Mental Health and Cognitive Function during Growing Up and in Later Life:

Three Key Periods of Life

- A Life Course Perspective

Kumulative Dissertation

zur

Erlangung des akademischen Grades

doctor rerum politicarum (Dr. rer. pol.)

der Wirtschafts- und Sozialwissenschaftlichen Fakultät

der Universität Rostock

vorgelegt von

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Berlin, 30 Sep 2024

https://doi.org/10.18453/rosdok_id00005301

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Datum der Einreichung: 30 Sep 2024

Datum der Verteidigung: 28 Apr 2025

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Eidesstattliche Versicherung

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Berlin, 30 Sep 2024

Ying Zhou

Acknowledgements

I would like to express my sincere thanks to Gabriele Doblhammer for your supervision for the dissertation. Thank you for giving me the opportunity to do my PhD under your supervision, learning from your experience and expertise, hearing your advice and comments, and receiving a lot of motivation and support from you.

I would also like to thank Roland Rau for your impressive and attractive courses, which has provided me with a good basis for demography and empirical analysis.

I would also like to thank my co-authors (Hein Putter and Annelene Wengler in addition to Gabriele Doblhammer) for our fruitful collaboration. I have learned a lot from you.

Finally, I would like to thank my family including my husband Wei Wan, my parents Qiulong Zhou and Fengying Shao, and my little daughters Sophie Ruxue Wan and Luna Qinglan Wan. Thank you so much for your support and encouragement, and for your smiles and hugs.

Summary

Mental health refers to a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community; Cognitive function refers to mental capabilities or thinking skills by using which a person perceives, acquires, understands and responds to information from their environment. Cognitive decline may end up in dementia; poor cognitive function can be a sign of poor mental health but it must not be the case. In addition to this overlapping of definitions, there are associations between cognitive function and mental health. For example, the cognitive function at late working age is associated with mental health at early stages of life, and at later stages of life as well.

A life course perspective emphasizes that the development across generations requires a holistic consideration and that the development of an individual is lifelong. A life course perspective considers particularly critical stages, transitions and settings in order to optimize the functional ability, promote and restore health. For the development across generations or cohorts, this thesis investigates the time trend of cognitive function at late working age (55-69 years old), since this age group is sensitive to cognitive decline and may experience the retirement, an important transition in life. Such studies for this age group were few, but important as practical evidence for retirement policy. For the individual life-long's development, this thesis investigates another two periods of life: the first five years of life and the old old age of 75+. These two periods are particularly sensible to some factors for mental health and cognitive functions, since the individuals are relatively vulnerable and the functions may develop or weaken quickly during these two periods of life span.

Life course approach has two important models. In this thesis, the sensitive period model is applied and discussed for the abovementioned three sensible period of life. In addition, the education is a special variable of interest for mental health and

cognitive function, since there is a common sense that education is a protective factor for the mental health and cognitive function. The accumulation of risk model is discussed for the education effect on mental health and cognitive function, in particular to explore whether the earlier the better, and whether the longer the better?

For the late working age (55-69 years old), previous literature has showed that poor cognitive health is one of the main causes of early and unplanned retirement, and that approximately 10% of workers experienced a steep cognitive decline between 55 to 69 years old. Therefore, I conducted a study to investigate the time trend of cognitive decline at late working age in Europe, and analysed the time trend stratified by region, gender and education (in Study 1).

For the first five years of life, the start age of non-parental early education and care (ECEC) is an important factor, which still remains controversial for its effect on children's long-term mental development. Therefore, I conducted a study with coauthors to investigate the association between start age of ECEC and psycho-social problems in adolescence (in Study 2).

For the old old age (75+ years old), previous research has showed that lower extremity injury (LEI) increases the risk of mobility, social participation, dementia, long-term care and mortality. However, no previous studies were conducted to simultaneously evaluate the effect of LEI on functional and survival outcomes. Therefore, I conducted a study with coauthors to establish a multi-state model to exam the effects of LEI on both the functional outcomes (dementia and care need) and the survival outcomes (death) holistically (in Study 3).

As results, study 1 had three important findings. First, cognitive function of 55–69 year olds improved significantly between 2006 and 2015 in southern and central Europe, but not in northern Europe, although the latter had generally higher levels to begin with. Thus, the gap between European regions was narrowing. Second, in southern and

central Europe, the relatively low educated group, starting from the lowest level of cognitive function, tended to improve their cognitive functions faster than the middle and higher educated groups. Thus, the gap between the relatively low educational group and other educational groups was getting smaller. Third, among the less educated in southern Europe, men improved their cognitive functions faster than women.

Study 2 found that those who started non-parental ECEC between 2-3 years of age (reference) had the lowest scores of psycho-social problems in adolescence in the whole Germany and in West Germany. In comparison, those who started ECEC later than 3 years of age had higher scores of internalizing psycho-social problems in both West Germany (with statistically significant results) and East Germany (with a relatively larger effect size but insignificant results). Those who started ECEC before the age of 1 had statistically significantly higher scores for externalizing psycho-social problems in West Germany but not in East Germany, although fewer children started ECEC before the age of 1 in West Germany than in East Germany. These regional differences might indicate a selection effect in West Germany, where fewer parents took their children under one year to ECEC. Those who started ECEC at 1-2 years of age tended to have higher scores of externalizing psycho-social problems in both West and East Germany.

In Study 3, a key finding was that LEI in older people over 75 years old significantly increased the risk of the whole chain of adverse outcomes, from health to dementia, care need and death, and resulted in a large loss of years of life. Equally importantly, it has been found that these lost years were mainly years of better health and fewer limitations, regardless of whether the person started out healthy or with dementia or in need of care. LEI increased all age-specific probabilities of death and shifted the age peak of the probabilities of the transient transitions forward. LEI was generally associated with reduced life expectancy, but with a relatively longer life with dementia

and need for care.

As implications, the findings of Study 1 indicate that increases of the retirement age may be reasonable in southern and central European countries, because cognitive health is a key prerequisite for deciding the age at which people retire. Moreover, the findings provide evidence that education-based intervention approaches should be prioritized to low-educated people in southern and central Europe.

The findings of Study 2 suggest that for those starting ECEC over the age of 3 years old, more attention may be needed to prevent potential internalizing psycho-social problems, for example by providing more opportunities for social interaction through peer play. For those starting ECEC before the age of 2 years old, more attention is needed to prevent potential externalizing psycho-social problems. A stable and continuous relationship with nursery teachers, as well as not too long daily hours of ECEC, could be helpful. For parents who want to work earlier in the child's life, part-time participation in ECEC may be a compromise but a better option.

The findings of Study 3 suggest that for older people over 75 years old, prevention and timely treatment of LEI, as well as rehabilitative care after LEI, may be very important in delaying or reducing the onset of care need and death, not only in cognitively intact older people, but also in those with dementia. These measures will not only help to save years of life, but will also improve the quality of life of older people and reduce the burden on families, public health, and care system.

