-2 displays estimated age-specific scores on the basis of fixed effects of the GC, EM and MS at three different PGS levels. Comparing older adults with low and high PGS levels of education, the initial adjusted mean scores on global cognition at age 55 is 80 and 84 out of 100

respectively. By age 90, the score differences disappear for different levels of PGS. The heterogeneity among three PGS levels disappears even earlier for EM, at around 80 years old. Thus, persons with higher PGS levels scored higher on GC and EM at the late stage of middle age, but they also experienced a more rapid rate of decline than respondents with a lower level of PGS. The advantage of a higher PGS level on GC and EM fades at around 80 and 85 years old respectively. However, on the MS, PGS level differences on MS was indistinguishable at age 55, and respondents with higher PGS levels scored higher and experienced a slower rate of decline relative to respondents with lower PGS levels. Essentially, cognitive performance among PGS groups converges with age on GC and EM, whereas cognitive performance on MS diverges with age in later life.

4.4.3 Gender, Social Engagement, Health Behaviour and Health Condition on Cognitive Ability

Gender, lifestyle and health conditions are also related to the baseline cognitive score and rate of decline (H4a-d). Women had a higher baseline score on GC, EM and Vocab by 4%, 7% and 3% respectively, but lower scores on WM by 5%. The gender difference on MS is not statistically significant. History of multi-morbidity is related to lower baseline scores on EM and MS. Smoking is related to adverse initial results in GC and MS. Social engagement is not related to better cognitive performance, but is found to be negatively related to MS (coef. = -4.8, std.err. = 1.48).

In terms of other sources of variance in the rate of cognitive change, interactions between these covariates and age are also tested. Gender is a significant predictor of cognitive change in GC, EM and WM, such that cognitive decline occurred at a faster

rate in women. The result is in line with previous studies using HRS (Alley et al., 2007). Social engagement has a persistent protective effect on cognitive decline of GC, EM, and accelerates the rate of decline in MS. Individuals with a high level of social interaction experience a slower decline in GC and EM relative to individuals with a low level of social interaction. No social engagement differences were present in the rate of decline on WM and Vocab. Smoking is not related to the rate of cognitive decline in four of the measures, but correlated with a slower decline in MS. Mild drinking attenuates the rate of decline in GC, EM and WM, compared with that of non-drinkers. This relationship may be related to the correlation between drinking and socioeconomic status. Those who drink may have represented a population with higher social status, and thus a healthier population. Finally, a higher number of existing chronic health conditions greatly accelerates cognitive decline across all cognitive measures except Vocab.

4.4.4 Sensitivity Analyses

I conducted sensitivity analyses to evaluate consistency of findings. First, I repeated the analyses including 715 HRS genotyped African Americans (n = 5,710). The findings are similar to the sample with European ancestry only (Appendix 4-2). Genetic variants lose significance on MS in this sample, although the direction of the effect is consistent with those in the white, non-Hispanic sample. PGS effects on other cognitive measures also weaken. This difference is likely due to fact that the genetic weighting used to construct PGS levels for African Americans comes from Okbay et al. (2016) on European ancestry groups: PGS levels for African Americans thus may not have the same predictive capacity (Martin et al., 2017).

Furthermore, due to the possible insensitivity of the cognitive tests to changes at the lowest level of the values, to reduce the impact of possible floor effects (Nyenhuis & Garron, 1997), I repeated the primary analyses after excluding individuals in the lowest 5% of scores at baseline within each cognitive domain (Appendix 4-3). The results are consistent with the main analyses.

Keller (2014) has expressed scepticism on positive findings from gene-environment interaction studies that potential confounders are not properly accounted for in the statistical models used to test G×E effects. Including the potential confounders as covariates alone in the models may not be sufficient, as this practice does not control for the effects these variables might have on the gene-environment interaction. To show that the results in this study are robust after properly controlling for confounders, I reran the G×E models adding the covariate-by-environment (C×E) and the covariate-by-gene (C×G) interaction terms (Appendix 4-4). The results are similar to the main analyses.

Table 4-3 Results of Linear Mixed Models on GC (HRS 1998-2012), European Ancestry Only.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Fixed Effects										
Intercept	72.312***	0.149	50.234***	0.806	52.594***	0.795	52.334***	0.841	52.182***	0.858
Age	-0.869***	0.014	-0.899***	0.077	-0.893***	0.077	-0.846***	0.081	-0.669***	0.084
PGS_{edu}	1.906***	0.150	1.150**	0.143	1.139**	0.043	1.076***	0.149	1.050***	0.148
Age × PGS_{edu}	-0.026*	0.012	-0.032*	0.014	-0.032*	0.014	-0.028*	0.013	-0.028*	0.015
Female			3.926***	0.282	3.907***	0.281	3.938***	0.296	3.900***	0.294
Age × Female			-0.118***	0.028	-0.115***	0.028	-0.100**	0.029	-0.114***	0.029
Years of Education			1.324***	0.058	1.323***	0.057	1.357***	0.061	1.357***	0.061
Age × Years of Education			0.009	0.006	0.008	0.006	-0.001	0.006	-0.002	0.006
Social engagement (Ref. = Low)										
Middle Social engagement					0.649*	0.321	0.464	0.338	0.480	0.336
High Social engagement					0.052	0.556	-0.016	0.598	0.076	0.596
Age × Middle Social engagement					0.050*	0.028	0.067*	0.029	0.059*	0.029
Age × High Social engagement					0.264***	0.063	0.288***	0.068	0.264***	0.068
Smoke							-1.050**	0.374	-0.938*	0.374
Age × Smoke							0.083*	0.043	0.055	0.048
Number of Drink per Day (Ref.= 0)										
Less than 4							-0.105	0.237	-0.083	0.236
More than 4							-0.269	0.998	-0.148	0.995
Age × Less than 4							0.103***	0.023	0.093***	0.003
Age × More than 4							0.364**	0.130	0.335*	0.130
Number of Chronic Conditions (Ref. = 0)										
Few Conditions									-0.007	0.239
Many Conditions									-0.800	0.490
Age × Few Conditions									-0.136***	0.025
Age × Many Conditions									-0.247***	0.042