Overall, the thesis helps to understand and extend the knowledge of life course approach. In addition to the abovementioned implications which fulfil the theories of life course approach, the findings of Study 1 indicates that the cumulative positive effect of education on cognitive function may disappear once the length of education arrives a threshold. Furthermore, the results of Study 2 show that ECEC-exposure is more than a risk or preventive factor. An earlier start to non-parental education doesn't

always predict better or worse mental development in children. Neither does a later start to non-parental education. Therefore, the accumulation models of risk factor and sensitive period model alone cannot explain the effect of education on mental health and cognitive function. Instead, the relationship is more complex and depends on the age of children and length of education to a large extent. For such kind of relationship, an adaption-based approach or a relational developmental systems theory can add another dimension to life course thinking.

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ADL	Activities of daily living
AOK	Allgemeine Ortskrankenkasse (a public health insurer in Germany)
BADL	Basic activities of daily living
CIs	Confidence intervals
ECEC	Early Childhood Education and Care
FRG	Federal Republic of Germany
GEE	Generalized Estimating Equation
GDR	German Democratic Republic
ICD	International Classification of Diseases
ISCED	International Standard Classification of Education
KiGGS	German Health Interview and Examination Survey for Children and Adolescents
LEI	Lower extremity injury
Q1	First quartile
Q3	Third quartile
QIC	Quasi-likelihood under the Independence Model Criterion
QQ plots	Quantile-Quantile plots
rLE	remaining Life Expectancy
RDST	relational developmental systems theory
SDQ	Strength and Difficulties Questionnaire
SES	Social economic status
SHARE	Survey of Health, Aging and Retirement in Europe
YLL	Years of life lost

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List of Original Publications

Study I:

Zhou, Y. "Development over Time in Cognitive Function among European 55-69-Year-Olds from 2006 to 2015, and Differences of Region, Gender, and Education". *Comparative Population Studies*, 47 (Mar. 2022).

Study II:

Zhou, Y., Wengler, A., Doblhammer, G. "Association between the starting age of non-parental Early Childhood Education and Care (ECEC), and psycho-social problems in adolescence in West and East Germany – a natural experiment using data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)". *BMC Psychol*, 11, 403 (2023).

Study III:

Zhou, Y., Putter, H., & Doblhammer, G. "Years of life lost due to lower extremity injury in association with dementia, and care need: a 6-year follow-up population-based study using a multi-state approach among German elderly". *BMC Geriatrics*, 16(1), 1 (2016)

1. Introduction

This chapter begins with the definitions of mental health, cognitive function and the association between them. A life course approach for health is then introduced, which emphasizes that the stages of an individual's life are intricately intertwined, and that past, present and future generations influence each other. Following that, as an example of development over time across cohorts or generations, development over time in cognitive function at late working age is mentioned and shortly discussed. I also present that cognitive function at late working age is associated with mental health at early life stages, and with mental health at later life stages as well. After that, the two main models of life course approach (sensitive period model and accumulation of risk model) are introduced. Last but not least, the thesis objectives are presented, and the structure of thesis is clarified.

1.1 Mental Health and Cognitive Function

1.1.1 Definition of Health and Mental Health

According to World Health Organization, the definition of health is as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (1); the definition of mental health is as "a state of mental well-being that enables people to cope with the stresses of life, realize their abilities, learn well and work well, and contribute to their community. It is an integral component of health and well-being that underpins our individual and collective abilities to make decisions, build relationships and shape the world we live in." (2)

Mental health conditions include mental disorders, psychosocial disabilities, and other mental states associated with significant impairment in functioning, or distress (2).

1.1.2 Definition of Cognitive Function

Cognition refers to the mental capabilities or thinking skills by using which a person perceives, acquires, understands and responds to information from their environment (3). Cognition denotes „a relatively high level of processing of specific information including thinking, memory, perception, motivation, skilled movements and language" (4).

The cognitive function has several different names which might mean the same or slightly different, including cognitive ability, mental ability and general intelligence (5, 6).

1.1.3 Association between Cognitive Function and Mental Health

Per the definition itself, there is an overlap between mental health and cognitive function since mental health refers to behavioral, emotional and cognitive wellbeing as well (7). Also, cognitive decline may end up in dementia (7).

In addition to the overlapping part of the definition, there is also relationship between cognitive function and mental health in both directions and across the life span.

On the one hand, children's mental health is associated with cognitive development (8, 9). On the other hand, cognitive ability is associated with the incidence of mental health conditions (5, 10). These relationships will be shortly mentioned in a more detailed way in the below section 1.2.

1.2 A Life Course Perspective for Mental Health and Cognitive Function

1.2.1 Life Course Approach for Health

According to World Health Organization, "A life-course approach for health and well-being builds on the interaction of multiple promotive, protective and risk factors throughout people's lives." (11). "The life-course approach takes a temporal and

societal perspective on the health and well-being of individuals and generations, recognizing that all stages of a person's life are intricately intertwined with each other, with the lives of others born in the same period, and with the lives of past and future generations" (12). From the perspective of life course, the development of an individual is lifelong and no life stage is isolated from others; the development across generations also requires a holistic and historical consideration (13).

Adopting the life course approach means addressing the wider determinants of health throughout life and across generations and conducting evidence-based interventions to minimize risk factors and enhance protective factors at key life stages. Instead of focusing on a single condition at a single life stage, a life course approach considers the critical stages, transitions, and settings to optimize the functional ability, promote and restore health and wellbeing.

During my PhD study, I aim to better understand the three key stages of the life (i.e. late working age, first five years of life, and older than 75 years of life) from a life course perspective. Concretely, for mental health of individuals, how the exposure in these key stages of life will influence other stages of life, and how the factors exposed in other or the same stages of life will influence these key stages of life; for the cognitive functions of generations, how the development over time happens and how the factors influence these development over time across generations. Using more concrete research questions as examples, I aim to explore the risk or protective factors for these key life stages, and to better understand the trend over time.

1.2.2 Development over Time in Cognitive Function at Late Working Age

In the context that the world's population is aging, the development over time in the cognitive function at late working age is important for planning pension policies and for successful aging at work. However, there are few studies to investigate such a research question for this age group. In addition, the Survey of Health, Aging and

Retirement in Europe (SHARE) has data covering 10+ countries over 10+ years, which provides a good data base for investigating such a question.

Therefore, I conducted a study to investigate the time trends in cognitive function among 55-69-year-old Europeans from 2006 to 2015 and investigate how the development over time in cognitive function differ with person (age, gender, social status), place (geography) and time (birth cohorts) (as Study 1 in this thesis).

The investigation of development over time or across generations is one of the key points of life course, which emphasizes the past generations influence the current one, and the current one influences the future generations. The investigation of cognitive function over time at late working age, and the factors associated with it, can provide crucial information for predicting the future burden of disease and demand on health and social services (14), and may help to provide evidence of cognitive function at this key life stage for retirement policies.

In addition, the cognitive function at late working age is associated with the mental health at early life stages, and with the later life stages as well. These will be discussed briefly below in the sections 1.2.3 and 1.2.4.

1.2.3 Cognitive Function at Late Working Age is Associated with Mental Health at Early Stages of Life

The mental health at early stages of life is associated with the cognitive development (8, 9), thus further associated with cognitive function at late working age. The association between mental health at early life stages and the cognitive function at late working age may be explained by educational background, poverty, malnutrition, physical health, or bad parenting styles or friendships or partnerships, or other unhealthy lifestyle (such as stress and sedentary lifestyle), which are in turn closely related to mental health conditions (8). For example, boys in Grades 5 to 9 who are classified as having abnormal mental health scores have lower cognitive test

scores (8). Children with mental health problems such as Attention Deficit Hyperactivity Disorder (ADHD) obtain less schooling, are less likely to graduate from high school or university, and are more likely to do lower salary job (9, 15). Thus, children with mental health problems are more likely to have lower levels of cognitive function in early adulthood. This lower preserved cognitive ability could lead to earlier age onset of the beginning of cognitive impairments, which influences the cognitive function status at the late working age. Moreover, the children with mental health problems are less likely to get jobs demanding higher cognitive ability, thus less opportunity to use or train the cognitive function at daily work. This also has negative influence on the cognitive function status at the late working age.

Thus, the mental health of children is of great importance for cognitive abilities and mental health throughout life, including cognitive functions at late working age. One of the important influencing factors for children's mental health is the non-parental Early Childhood Education and Care (ECEC), in particular at the beginning years of the life.

Therefore, I conducted a study with coauthors to investigate the association between ECEC and mental health in adolescence (as Study 2 in this thesis).

1.2.4 Cognitive Function at Late Working Age is Associated with Mental Health at Later Stages of Life

The cognitive function at late working age is associated with mental health conditions such as dementia at later stages of life (5, 10). According to the diagnostic criteria of American Psychiatric Association, dementia is a syndrome that includes cognitive decline in more than one cognitive functional domain with consequences for daily social or occupational activities. People reach the thresholds of dementia diagnosis at different points in older age because they start with different levels of cognitive function at young adulthood (for example, compare the solid lines in Figure 1), or because they have different rates of cognitive decline (compare the solid lines with the dashed lines

in Figure 1), or because of the combination of this (for example, compare the earliest and quickest declined dashed line versus the latest and slowest solid line in Figure 1) (16). All of these three ways will present an association between the cognitive function at late working age and the incidence of dementia. For the first way, for example, the young people with lower cognitive ability are less likely to have longer years of education, to participate in enjoyable activities, or to be coping or valued, or to belong to a family of high social economic status (SES) (17). Thus, the lower preserved cognitive ability in the young adulthood may lead to poorer cognitive ability at the late working age, and consequently to earlier onset of dementia at later stages of life as well. The associations between the lower level of cognitive ability in young adulthood and a higher risk of dementia in old age were reported (10, 18–20). For the second way, for example, approximately 10% of workers experience steep cognitive decline during 55-69 years old (21). Such a steep cognitive decline at late working age is probably associated with the onset of dementia, if the cognitive impairment reaches the threshold of dementia diagnosis clinically and consequently the cognitive decline has strong influence on the daily life. The third way would be a combination of the abovementioned two ways.

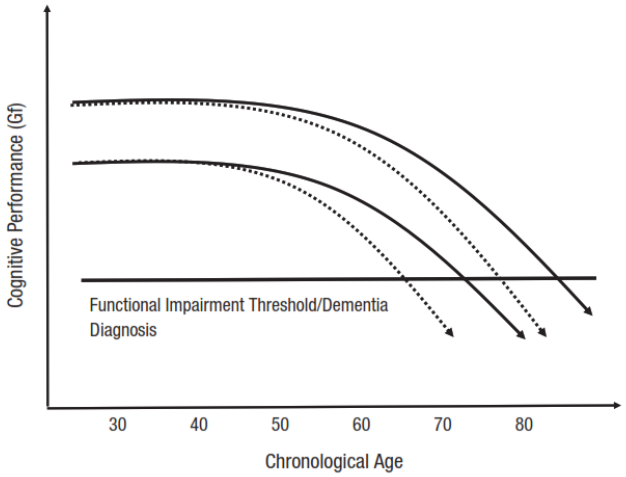

Figure 1: Schematic depiction of the importance of both levels of and changes in cognitive performance for understanding functional independence and dementia in older age
Gf = fluid abilities. This figure comes from the article of Lövdén et al (16).

In addition, the physical health may also influence the cognitive function at late working age and the mental health at the later stages of life. The traumatic injuries, in particular the lower extremity injury (LEI), increases the risk of mortality and limits the social participation, which in turns has negative impact on the mental health and cognitive function of the elderly (22–25). Moreover, the LEI and dementia as well as the physical limitation and cognitive dysfunction in the elderly can interact and, in particular, exacerbate each other, resulting in a profound combined effect on long-term care need and mortality (26, 27).

Thus, I conducted a study with coauthors to investigate simultaneously the association between LEI and dementia, care need, as well as death (as Study 3 in this thesis).

1.2.5 Sensitive Period Model: Three Key and Vulnerable Periods

From the life-course perspective, one of the main models is the sensitive period model. In the sensitive period model, the timing of an exposure during specific periods of development matters (28). Exposure at one particular point become more influential and effective than the same exposure happening earlier or later (28).

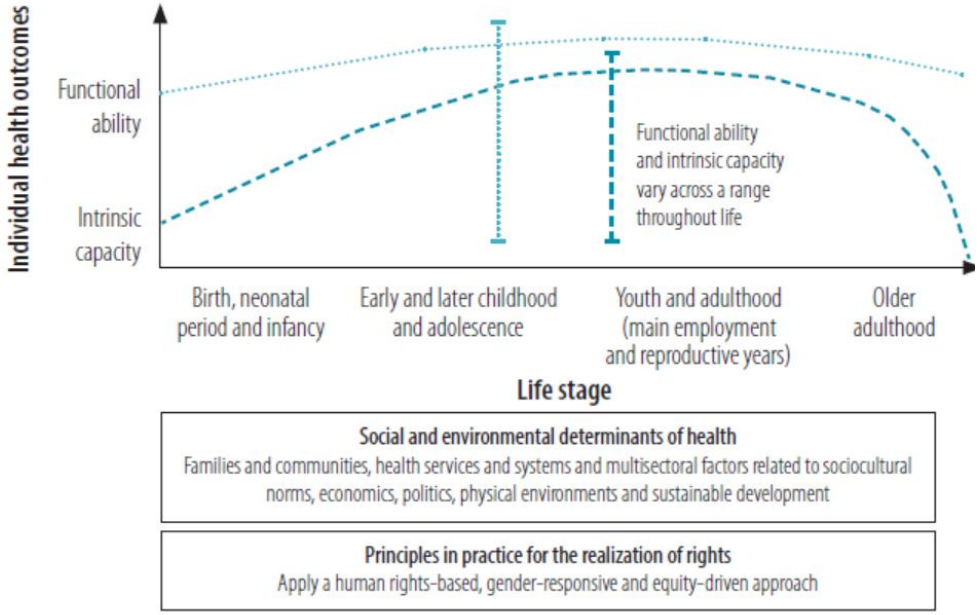

Figure 2: Conceptual framework for a life-course approach to health
This figure comes from the article of Kuruvilla et al.(29)

The Figure 2 illustrates the conceptual framework for a life-course approach to health (29). Intrinsic capacity refers to the sum of all physical and mental capacities; functional ability refers to the sum of the individual and environmental attributes that enable a person to be or do what they have reason to value, and is determined by the individual intrinsic capacity and the environmental and their interaction (29).