Table 4-3 Results of Linear Mixed Models on GC (HRS 1998-2012), European Ancestry Only. Continued.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Random Effects										
Intercept Variance	8.448***	0.137	7.567***	0.132	7.532***	0.132	7.503***	0.142	7.423***	0.142
Age Variance	0.615***	0.016	0.597***	0.015	0.596***	0.015	0.593***	0.017	0.597***	0.017
Covariance of intercept, age	-0.301***	0.026	-0.310***	0.027	-0.308***	0.027	-0.312***	0.030	-0.314***	0.030
Model Fit										
-2LL	-116806.7		-116378.6		-116355		-107992		-107930	
AIC	233649.4		232801.2		232761.8		216049.4		215931	
BIC	233800		232985		232979.3		216314.7		216229	
n	5,005		5,005		5,005		5,005		5,005	
N	31,744		31,744		31,744		31,744		31,744	

Note: *** p<0.001, ** p<0.01, * p<0.05. 10 principal components to adjust for population stratifications.

Table 4-4 Results of Linear Mixed Models on EM, WM, MS, and Vocab (HRS 1998-2012), European Ancestry Only

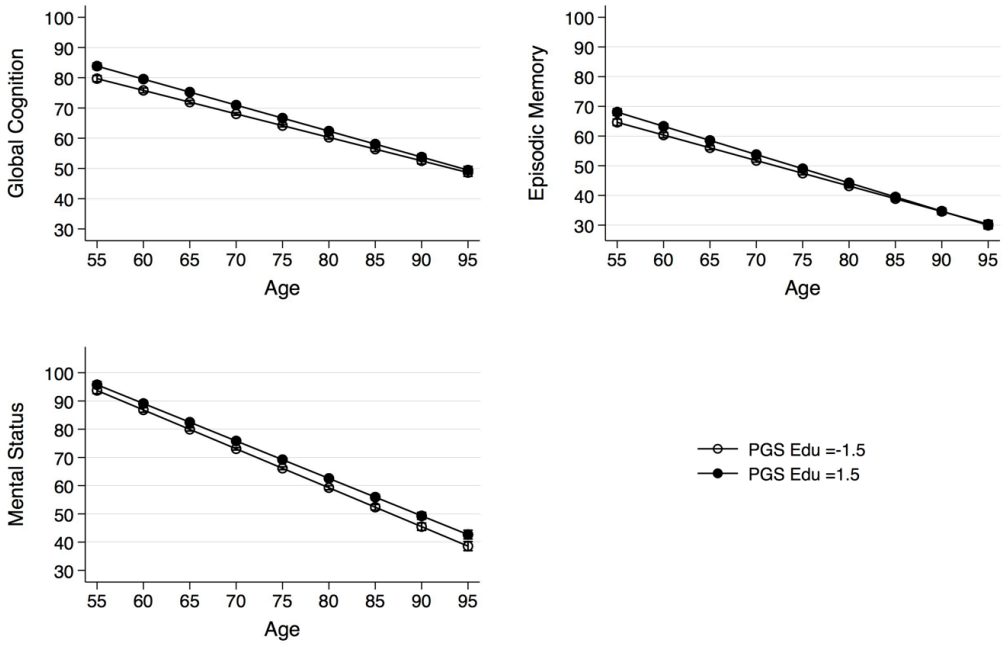
	EM		WM		MS		Vocab	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Fixed Effects								
Intercept	31.467***	1.026	48.368***	1.832	84.069***	1.694	29.365***	1.753
Age	-0.591***	0.086	-0.675***	0.148	-1.076***	0.207	0.264	0.149
PGS_{edu}	0.766***	0.178	2.440	0.319***	1.759***	0.289	1.464***	0.317
Age × PGS_{edu}	-0.032*	0.015	0.012	0.025	0.034*	0.010	-0.020	0.026
Female	7.251***	0.353	-4.611***	0.633	-0.271	0.575	3.158***	0.624
Age × Female	-0.107***	0.029	-0.208***	0.050	-0.089	0.072	0.031	0.052
Years of Education	1.546***	0.073	2.649***	0.131	0.988***	0.119	2.384***	0.125
Age × Years of Education	-0.017***	0.006	0.024*	0.010	-0.076***	0.015	-0.001	0.010
Social engagement (Ref. = Low)								
Middle Social engagement	0.316	0.376	0.583	0.651	1.104	0.768	-1.077	0.798
High Social engagement	0.426	0.588	1.614	1.015	-4.797**	1.484	-0.613	1.456
Age × Middle Social engagement	0.066*	0.032	0.090	0.055	-0.310***	0.076	0.099	0.067
Age × High Social engagement	0.225**	0.069	0.196	0.120	-0.594**	0.187	0.202	0.180
Smoke	-0.239	0.370	-0.948	0.646	-3.721***	0.832	-1.606	0.853
Age × Smoke	-0.036	0.044	0.128	0.078	0.319*	0.130	0.161	0.099
Number of Drink per Day (Ref.= 0)								
Less than 4	0.364	0.249	-0.099	0.433	0.075	0.565	0.602	0.575
More than 4	1.453	0.909	2.254	1.579	-2.413	2.488	-2.207	2.854
Age × Less than 4	0.078**	0.024	0.139*	0.042	-0.049	0.061	0.086	0.051
Age × More than 4	0.147	0.123	0.342	0.214	0.764*	0.365	0.523	0.320
Number of Chronic Conditions (Ref. = 0)								
Few Conditions	-0.589*	0.241	0.147	0.419	1.116*	0.552	0.215	0.542
Many Conditions	-1.712**	0.576	0.293	1.024	-1.789	1.161	0.900	1.255
Age × Few Conditions	-0.098***	0.025	-0.206***	0.043	-0.735***	0.065	-0.051	0.051
Age × Many Conditions	-0.172***	0.048	-0.463***	0.085	-1.167***	0.110	-0.176	0.097

Table 4-4 Results of Linear Mixed Models on EM, WM, MS, and Vocab (HRS 1998-2012), European Ancestry Only. Continued.