As the Figure 2 illustrates, during the period of growing from birth to the early childhood, as well as during the period from the end of the employment years to the older adulthood, the distance between functional ability and intrinsic capacity is relatively large. This reflects that these periods are key and vulnerable when the intrinsic capacities are developing very quickly in the early life and reducing very fast in the late life. During these periods, the influence of environments including risk or preventive factors are probably more critical.

Therefore, I want to discuss the following three key and vulnerable periods in this thesis.

1.2.5.1 Late Working Age

In the late working age (between 55 and 69 years of age), retirement can be one of the most important turning points. A better understanding of functional trajectories (e.g. turning points) may help for effective and efficient interventions from the perspective of life course approach (14).

Regarding the late working age, studies reported “On-the-job” mental retirement effect, i.e. the reduction in mental exercise may begin before actual retirement since workers have little motivation to invest in their human capital at late working age (30). Previous studies observed a negative effect of retirement on cognitive function and a positive effect of retirement on mental health such as depression, whereas a reverse causality may exist if the cognitive and mental condition of a worker influence his decision of retirement (7). Fisher et al. found that poor cognitive health at late working age is one of the main causes of early and unplanned retirement (31). Around 10% of workers

aged 55 - 69 experienced a steep decline in cognitive function (21). These workers experiencing steep cognitive decline were more likely to retire early, to “downshift” to a less cognitively demanding job, or to perform poorly at work (21, 32).

Therefore, the cognitive functioning of older adults at late working age is a critical factor in successful aging at work for individuals and in making policy of retirement age for society (32).

1.2.5.2 First Five Years

From birth to the age 5, the brain develops at an unrepeated lightning speed, and the responsive stimulation that comes from play, reading, singing and interactions with loving adults and peers play an essential role for the rapid brain developments (33-36). The early experiences is stored as a latent memory trace for a long time, and profoundly influence brain functions (including cognitive function) and health (including mental health) later in life (37). Early negative experiences such as insecure attachment, poor stimulation, maltreatment and stressful life in childhood may have long-run negative effects throughout the lifespan including low educational attainment and problem behavior in adulthood, by negatively changing brain architecture and later impairments in learning, behavior, and both physical and mental well-being (34, 38). If the mental health condition is not addressed well during growing up, then the mental health condition will extend to adulthood and consequently have a negative influence over the life course (39). In other words, the foundations of adult health (including adult mental health) are laid in early childhood (38), in particular the first five years of life.

Thus, how, where and with whom children spend their first five years is of great importance. Among them, the question “when to start with non-parental early education and care is best for children’s development” remains controversial but important.

1.2.5.3 Old old age

The old old age refers to the age at 75 and up (40). For the elderly at the old old age, the structure and function of brain dramatically changes with aging, and along with this, the cognitive abilities also declines (41). Moreover, people at old old age have higher risk of chronic diseases and physical functional decline such as reduced mobility, which may also lead to mental health conditions (42). Furthermore, people at old old age are more likely to experience events such as bereavement, or relocation (e.g. in another city or country) of children due to children's work or marriage. These may also result in loneliness, isolation or psychological distress in older people (42).

From the perspective of life course, *healthy biological aging* has three main components: first, survival to old age; second, delay in the onset of disability or chronic disease; and third, optimal functioning for the maximal period of time (43). The old old age is the age group during which the transitions to disability, chronic disease or die probably happen. A concrete example is the transition from health to dementia or care need, then to a combination of dementia and care need, and then to die. These transitions may be influenced by LEI (22–25). Previous research showed that LEI increases the risk of mortality and long-term care due to disability (22, 23). LEI also increases the risk of depression, delirium and restricted social participation due to limited mobility, all of which contributes to a cognitive decline and dementia onset (24, 25, 44, 45).

1.2.6 Accumulation of Risk Model: Education?

From the life-course perspective, another main model is the accumulation of risk model. In an accumulation of risk model, the total amount of exposure matters (46). Ben-Shlomo pointed out that the sensitive period models can be regarded as special sub-sets of accumulation model (14). In other words, the effects of exposure over different time periods can be added, but with increased weights for sensitive periods, instead of in a simple additive fashion (14).

In this thesis, I want to discuss education for this accumulation of risk model. There is a common sense that education is a protective factor for the mental health and cognitive function. But is this true over the whole life span? For example, for the first five years of life, is the exposure of earlier non-parental education and care associated with better mental health later on? For the late working age, whether and how the education influences the development in cognitive function over time in the population? Does education fulfil the accumulation of risk model, i.e. dose the total amount of education matter? If so, the earlier the start of education, the better the effect of education on mental health and cognitive function? The higher the level of education, the better the effect of education on mental health and cognitive function?

Education may influence cognitive function or risk of dementia in three ways, through a relationship between educational attainment and peak-level ability in the early adulthood, age-related changes in cognitive function, or the mixture of two (16). Education influences the cognitive ability in early adulthood, and this influence continues to lead to the individual differences of cognitive function at late working age and even later on (16). Well-educated people are more likely to have higher levels of cognitive function in early adulthood, leading to later age at which thresholds for cognitive impairment are reached (16). Moreover, well-educated people are more likely to acquire jobs demanding higher cognitive ability. Based on “use it or lose it” hypothesis, one who acquires an intellectually stimulation job will have higher preserved cognitive ability and experience on average slower cognitive decline, and thus postponing or preventing the age-related cognitive decline (32). In addition, well-educated people are more likely to get higher income and social economic status, as well as to have more healthy lifestyles and habits, which may help to improve cognitive function and to prevent the age-related cognitive decline at late working age (47, 48).

Education may also help with mental health. As mentioned above, good-education is

related with higher income and social economic status, more healthy lifestyles and habits, higher levels of cognitive function. These are also protective factors for mental disorders. However, it remains controversial whether it is better to bring the children to the non-parental early education, in particular at a very young age. The first life years are the sensitive period to build an attachment between young children and their parents (49). A secure attachment at early life years is the key for social and emotional development (36). If a child visits an institute of non-parental early education and care, then he or she may have a risk for insecure attachment with parents (50), and have to deal with the separation anxiety. Children get fear when they are getting away from their parents, which is called separation anxiety. Separation anxiety is a normal part of children's development, typically starting at around 6-12 months of age, remaining clearly observable until around 3 years of age, and then gradually decreasing (51). These points bring questions to the accumulation of risk model about education.

1.3 Thesis Objective

The thesis aims to investigate mental health and cognitive function during three key periods of life (first five years of life, late working age, and old old age) from a life course perspective, by determining the risk or protective factors at earlier stages of life which may influence the mental health and cognitive function at later stages of life, or by exploring the trends of cognitive function over time and how it differs with education, gender and place.

Concretely, the thesis has three sub-objectives during the three key periods of life:

- to investigate the changes in cognitive function over time at ages 55-69 in Europe and the differences linked to region, gender, and education (in Study 1);
- to investigate the association between starting age of non-parental Early Childhood Education and Care (ECEC) and psycho-social problems in adolescence (in Study 2);

- to investigate the effect of low extremity injury (LEI) on dementia, care need, and mortality in terms of remaining life expectancy at age 75 (rLE) and years of life lost (YLL) (in Study 3).

The intent of this thesis is to highlight how the risk or protective factors at earlier stages of life may influence mental health at later stages of life, and how the development over time in cognitive function differ with education, gender, place and time. The three examples are used to explore the risk and preventive factors for improving mental health and cognitive function, and to help develop effective preventive or health strategies.

1.4 Structure of Thesis

This thesis is divided into seven chapters. This introduction is followed by a literature review (chapter 2) regarding the three key periods (first five years, late working age and old old age), including detailed literature review for health issues and exposure factors of interest.

This thesis is a cumulative work consisting of three peer-reviewed articles (Studies 1, 2 and 3). In chapters 3, 4, and 5, these are presented and discussed with regard to hypotheses; materials and methods; and their main results. Finally, in chapter 6, reflection on the hypotheses is discussed. Moreover, this chapter also includes a discussion of the methodological strengths and limitations of the studies, the implications for theory, research and policy, as well as future research directions and prospects. In the end, an overall conclusion is presented in chapter 7.

2. Literature Review

2.1 Key Period of Life: Late Working Age

2.1.1 Health Issue of Interest: Trends in Cognitive Function

Previous research analyzing trends in cognitive function remains inconsistent in theories (*"success of success"* hypothesis versus *"failure of success"* hypothesis, *"Flynn-effect"* versus *"anti-Flynn-effect"*), as well as in results and conclusions of studies.

On the one hand, the *"success of success"* hypothesis suggests that there are factors that can improve the cognitive function of a population over time, delaying the onset of disability and leading to more people living longer and healthier lives (52). These positive factors for younger generations include higher education, better nutrition, more physical activity, less smoking, and better management of cardiovascular disease and diabetes (53, 54). In addition, according to the "*cognitive reserve*" hypothesis, younger generations also have more experience in cognitively demanding jobs, which leads to an increase in neural development and thus acts as a buffer against cognitive decline (32). Later-born cohorts at old ages have been reported to be associated with higher levels of cognitive performance, slower rates of age-related cognitive decline and a lower risk of incident cognitive impairment in Europe and United States (54–57).

The increase in cognitive ability from one generation to the next, the so-called *"Flynn effect"*, has been reported in both developed countries (including 15 European countries, United States, Japan, South Korea, Australia, Canada, and New Zealand) and developing countries (including China, India, Brazil, Dominica, Saudi Arabia, and Sudan) (53, 58, 59). A meta-analysis has estimated a global average IQ increase of 3 points per decade from 1909 to 2013 (53).

On the other hand, the *"failure of success"* hypothesis suggests that lower age-specific

mortality and longer life expectancy may increase the prevalence of chronic conditions including cognitive impairment, leading to poorer overall cognitive health in the older population (52). Studies looking at trends in cognitive function showed that prevalence of cognitive impairment tended to increase over time in the Netherlands (60) and the United States (56), and prevalence of dementia tended to increase over time in Japan (61) and Sweden (62). These studies of cognitive impairment and dementia usually focus on the population aged 65 and over, 75 and over, or 85 and over. However, little is known about the cognitive function and its development over time for adults at late working age (55–69 years old), although steep cognitive decline was reported during this period (21).

The plateauing or decline in cognitive ability from one generation to the next, the so-called *"negative Flynn effect"* or *"anti-Flynn effect"*, has been reported in European countries, including Norway (63), Denmark (64), the Netherlands (65), Finland (66), France (67), and Britain (68). However, most research on the negative Flynn effect has used samples of people under the age of 20 (63–69). Little evidence about this is available for late working age.

2.1.2 Additional Factors of Interest: Region, Gender and Education

Taking dynamic time periods, geographical areas, and gender into consideration, the trends in the cognitive function studies are more complicated, as the development of cognitive function over time may vary between different population subgroups of geographical regions, gender, and other potential factors such as education (57, 69, 70). Studies of both Denmark and Norway found early increases in the Flynn effect, followed by stagnation through the 1990s in both countries, and a slight decline since the late 1990s in Denmark (63, 71). Weber et al. reported greater increases in cognitive performance for southern Europeans (compared to central and northern Europe) and for females (compared to males) in northern and central Europe (72). However, the larger gain of females was not observed in the southern Europe (72).

Education appears to be one of the key factors in time trends in cognitive ability in some countries, while it does not appear to be influential in others (71, 73). Well-educated people are more likely have higher earnings and incomes, greater social and cultural participation, healthier habits and lifestyles, and jobs which require higher cognitive skills. All of these can help prevent age-related cognitive decline (47, 48). However, it remains unclear whether and how education moderates the trajectory of cognitive change (74, 75). Some of the inconsistency in previous evidence may lie in the threshold level of education required for an effect to occur (74).

2.2 Key Period of Life: First Five Years

2.2.1 Health Issue of Interest: Psycho-Social Problems

Psycho-social problems are one of the major health issues with a prevalence of around 17% - 20% among children and adolescents in Germany, and lower SES increases the risk (76). Psycho-social problems in children and adolescents have a significant impact on their ability to achieve, their quality of life and their participation in society, as well as leading to significant medical costs to the society (77). Psycho-social problems consist of externalizing problems (such as aggressive and oppositional behavior, high impulsivity and hyperactivity) and internalizing problems (such as high social anxiety, depressive symptoms and withdrawal) (78).

2.2.2 Exposure Factor of Interest: Starting Age of ECEC

ECEC refers to any regulated non-parental arrangement that provides education and care for children from birth to compulsory primary school age (79). Although there is growing evidence of the beneficial effects of ECEC for children over the age of 3 (79, 80), the empirical evidence is mixed for children under the age of 3 starting ECEC (79, 81, 82).

The *"attachment theory"* may support the assumption "*earlier is worse*" regarding

ECEC-start-age on children's psycho-social development. It states that a secure and warm attachment at early years of life forms the core of the human social and emotional development, and a basis for developing a sense of trust (36). Previous studies reported the early ECEC as a risk factor for insecure attachment, particularly when the quantity of ECEC exposure was high in the first 15 months, or the ECEC was of low quality or unstable (50). Early attachment insecurity may increase the risk of externalizing psycho-social problems (83).