	EM		WM		MS		Vocab	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Random Effects								
Intercept Variance	9.421***	0.151	17.494***	0.252	1.016***	0.042	9.315***	0.332
Age Variance	0.555***	0.020	0.806***	0.039	7.575***	0.395	0.312***	0.084
Covariance of intercept, age	-0.364***	0.027	0.064**	0.041	0.998***	0.007	0.254	0.252
Model Fit								
-2LL	-140140.2		-160417.7		-136360.8		-51688.33	
n	5,005		5,005		5,005		3,070	
N	35,141		35,141		29,039		12,451	

Note: *** p<0.01, ** p<0.05, * p<0.1. 10 principal components to adjust for population stratification.

Figure 4-2. Estimated Score on Total Cognitive Function, Episodic Memory and Mental Status by Age at Three Groups PGS education



4.5 Discussion

I tested whether genetic traits discovered by GWAS indicating a predisposition to educational attainment are associated with higher initial level of cognitive abilities at the early stages of older adulthood, and the variation of its effect over later life among a representative sample of Americans with European Ancestry over 55 years of age. I analysed data on the trajectory of cognitive performance in over 5,000 individuals interviewed longitudinally as part of the HRS. Because this study is the first to investigate a relationship between an education-associated polygenic risk score and the rate of cognitive decline among older adults accounting for socio-demographic, lifestyle and health-related heterogeneity, the findings provide new knowledge on whether the effect of a polygenic risk score on cognitive functions varies over age and across cognitive subdomains. These findings are in agreement with the implications

made by the small amount of existing literature on the relationship between education and cognitive decline, indicating that education acts as a protector towards mental status (active cognitive reserve hypothesis), but not on fluid-intelligence-related measures (compensation hypothesis / passive cognitive reserve hypothesis) (Alley et al., 2007; Anstey & Christensen, 2000).

Results across a range of cognitive domains suggest that the polygenic score of education is related to a significantly higher baseline (age at 67) cognitive function. Even after controlling for observed years of education, the relationship between education-associated genetic variants and cognitive ability still persists. These results are consistent with the evidence from Okbay et al. (2016), Rietveld et al. (2013) and Rietveld et al. (2014) that there is common genetic basis between educational attainment and cognitive ability. The shared genetic variants are associated with a particular neurotransmitter pathway involved in synaptic plasticity, which is the main cellular mechanism for learning and memory. The associations between a genetic predisposition to educational attainment and baseline cognitive performance is strongest for working memory and weakest for episodic memory.

The analysis of cognitive trajectories caused by normal aging showed that the polygenic score of education is also related to the rate of cognitive decline, but the effect varies across cognitive measures. Performances in global cognition and episodic memory are higher in high levels of PGS education groups compared to low PGS education groups for those under 85 years old, but this difference is completely attenuated over the age of 90 due to faster cognitive decline in the high PGS education group. In contrast, genetic variants buffer the age effect on mental status

after the age of 75. Individuals in the high PGS education group have a lower rate of decline in mental status.

The findings on cognitive decline are in agreement with recent studies showing that genetic effects vary in cognition with age (Lee et al., 2016). In addition, several studies have reported faster cognitive decline in high education groups compared to the cognitive decline in low education groups (Gottesman et al., 2014; Karlamangla et al., 2009; Rusmaully et al., 2017). The finding that a higher genetic predisposition to educational attainment is associated with a faster rate of cognitive decline might reflect the transience of global cognition and episodic memory gains associated with this genetic predisposition, which is lost as individuals age. In contrast, the genetic protective effect on mental status commences around age 70-75. Genetic predisposition for educational attainment is not associated with the rate of change in working memory and vocabulary.

After accounting for genetic effects, the decline in cognitive abilities is also evident for sociodemographic, lifestyle and health indicators. Women outperform men in most of the cognitive baseline measures, but also decline at a faster rate. Higher levels of social integration have a protective effect on cognitive deterioration in episodic memory and mental status, but are not related to the baseline cognitive level. History of chronic multi-morbidity consistently predicts a faster loss of cognitive decline across domains.

This variability in the genetic effect may be due to ceiling and floor effects inherent in cognitive measures that narrow the potential range of decline. Mental status as a crystallised intelligence tends to start declining at a later age compared to fluid

intelligence, and is most pronounced in older adults with pathological brain damages (Albert, 1995). The findings that older adults with a lower level of genetic predisposition to educational attainment experience a more rapid cognitive decline compared to a more gradual decline for those with higher level of PGS, could be due to ceiling effects in the measurement that limit the variability of change for well-educated older adults with higher initial scores. People with higher PGS thus enjoy higher cognition for their entire adult life. More sensitive measures that cover greater variability in cognitive function might provide more accurate estimates in future research. Sensitivity analyses excluding the individuals who scores the lowest 5% in each measure retained similar results, suggesting floor effects do not challenge the analysis.