Contrarily, the theory of "*critical and sensitive periods for social skills and language developments"* may support the assumption "*earlier is better*" regarding ECEC-start-age on children's psycho-social development. During the critical and sensitive periods for social skills and language, skill developments and brain architecture are shaped in a quick and efficient way (84). Nelson et al. reported that the sensitive period for language 'closes' at 15 months, and for social skills at 20 months (85). Attending ECEC is likely to provide more opportunities to play and interact with peers, develop social skills and have close friends, which may reduce the risk of internalizing problems (86).

Furthermore, it remains unclear whether and to what extent the effect of ECEC on psycho-social problems continues beyond early childhood. Most studies, which investigated the impacts of ECEC on psycho-social problems, had a short-term follow-up, such as up to primary school (81, 79); or were limited to investigating long-term effects on secure attachment states of mind or on school performance only (87, 88).

2.2.3 Additional Factor of Interest: West and East Germany

When reunited in 1990, the German Democratic Republic (GDR) adopted the political, economic and legal institutions of West Germany. This included one year of paid parental leave from 2005 and another two years of unpaid parental leave per child. As

two parts of one country, West and East Germany also have lots of similarities, including language, family policies and education systems.

However, between 1949 and 1990 Germany was divided into the GDR and the Federal Republic of Germany (FRG). The different historical backgrounds resulted in different cultural and societal norms regarding women's work and family roles, which continue to today. In the GDR, women were encouraged to work by emphasizing the principle of equal pay for equal work, a generous maternity leave policy, and the availability of free non-parental ECEC. Housewives were devalued by being called “parasites”. This was in an environment where Soviet-style gender equality was popular. On the other hand, in the FRG women were discouraged from working by the tax and benefit system and scarcity of non-parental ECEC. Working mothers were devalued by being called “raven mothers”. This took place in an environment where more traditional attitudes to gender roles were evident (89). Therefore, the proportion of women in employment is different between West and East Germany (56% of women in West Germany and 89% of women in East Germany worked in 1989; 12% of mothers in West Germany and 30% of mothers in East Germany worked fulltime in 2017). Moreover, the availability and quantity of ECEC and its usage is also different between West and East Germany (8% of children aged 0-3 years in West Germany and 40% of children aged 0-3 years in East Germany attended ECEC in 2006) (89, 90, 91). Even today, several decades after reunification, cultural differences regarding the role of women persist (89). Mothers in East Germany still follow the more egalitarian gender norms they grew up with, returning back to work earlier and tending to work more hours after childbirth than mothers in West Germany (89).

The different development in the two parts of Germany is an opportunity to investigate the effect of ECEC on psycho-social problems in adolescence as a kind of *natural experiment*. Similarly to twin studies, this natural experiment can to some extent control for unmeasured or unknown confounders.

2.3 Key Period of Life: Old Old Age

2.3.1 Health Issue of Interest: Dementia

Dementia is a key age-dependent disorder, characterized by progressively disabling impairment of several cognitive functions, and dramatically contributes to disability and dependency, thereby challenging the health care system substantially (92). The incidence and prevalence of dementia increases significantly with age, once the older adult is over 75 years of age (93). Incidence with dementia doubles approximately every 5-9 years in age, and the global number of people with dementia is estimated to be approximately double every 20 years from 44.4 million in 2013 to 75.6 million in 2030 and to 135.5 million in 2050 (92). In particular, the behavioral and psychological symptoms of dementia often result in disability and dependence, thus having considerably adverse influence on the patients' quality of life, on the caregivers' strain, and on the burden of health care system such as institutionalization and long-term care need (92).

2.3.2 Exposure Factor of Interest: Lower Extremity Injury

Geriatric traumatic injury is as another disorder associated with old age (94). At old old age, physiological reserve capability decreases; physiological response to injury degenerates; age-related multimorbidity and polypharmacy are also on the rise. All of these increase the risk of geriatric trauma, and worsen disability and mortality after injury (95, 96). Traumatic injuries are the fifth most common causes of death among older people, and pose a health care challenge (94, 95).

The lower extremities include the hip, thigh, knee, lower leg, ankle and foot, and these are one of the most likely areas of the body for traumatic injury in older adults (97, 98). In other words, LEI includes not only hip fractures but also other types of fractures and fall-related LEI. All of these LEI increase the risk of dying, becoming disabled and needing long-term care (22, 23). LEI is also associated with a reduction in mobility and

participation in social life (25, 24) .

Previous research suggests a link between LEI and dementia in older adults (44, 99, 100). Dementia over-proportionally increases the risk of falls and LEI (101, 102). In turn, LEI can cause depression, delirium, reduced physical and social activity. All of these could contribute to a cognitive decline and the onset of dementia (44, 45, 103-106).

2.3.3 Additional Health Issues of Interest: Death and Long-term Care Need

A number of studies have given evidence that geriatric LEI significantly increases mortality (23, 24, 107–111). The mortality rate after a LEI is even higher in people with dementia than in people without dementia (107, 112, 113). Moreover, the impairment in basic activities of daily living (BADL), which is highly associated with long-term care need, before LEI is also significantly associated with increased risk of mortality after LEI (114).

3. Hypotheses

3.1 Study 1: Development over Time in Cognitive Function in Europe

Hypothesis 1.1: Cognitive performance became better over time among 55-69-year-old adults in Europe from 2006 to 2015.

Hypothesis 1.2: There existed differences of changes in cognitive function over time linked to region, gender and education for 55-69-year-old adults in Europe from 2006 to 2015.

3.2 Study 2: Association between Starting Age of ECEC and Psycho-Social Problems in Adolescence in West and East Germany

Hypothesis 2.1: There is an association between ECEC-start-age and psycho-social problems in adolescence.

Hypothesis 2.2: There is no difference in West versus East Germany regarding the association between ECEC-start-age and psycho-social problems in adolescence.

3.3 Study 3: Years of Life Lost due to Lower Extremity Injury in Association with Dementia, and Care Need

Hypothesis 3.1: LEI increases the risk of getting dementia, care need and dying in the elderly aged 75+.

Hypothesis 3.2: There exist years of life lost due to LEI for the elderly aged 75+.

4. Materials and Methods

4.1 Data Sources

4.1.1 Study 1: Development over Time in Cognitive Function in Europe

For Study 1, the data source was the Survey of Health, Aging and Retirement in Europe (SHARE), which is a longitudinal, nationally representative, population-based, international, and harmonized survey (115). Data from adults aged 55-69 years in Waves 2, 4, 5, and 6 of SHARE were used for Study 1. Wave 1 was excluded because education was measured differently from subsequent waves. Wave 3 was also excluded because of its focus on respondents' life histories. Wave 7 was excluded because it was designed to focus on both life history and panel information using a shorter, condensed set of questions compared to the regular panel questionnaire. Thus, Verbal Fluency at Wave 7, one of the key variables in this study, has a large number of missing values because only respondents who participated in SHARELIFE at Wave 3 were asked about Verbal Fluency. Only countries that participated in all waves were included in this study, except for the Netherlands because the Netherland had different design in Wave 6 compared to other countries. Ten countries were therefore included in the analysis: Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, Spain, Sweden, and Switzerland. Although some waves covered two calendar years, the first calendar year was used as the survey year, i.e. 2006, 2011, 2013, and 2015 for Waves 2, 4, 5, and 6 respectively. Italy and Spain were classified as southern Europe; Austria, Belgium, the Czech Republic, France, Germany, and Switzerland as central Europe; and Denmark and Sweden as northern Europe.

4.1.2 Study 2: Association between Starting Age of ECEC and Psycho-Social Problems in Adolescence in West and East Germany

For Study 2, the data source was the German Health Interview and Examination

Survey for Children and Adolescents (KiGGS), which is a prospective cohort study of 17640 children who were first interviewed in 2003-2006 (baseline wave) and followed up in two waves until 2014-2017 (wave 2) (116, 117). Wave 1 was excluded from our descriptive and inferential analysis, because telephone interviews were used in wave 1 whereas self-administered questionnaires were used in the baseline wave and wave 2. Wave 1 data were only used to classify the age at which ECEC started, as this age could only be clearly defined by using the data from the baseline wave and wave 1 together (described in Section 4.2.2.1).

The sample flow chart (Figure 3) shows how the sample for the Study 2 was selected. We included children who were 3 and 4 years old at the baseline wave and those who were younger than 18 years old and participated in wave 2. In addition, only children with a complete Strength and Difficulties Questionnaire (SDQ) and ECEC-start-age were included. Thus, our analysis sample consisted of 1022 children.

We selected children aged ≥ 3 years at the baseline wave, so that a clear classification of ECEC-start-age can be made based on the data from the baseline wave and wave 1. We excluded children aged 5 and over, as they may be preparing to start school or may even be in school in Germany.

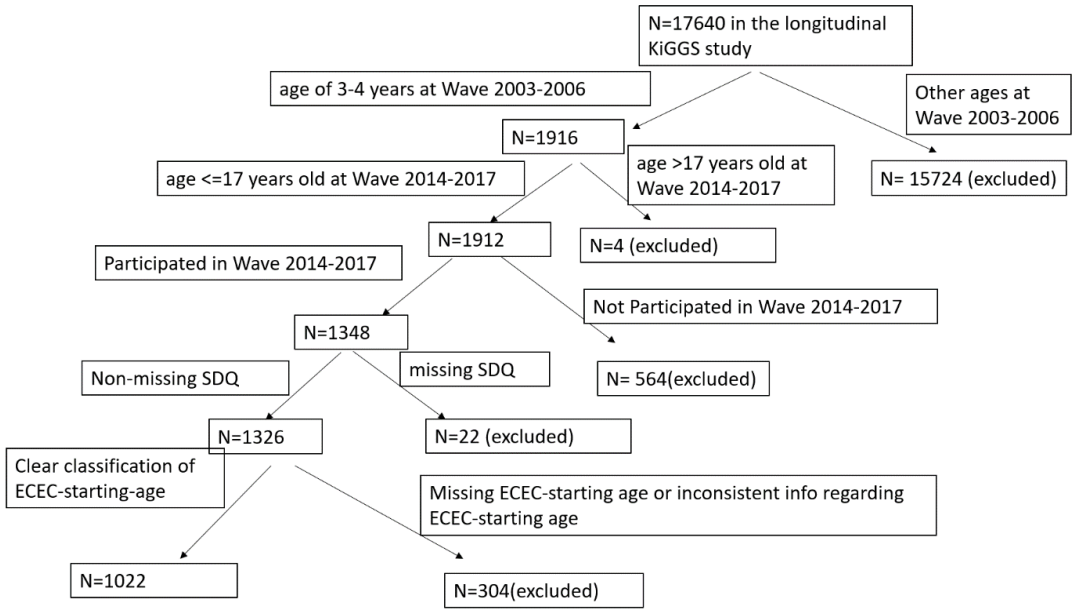

Figure 3: Flow chart for the sample in Study 2

4.1.3 Study 3: Years of Life Lost due to Lower Extremity Injury in Association with Dementia, and Care Need

For Study 3, the data source was claims data from Allgemeine Ortskrankenkasse (AOK), the largest public health insurer in Germany, which covered about a third of the German population. In the first quarter of 2004, a national random sample of 2.2% was drawn from AOK members aged 50 and over, regardless of whether they visited a doctor. Data from 2004 were used to classify the initial states, and 62103 individuals in our sample aged between 75 and 95 were followed from 2005 to 2010. This age group typically undergoes various transitions to dementia, needing care and dying. Medical and care needs data were available for each person for each quarter from both the inpatient and the outpatient sectors, with the exception that the data on the need for long-term care from 2004 to 2006 were only documented once a year.

4.2 Methods and Statistical Analysis

4.2.1 Study 1: Development over Time in Cognitive Function in Europe

4.2.1.1 Variables of Interest

Cognitive Function Measures

In order to measure cognitive function, SHARE uses temporal orientation, numeracy, immediate and delayed recall testing, and verbal fluency. The focus of this study is on recall tests and verbal fluency for the following four reasons. First, recall tests and verbal fluency are sensitive to cognitive ageing (118, 119). Second, recall and verbal fluency separately reflect two key dimensions of cognitive performance, namely fluid intelligence/working memory and crystallized intelligence/knowledge (72, 120, 121). Crystallized intelligence refers to an individual's stored knowledge and learned ways of operating; fluid intelligence refers to the ability to think logically and solve novel problems regardless of the prior knowledge one has acquired, and is highly related to

working memory (120-124). Third, the temporal orientation in SHARE was heavily influenced by ceiling and floor effects due to its skewed distribution. Fourth, there was limited variability in the ordinal variable resulting from the numeracy test, and there was a large number of missing values in the numeracy tests at Wave 6 (125, 126).

The recall test was used as a measure of the performance of the episodic memory. The respondent listened to a list of ten words, performed one recall test immediately (immediate recall test), and another after a delay (delayed recall test). The number of words correctly remembered by the respondent was recorded and ranged from 0 to 10 for both tests. The Recall variable was the average of the scores on the immediate and delayed recall tests.

Verbal fluency was used as a measure of executive function. Respondents were asked to list animals. The number of animals that were correctly named by the respondent in one minute was counted and stored as a raw variable of verbal fluency. Outliers were defined as scores more than 2.5 standard deviations away from the mean per wave. These outliers were replaced by the wave-specific maximums within 2.5 standard deviations. Verbal fluency without outliers therefore ranged from 0 to about 40. In addition, the variable was multiplied by 0.25 so that it had a comparable scale from 0 to about 10, similar to the Recall variable.

Educational Level

The International Standard Classification of Education (ISCED) 1997 was used to make the education comparable between countries. ISCED categories ranged from 0 to 6, with higher categories indicating higher formal education. In order to improve comparability between groups over time, the ISCED 1997 grades were multiplied by years of education and further categorized into groups of “low”, “middle”, and “high” Adjusted Educational Levels for each survey wave. These three groups are the bottom 25% (lowest to first quartile Q1), the middle 50% (first quartile Q1 to third quartile Q3)

and the top 25% (third quartile Q3 to highest) for each survey wave.