Another limitation is that the study is based on largely homogeneous groups of non-Hispanic Caucasian older adults in the U.S. The findings may not extend to individuals of other ethnic or cultural backgrounds, or later-born cohorts. However, this limitation is ameliorated by including African-American respondents in the sample in the sensitivity analyses. The effects size of PGS shrank in models including both Caucasian and African-American respondents, mainly due to the reduced predictive power of PGS on educational attainment for African-American older adults. But the directions of the coefficients are largely in line with the main analyses, alleviating some of the concerns about the generalisability of the findings.

Despite its limitations, this study provides an important contribution to the existing knowledge about the variability of cognitive decline by genetics. The associations between a genetic predisposition to educational attainment and cognitive decline that have been identified are especially relevant because it helps clarify the contributions

of observed education and genes to cognitive aging. Future research should also consider genetic effects when tapping on non-genetic factors in cognitive decline. The finding that the effect of genetic predisposition to educational attainment on cognition magnifies for mental status but declines for episodic memory and global cognition represents a need to understand the mechanisms between genetic endowment of educational attainment and cognitive decline from a biological angle.

Chapter 5. Conclusion

The overarching goal of this thesis was to provide a more comprehensive understanding of how health is influenced by both fundamental social causes and biological factors from a life course perspective. The three empirical papers illustrated several pathways through which fundamental causes theory and life course perspective can inform the study of biosocial determinants of health in later life.

This thesis makes several key contributions to the existing literature. First, research in sociology in particular has almost exclusively focused on the social predictors of health and thus ignored biological and genetic determinants. Social factors may have therefore been overestimated, but it is also very implausible that biological and genetic factors do not have some sort of influence on health. Second, by virtue of adopting this biosocial approach, I was able to move from the commonly used self-reported measure of health to the use of more objective indicators of biomarkers and genetic scores. Third, the majority of research that examines the link between health and SES is able only to discuss correlations between the two. By adopting an Instrumental Variable or Mendelian Randomisation methodology I have been able to adopt a more causal approach. Fourth, the majority of research on this topic has been conducted in Western settings and largely within the United States. By including an examination of China I am able to separate universal effects from those that may be context-specific. Finally, although there has been an increasing take-up of the use of genetic scores of educational attainment, no study to date has linked the genetic basis of educational attainment with cognitive decline.

5.1 Summary of Findings

This thesis sought to address three main research questions. The first set was: Is the SES-health gradient observed in Western societies persistent in China? Do individual health outcomes vary across provinces by economic development, income inequality, and health infrastructure affect health? Controlling for macro social determinants, are micro-level factors still associated with health? Using a series of multi-level regression models with baseline data from CHARLS, I find that education is robustly associated with various health outcomes. At the provincial level, economic growth is associated with better self-rated health, but also with obesity. Better health infrastructure tends to be negatively associated with health outcomes. This current study did not find supportive evidence that income inequality leads to poorer health outcomes. In conclusion, Chapter 2 shows that, in addition to individual characteristics, provincial variations in economic development, income inequality, and health infrastructure are associated with a range of health outcomes for Chinese midlife and older adults. Economic development in China might also bring adverse health outcomes for midlife and older adults.

After testing the generalisability of the SES-health link, the second main research question takes a step forward to identify causal pathways. How is educational attainment associated with health, and is the association causal? Can genetic marks be used as an instrumental variable in studying the causal relationship? What are the potential mechanisms mediating the relationship between education and health? Using genetic variants as an instrumental variable for education, I found evidence that a higher level of education has a causal effect on better health, measured by allostatic loads. Possible mechanisms include health behaviour, wealth, access to health

insurance and marriage satisfaction. The results support the hypothesis that education reduces the risk of poor health in older adults. Since both genetics and educational attainment matter for health, potential preventive interventions based on educational attainment may be able to improve the health of lower SES groups. This study also provides promising evidence that genetic factors may be a useful instrument for studying behavioural effects.

The third main research question focuses on whether the relationship between genetic predisposition of education, years of education and health strengthens or attenuates as individuals move into old age. How is the polygenic score for education associated with level of cognitive function? How is the polygenic score for education associated with cognitive change? After controlling for genetic effects, how do fundamental social causes associate with the level and slope of cognitive function with age? The results show that the trajectory of the link between genetic risk score of education and health is not uniform, but rather varies across different cognitive domains. Performances in global cognition and episodic memory are higher in high levels of PGS education groups compared to low PGS education groups for those under 85 years old, but this difference is completely attenuated over the age of 90 due to faster cognitive decline in the high PGS education group. In contrast, genetic variants buffer the age effect on mental status after the age of 75. Individuals in the high PGS education group have a lower rate of decline in mental status. The cognitive performance gap between different PGS groups remains constant for working memory and vocabulary in later life.

5.2 Limitations

There are a number of limitations to the studies in this thesis. First, the findings based on cross-sectional data in Chapter 2 raise the question of causality of contextual factors on health. It is difficult to test the possible reverse causality between SES and health (Subramanian et al., 2002; Yoshikazu et al., 2009). In addition, the effects of socio-economic context on health operate over many years. Subramanian and Kawachi (2004) provide evidence that income inequality may have a lag effect on health of up to 15 years. However, due to data limitations (i.e. there is no public data available on the Gini coefficients across provinces for previous years, nor a CHARLS dataset before 2011, since CHARLS 2011 is the baseline survey for future longitudinal studies), the lagged effects of contextual SES on health could not be measured in this study. Moreover, the results of this study further confirm a huge health gap between rural and urban areas. Regional income inequality in China not only occurs between-provinces, but also from within-province rural/urban differences. Due to the limitation of the data, this study is not able to test the relationship between income inequality on health with separate rural and urban analyses. Future studies on income inequality and health link in China should try to control for the rural/urban income gap if data permits.

Second, in Chapter 3, there is still a possibility that the genetic instrument used may violate the exclusion assumption by its association with other socioeconomic and behavioural factors besides education, that may also affect allostatic loads. Even though there is currently no consistent evidence from the literature about a pathway between the genes we used to construct polygenic score and allostatic load other than education, it cannot rule out the possibility that MR suffers from exclusion restriction

violations due to genetic pleiotropy, particularly when genetic risk scores are used (Burgess, Timpson, Ebrahim, & Smith, 2015). Moreover, the genetic variants may not be powerful enough to identify causal effects for single biomarkers on their own. While the genetic risk scores are not a weak instrument in a statistical sense, their effect may be too small to detect. The lack of significant effect on most of the biomarkers and some potential pathways may simply be due to an insufficient sample size.

Third, the measurement of cognitive status in the HRS has raised concerns. The cognitive measures in the HRS are only a partial assessment of cognitive limitations, which is a common issue in large-scale surveys given the constraints of time and modes of administration (Lachman & Spiro, 2002). The assessment is designed primarily for identifying possible cognitive impairment and dementia-related declines, and place less emphasis on the assessment of normal cognitive aging. The measurements are also limited in their ability to examine cognitively intact or high-functioning respondents, and thus may suffer from ceiling effects for some items. Because the assessment is via telephone, the survey design has to exclude a nonverbal test, which limits the representativeness of the battery. One should also be aware that hearing loss might affect response on the battery in a telephone interview.

5.3 Future directions

The thesis could be extended in several ways in future research. First, an inherent problem in multilevel analyses is to separate correlation from causality. Chapter 2 explores only correlation instead of causation of the SES-health link. Many potential confounders might affect both micro and macro fundamental causes and health. In

order to identify the causal impact of contextual factors on health, future studies can use case studies, exploiting natural experiments to disentangle the causation between macro-level SES and health when data and appropriate methods are available. Second, the samples in Chapter 3 and 4 are all of European ancestry, as the same data used by the Social Science Genetic Association Consortium to construct the estimated SNP effects for educational attainment. However, as the education-health gradient is still unclear in other populations, future research could perform this study in samples of racial groups when the information required is available. Finally, in order to further explore the genetic gradient in health changes as individuals get older, one could also examine physical health in addition to cognitive health. A more comprehensive measure of health may provide a more detailed picture of the interplay between social and genetic risk of developing a particular type of disease.

Appendices

Appendix 2-1:
Provincial-level Values of Independent Variables, Chinese Statistical Year Book 2012, China

Province	Respondents	Gini	Economic Development	Health-related Public Infrastructure
Yunnan	984	0.51	-2.28	-0.43
Fujian	469	0.70	0.41	-1.02
Qinghai	150	0.43	-1.98	1.98
Sichuan	1421	0.59	-1.47	0.15
Hebei	695	0.55	-0.96	0.04
Jiangxi	791	0.55	-1.84	-0.43
Xinjiang	67	0.59	-0.76	2.66
Beijing	88	0.40	6.00	3.85
Neimeng	794	0.50	0.23	0.66
Jiangsu	806	0.50	2.25	-1.17
Chongqing	221	0.53	-0.14	-0.56
Gansu	415	0.52	-2.97	0.45
Heilongjiang	307	0.52	0.37	0.33
Guangdong	836	0.53	1.73	-1.65
Liaoning	491	0.47	1.15	-0.06
Shanxi	493	0.54	-2.11	0.98
Shanghai	50	0.38	5.10	-1.27
Tianjin	139	0.49	3.45	-0.15
Zhejiang	646	0.57	2.31	-1.61
Jilin	386	0.47	0.38	0.31
Guangxi	553	0.50	-1.73	-0.74
Anhui	814	0.56	-1.01	-0.92
Hubei	532	0.53	-0.21	-1.06
Shan Xi	526	0.54	-0.80	1.13
Shandong	1313	0.53	0.97	-0.62
Henan	1325	0.55	-1.15	-0.53
Hunan	759	0.57	-1.29	-0.77
Guizhou	178	0.50	-3.63	-0.44
			Mean (SD)	
Total	16,249	0.54 (0.04)	-0.37 (1.61)	-0.34 (0.83)

Source: Chinese Statistical Yearbook (2012) and own calculation

Appendix 2-2:
Correlation Matrix for Provincial Level Variables, Chinese Statistical Year Book 2012, China

	Gini	ED	HRPI
Gini	1.00		
ED	-0.41 *	1.00	
HRPI	-0.30	-0.00	1.00

Appendix 3-1: Description of 35 genetic variants and their association with educational attainment (Okbay et al., 2016)

SNP	Chrom	Position	A1	A2	Beta	SE	P-value
rs112634398	3	50075494	A	G	0.0424915	0.00624049	9.859e-12
rs34305371	1	72733610	A	G	0.0366137	0.00445206	1.965e-16
rs35761247	3	48623124	A	G	0.0327182	0.00587823	2.611e-08
rs12987662	2	100821548	A	C	0.0221218	0.0025729	8.138e-18
rs192818565	17	43991515	T	G	0.0201206	0.00334786	1.86e-09
rs148734725	3	49406708	A	G	0.0263103	0.00272533	4.738e-22
rs9537821	13	58402771	A	G	0.0226535	0.00279293	5.011e-16
rs11712056	3	49914397	T	C	0.0252884	0.00252758	1.455e-23
rs9320913	6	98584733	A	C	0.0237908	0.00251515	3.101e-21
rs13294439	9	23358875	A	C	-0.0251798	0.00260688	4.484e-22
rs7306755	12	123767929	A	G	0.0245739	0.00307558	1.351e-15
rs10061788	5	87934707	A	G	0.0208132	0.00344989	1.608e-09
rs11588857	1	204587047	A	G	0.0209907	0.00308098	9.559e-12
rs2456973	12	56416928	A	C	-0.0175767	0.00265348	3.485e-11
rs4493682	5	45188024	C	G	0.0191973	0.00338219	1.377e-08
rs17119973	14	84913111	A	G	-0.0187993	0.00286051	4.958e-11
rs11191193	10	103802408	A	G	0.0183223	0.00263214	3.379e-12
rs4863692	4	140764124	T	G	0.0186209	0.002694	4.778e-12
rs1043209	14	23373986	A	G	0.0163121	0.00256359	1.981e-10
rs13402908	2	100333377	T	C	-0.0145261	0.00252452	8.705e-09
rs1402025	5	113987898	T	C	0.0176832	0.00300683	4.078e-09
rs11210860	1	43982527	A	G	0.0171336	0.00258816	3.583e-11
rs7955289	12	14653667	A	T	0.0161059	0.00261629	7.446e-10
rs2457660	2	60757419	T	C	-0.0156641	0.0026238	2.379e-09
rs61160187	5	60111579	A	G	-0.0179848	0.00256888	2.543e-12
rs2992632	1	243503764	A	T	0.0164456	0.00278079	3.347e-09
rs1008078	1	91189731	T	C	-0.0161342	0.00255896	2.875e-10
rs4500960	2	162818621	T	C	-0.0147272	0.00251018	4.431e-09
rs1871109	9	1746016	T	G	-0.0143699	0.00251882	1.164e-08
rs16845580	2	161920884	T	C	0.0165097	0.00259098	1.867e-10
rs12969294	18	35186122	A	G	-0.0176646	0.00264439	2.391e-11
rs17824247	2	144152539	T	C	-0.0179673	0.00254711	1.736e-12
rs12682297	8	145712860	A	T	-0.013863	0.00252837	4.191e-08
rs12772375	10	104082688	T	G	-0.0171148	0.00256478	2.499e-11
rs2964197	5	57535206	T	C	0.013885	0.00251631	3.434e-08

Note: A1 = Effect Allele; A2 = the other allele

Appendix 3-2:
Estimates from main Cox models. Age and Age at first interview are mean-cantered (Hazards Ratio)

	(1) AL	(2) SRH	(3) AL + SRH
AL	1.29*** (0.04)		1.18*** (0.04)
Self-rated Health		1.60*** (0.05)	1.59*** (0.06)
Age	1.16*** (0.02)	1.18*** (0.02)	1.18*** (0.02)
Age at First Interview	1.25*** (0.02)	1.27*** (0.02)	1.27*** (0.02)
Male	1.50*** (0.10)	1.41*** (0.10)	1.46*** (0.10)

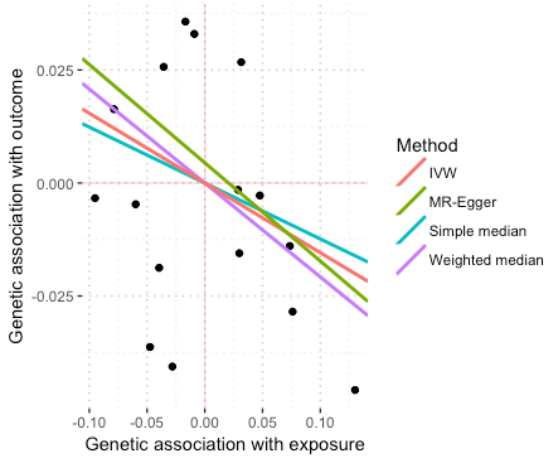
We performed several sensitivity analyses to test the robustness of our results and whether our genetic instrument violate any assumptions. Result from the main analyses is compared with results from MR-Egger regression (Bowden et al. 2015). MR-egger tests for pleiotropy.

Appendix 3-3: Sensitivity analysis with different MR methods

Method	Estimate	Std Error	95% CI	P-value
Weighted median	-0.208	0.109	-0.422 0.006	0.057
IVW	-0.154	0.070	-0.292 -0.016	0.034
MR-Egger	-0.217	0.138	-0.488 0.053	0.115
(intercept)	0.004	0.008	-0.012 0.021	0.595

MR-Egger regression found little evidence of pleiotropy (intercept: 0.004, p=0.595) and also a negative effect of education on allostatic load. However, the standard error is much larger, for the reason that MR-Egger take into account both intercept and slope, compared to our main analyses which only estimate the slope. In all, the casual effects are very similar.

Appendix 3-4 Comparison of different MR methods



Appendix 4-1 Model fit comparison

Model	Respondents	Observations	LL	AIC	BIC
GC					
(1) Empty	5,005	31,744	-120440.8	240887.6	240912.7
(2) Linear	5,005	31,744	-118298.9	236607.8	236649.6
(3) Quadratic fixed, linear random age effects	5,005	31,744	-116574.2	233162.4	233220.9
(4) Quadratic fixed, quadratic random age effects	5,005	31,744	-116596.1	233206.2	233264.8
EM					
(1) Empty	5,005	37,475	-153236.7	306479.4	306505
(2) Linear	5,005	37,475	-151719.6	303449.3	303491.9
(3) Quadratic fixed, linear random age effects	5,005	37,475	-150000.6	300075	300015.3
(4) Quadratic fixed, quadratic random age effects	5,005	37,475	-150084.5	300183.1	300242.8
WM					
(1) Empty	5,005	37,475	-172077.3	344160.6	344186.2
(2) Linear	5,005	37,475	-171795.4	343600.8	343643.5
(3) Quadratic fixed, linear random age effects	5,005	37,475	-171383.8	342781.7	342841.4
(4) Quadratic fixed, quadratic random age effects	5,005	37,475	-171416.4	342846.8	342906.5
MS					
(1) Empty	5,005	31,324	-148481.8	296969.5	296994.6
(2) Linear	5,005	31,324	-148308.7	296627.4	296669.2
(3) Quadratic fixed, linear random age effects	5,005	31,324	-145565.1	291136.1	291161.2
(4) Quadratic fixed, quadratic random age effects	5,005	31,324	-146258.2	292522.4	292547.5
Vocab					
(1) Empty	5,005	18,878	-78724.04	157454.1	157477.6
(2) Linear	5,005	18,878	-78716.29	157442.6	157481.8
(3) Quadratic fixed, linear random age effects	5,005	18,878	-78626.89	157267.8	157322.7
(4) Quadratic fixed, quadratic random age effects	5,005	18,878	-78626.89	157267.8	157322.7

Note: (1) is the random intercept-only model; (2) adds a linear random slope for centred age; (3) adds a fixed effect for age and age squared; (4) replaces linear random slope for age in (2) with a quadratic random slope for age. Additional random effect of ln(age) or age^3 does lead to non-convergence models.

Appendix 4-2 Results of Linear Mixed Models on Cognitive Measures (HRS 1998-2012), with African Americans

	GC		EM		WM		MS		Vocab	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Fixed Effects										
Intercept	48.403***	3.418	31.467***	1.034	19.953***	1.874	55.535***	2.814	21.784***	1.627
Age	-1.688***	0.270	-0.549***	0.090	-1.833***	0.090	-0.230***	0.020	-0.524	0.156
PGS_{Edu}	1.365**	0.275	0.488*	0.118	2.237***	0.158	0.429**	0.195	0.398***	0.115
Age × PGS_{Edu}	-0.026*	0.013	-0.028*	0.012	0.212	0.093	-0.004	0.011	-0.011	0.011
Female	1.196***	0.105	1.367***	0.667	-0.300***	0.033	-0.234***	0.051	0.227***	0.063
Age × Female	-0.043***	0.009	-0.021***	0.005	-0.009**	0.002	-0.010*	0.005	0.011	0.005
Years of Education	0.591***	0.020	0.332***	0.013	0.181***	0.006	0.235***	0.010	0.274***	0.012
Age × Years of Education	-0.001	0.001	-0.002	0.001	0.001**	0.001	0.006***	0.001	0.001	0.001
Social engagement (Ref. = Low)										
Middle Social engagement	0.240**	0.119	0.240	0.387	0.462	0.631	0.078	0.887	0.458	0.334
High Social engagement	0.036	0.259	0.369	0.976	1.482	1.016	2.836*	0.998	0.165	0.586
Age × Middle Social engagement	0.049*	0.025	0.455	0.423	0.069	0.056	0.258***	0.057	0.062	0.415
Age × High Social engagement	0.251***	0.059	0.472	0.612	0.187	0.112	0.497**	0.167	0.265	0.268
Smoke	-0.336**	0.124	0.069**	0.032	-0.051	0.030	-0.219***	0.063	-0.158*	0.082
Age × Smoke	0.020	0.016	0.227**	0.069	0.008	0.004	0.018*	0.009	0.011	0.009
Number of Drink per Day (Ref.= 0)										
Less than 4	0.108	0.081	0.113	0.048	0.007	0.044	-0.26	0.052	0.116*	0.057
More than 4	-0.557	0.328	0.201	0.177	0.059	0.079	-0.499	0.170	-0.279	0.263
Age × Less than 4	0.034***	0.008	0.016**	0.005	0.009***	0.003	0.018***	0.004	0.007	0.005
Age × More than 4	0.139**	0.043	0.039	0.023	0.022*	0.011	0.092***	0.021	0.070*	0.031
Number of Chronic Conditions (Ref. = 0)										
Few Conditions	-0.112	0.082	-0.168***	0.045	-0.017	0.021	0.073	0.049	-0.060	0.053
Many Conditions	-0.370*	0.165	-0.482***	0.104	-0.032	0.048	0.094	0.086	-0.012	0.126
Age × Few Conditions	-0.038***	0.008	-0.020***	0.006	-0.013*	0.006	-0.031***	0.004	-0.003	0.005
Age × Many Conditions	-0.091	0.015	0.032**	0.012	-0.021**	0.009	-0.070***	0.007	-0.016	0.009

Appendix 4-2 Results of Linear Mixed Models on Cognitive Measures (HRS 1998-2012), with African Americans. Continued.

	GC		EM		WM		MS		Vocab	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Random Effects										
Intercept Variance	5.334***	0.514	2.939***	0.332	2.497***	0.112	2.411***	0.242	6.045***	0.314
Age Variance	2.946***	0.047	1.910***	0.031	0.135***	0.002	0.109***	0.002	0.029***	0.009
Covariance of intercept, age	-0.316***	0.026	-0.365***	0.029	0.048	0.038	-0.253***	0.053	0.211	0.242
Model Fit										
-2LL	-88370		-95416		-62271		-64375		-26319	
AIC	176593		190761		128307		12889.9		51897.4	
BIC	176779.5		190998		128723		129694		52615.3	
n	5,710		5,710		5,710		5,710		3,436	
N	33,434		40,089		40,089		33,434		13,936	

Note: *** p<0.001, ** p<0.01, * p<0.05. 10 principal components to adjust for population stratifications.

Appendix 4-3 Results of Linear Mixed Models on Cognitive Measures (HRS 1998-2012), with European Ancestry Excluding Lowest 5%.

	GC		EM		WM		MS		Vocab	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Fixed Effects										
Intercept	51.652***	0.806	31.505***	1.023	48.368***	1.832	78.410***	0.879	29.365***	1.753
Age	-0.358***	0.070	-0.571***	0.085	-0.675***	0.148	-0.503***	0.092	-0.264	0.149
PGS_{Edu}	0.853***	0.139	0.765***	0.178	2.440***	0.319	1.087***	0.515	1.464***	0.317
Age × PGS_{Edu}	-0.026*	0.012	-0.032*	0.014	0.012	0.025	-0.008	0.016	-0.020	0.026
Female	3.630***	0276	7.249***	0.352	-4.611***	0.633	-1.132***	0.300	3.158***	0.624
Age × Female	-0.083***	0.024	-0.112***	0.029	-0.208**	0.050	-0.069*	0.032	0.031	0.052
Years of Education	1.380***	0.057	1.546***	0.073	2.649***	0.131	1.090***	0.062	2.384***	0.125
Age × Years of Education	-0.019***	0.005	-0.018**	0.004	0.024*	0.010	0.014*	0.007	0.001	0.010
Social engagement (Ref. = Low)										
Middle Social engagement	0.623*	0.315	0.339	0.374	0.583	0.651	0.743	0.361	-1.077	0.798
High Social engagement	0.377	0.557	0.488	0.585	1.614	1.015	0.769	0.646	-0.613	1.456
Age × Middle Social engagement	0.012	0.027	0.062	0.032	0.090	0.055	0.060	0.034	0.099	0.067
Age × High Social engagement	0.161*	0.064	0.202**	0.069	0.196	0.120	0.269***	0.181	0.202	0.180
Smoke	-0.520	0.347	-0.222	0.367	-0.948	0.646	-1.115**	0.393	-1.606	0.853
Age × Smoke	0.026	0.043	-0.036	0.044	0.128	0.078	0.099	0.055	0.161	0.099
Number of Drink per Day (Ref.= 0)										
Less than 4	0.097	0.221	0.324	0.248	-0.099	0.443	-0.104	0.256	0.602	0.575
More than 4	0.205	0.926	1.390	0.902	2.254	1.579	-0.504	1.070	-2.207	2.854
Age × Less than 4	0.052*	0.021	0.072**	0.024	0.139***	0.042	0.076**	0.027	0.086	0.051
Age × More than 4	0.226	0.121	0.160	0.122	0.342	0.214	0.335*	0.147	0.523	0.320
Number of Chronic Conditions (Ref. = 0)										
Few Conditions	-0.364	0.221	-0.617***	0.239	0.147	0.419	0.349	0.255	0.215	0.053
Many Conditions	-1.845***	0.459	-1.788**	0.570	0.293	1.024	-0.900	0.546	0.900	0.256
Age × Few Conditions	-0.058**	0.022	-0.088***	0.024	-0.206***	0.043	-0.160***	0.028	-0.051	0.051
Age × Many Conditions	-0.073	0.039	-0.152**	0.048	-0.462***	0.085	-0.183***	0.050	-0.176	0.097

Appendix 4-2 Results of Linear Mixed Models on Cognitive Measures (HRS 1998-2012), with European Ancestry Excluding Lowest 5%. Continued.

	GC		EM		WM		MS		Vocab	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Random Effects										
Intercept Variance	47.497***	1.776	88.751***	2.836	17.494***	0.252	48.616***	2.067	86.777***	6.181
Age Variance	0.128***	0.013	0.284***	0.021	0.806***	0.039	0.256***	0.024	0.097*	0.053
Covariance of intercept, age	-0.901***	0.134	-1.951***	0.194	0.064	0.041	-0.526***	0.209	0.738	0.536
Model Fit										
-2LL	-116250		-129187		-158273		-130182		-49273	
AIC	204538.6		278741.1		320907.4		187886.8		103448.7	
BIC	204835.9		279045.8		321212.2		188179.6		103716.1	
n	4,664		4,891		4,981		4,664		3,047	
N	27,675		34,303		34,974		27,281		12,359	

Note: *** p<0.001, ** p<0.01, * p<0.05. 10 principal components to adjust for population stratifications.

Appendix 4-3 Results of Linear Mixed Models on Cognitive Measures (HRS 1998-2012), with European Ancestry, controlling for covariates-gene interaction terms.

	GC		EM		WM		MS		Vocab	
	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.	Coeff.	Std.Err.
Fixed Effects										
Intercept	52.192***	0.859	31.408***	1.027	48.797***	1.829	84.219***	1.695	29.209***	1.752
Age	-0.669***	0.084	-0.592***	0.086	-0.679***	0.148	-1.080***	0.207	-0.266	0.149
PGS_{Edu}	1.972**	0.670	0.118	0.825	9.977***	1.616	4.794***	1.389	-0.759	1.237
Age × PGS_{Edu}	-0.029*	0.013	-0.032*	0.015	0.001	0.027	0.026*	0.012	-0.002	0.027
Covariates	yes		yes		yes		yes		yes	
Covariates × Age	yes		yes		yes		yes		yes	
Covariates × PGS_{Edu}	yes		yes		yes		yes		yes	
Random Effects										
Intercept Variance	55.194***	2.107	88.719***	2.849	303.563***	8.743	57.015***	5.966	85.672***	6.158
Age Variance	0.356***	0.020	0.208***	0.022	0.652***	0.062	1.031***	0.085	0.093**	0.052
Covariance of intercept, age	-1.397***	0.179	-1.906***	0.199	0.856***	0.552	7.667***	0.439	0.786	0.535
Model Fit										
-2LL	-107920.5		-140133		-160398.8		-136354.6		-51680.66	
AIC	215931		280355		320887.6		272799.2		103451.3	
BIC	216304.1		280736.1		321268.6		273171.7		103785.7	
n	5005		5,005		5,005		5,005		3,070	5,005
N	31,744		35,141		35,141		29,039		12,451	35,141

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