4.2.1.2 Modelling Strategies and Statistical Analysis

In addition to descriptive analysis, Generalized Estimating Equation (GEE) models were estimated using a linear link function with normally distributed error terms and an unstructured covariance matrix to account for the dependency of observations between waves. The GEE model is also able to handle missing values and unbalanced cases, and is particularly robust to large sample sizes.

Separate GEE models were run for Recall and Verbal Fluency to explore their association with the time trend measured by the numeric survey year, adjusting for gender, region, education, and the interactions of gender by survey year, education by survey year, and region by survey year. Further adjustment was made for age at interview and whether this was the first time having participated in SHARE. In subsequent stratification analyses, the association between cognitive function and time was further explored using GEE models stratified by region, gender, and education.

A sensitivity analysis was performed for the other common covariance structures (autoregressive, exchangeable, and independent). The goodness of fit statistic Quasi-likelihood under the Independence Model Criterion (QIC) was used to compare the GEE models (127). Furthermore, a sensitivity analysis was carried out to include Wave 7. Finally, in order to investigate the differences and similarities between the two operationalizations of education, the conventional ISCED classification of education (ISCED-97 = 0-2, 3-4, 5-6 as low, middle, and high levels of education) was additionally used in a separate analysis.

All analyses were performed using SAS 9.4 (SAS Institute, Cary NC).

4.2.2 Study 2: Association between Starting Age of ECEC and Care and Psycho-Social Problems in Adolescence in West and East Germany

4.2.2.1 Variables of Interest

Psycho-social problems

To measure psycho-social problems in adolescence, we used the total difficulties score and four subscales of the SDQ at wave 2 (128). The scores for conduct problems and hyperactivity were summed to obtain the score for externalizing psycho-social problems. The scores for emotional symptoms and peer problems were summed to obtain the score for internalizing psycho-social problems. Each score ranged from 0 to 20 (for externalizing or internalizing psycho-social problems). The total score for the SDQ was the sum of the scores for externalizing and internalizing psycho-social problems, and it ranged from 0 to 40. The higher the scores, the more psycho-social problems the children may have.

ECEC-start-age

The age at which ECEC was started (ECEC-start-age) was derived from the data of the baseline wave and of wave 1 on the basis of the following two questions: “Was or is your child only cared for in the family before starting school?”. If the answer was no, then parents were asked about the ECEC-start-age. Concrete derived rules can be found in the Supplementary Materials of Study 2.

Potential confounders

The majority of confounding variables – SES, migration status, number of older siblings (order of birth), family situation and family cohesion, birth weight, obesity/overweight, age of mother at childbirth, employment status of mother, and region (east/west Germany) - were collected at the baseline wave. Only a few confounding variables -

age as adolescents, schooling type, and parents' divorce - were collected or derived at wave 2. Exact operationalizations and some previous findings on these confounders can be found in the Supplementary Materials of Study 2.

4.2.2.2 Modelling Strategies and Statistical Analysis

In addition to descriptive analysis, linear regression was used to explore the relationship between ECEC-start-age and psycho-social problems in adolescence in the whole Germany, adjust for age, gender and other potential confounders (as mentioned above) in the model. We also ran a similar linear regression, but with stratification by West and East Germany. In an additional analysis, we included an interaction variable of region (West/East Germany) by ECEC-start-age in the linear regression of the whole Germany. In all linear regressions, we used the longitudinal weight in order to adjust for possible sample bias due to selective re-participation in the follow-up study (129). Moreover, in all linear regressions, we used the category "Age 2-3" as the reference group for the ECEC-start-age. Furthermore, we checked the linear regression assumptions (including normality and homoscedasticity) by means of using standardized residual graphics including histograms, normal Quantile-Quantile (QQ) plots and scatterplots of standardized residuals versus predicted values. We also used the "PROC SURVEYREG" procedure in SAS for a robust variance estimation method (Taylor series linearization method) to address the deviation from linear regression assumptions. A sensitivity analysis was carried out to compare the results with and without outliers. Outliers were defined as values more than 2 standardized residuals away from zero in the linear regression.

In an additional analysis, Chi-square tests were used to analyze the distribution of baseline variables of interest (including SES) by ECEC-start-age in West and East Germany separately.

All analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

4.2.3 Study 3: Years of Life Lost due to Lower Extremity Injury in Association with Dementia, and Care Need

4.2.3.1 Variables of interest

The International Classification of Diseases (ICD)-10 was used to identify dementia (Dementia: G30, G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05.1). A validation procedure was developed to take account for false positive diagnoses. First, for outpatient services, only diagnoses reported as “verified” by a physician were included, whereas for inpatient services, only discharge and secondary diagnoses were included. Second, only diagnoses with a second occurrence in the same quarter by different types of physicians or over time were included. The only exception was when a patient died immediately after being diagnosed with dementia in the same quarter (130).

Care need was defined as having received benefits from the statutory long-term care insurance in Germany. This insurance, which is compulsory for all citizens in Germany, covers long-term care at home or in an institution (131). All insured persons, regardless of age or wealth, are entitled to long-term care benefits. The need for care is assessed by the Medical Advisory Service of the Statutory Health Insurance Funds. On the basis of the German law on long-term care insurance in the period of the study (2004-2010), care need in our study refers to a minimum of 90 minutes of assistance per day, with more than 45 minutes per day being for basic care in the BADLs such as washing, eating or dressing. This means that dementia patients with intact Activities of Daily Living (ADLs) do not receive benefits and are therefore not coded as being in need of care in our study.

Our exposure of interest was LEI, namely injuries to the hip and thigh, knee and lower leg, and ankle and foot (98). ICD was used to identify LEI (S70 - S99 and the associated T-section of the ICD codes, see details in the Supplementary Materials of Study 3).

4.2.3.2 Modelling Strategies and Statistical Analysis

In addition to descriptive analysis, a multi-state model was applied to assess the risk of LEI for the eight possible transitions. The eight possible transitions are between the four transient states *Healthy*, *Dementia*, *Care*, *Dementia & Care*, and the only absorbing state *Dead* (Figure 4). The state *Healthy* includes persons without a diagnosis of dementia and without need for care; the state *Dementia* includes persons with a diagnosis of incident or prevalent dementia but not in need of care; the state *Care* includes persons with incident or prevalent care needs but without a diagnosis of dementia; the state *Dementia & Care* includes persons who have both a diagnosis of dementia and are in need of care. The model does not take into account recovery from dementia and from needing care, which is reflected in Figure 4 since the relevant transitions are absent. Because there is currently no treatment for dementia, and mild cognitive impairment, which can be reversible, has its own ICD-10 number and is not part of our study. Recovery from need for care is excluded due to the very small number of cases with a transition from need for care to no need for care. Individuals may experience multiple transitions between different states during the follow-up period; since it is not possible to recovery, no multiple transitions of the same type exist.

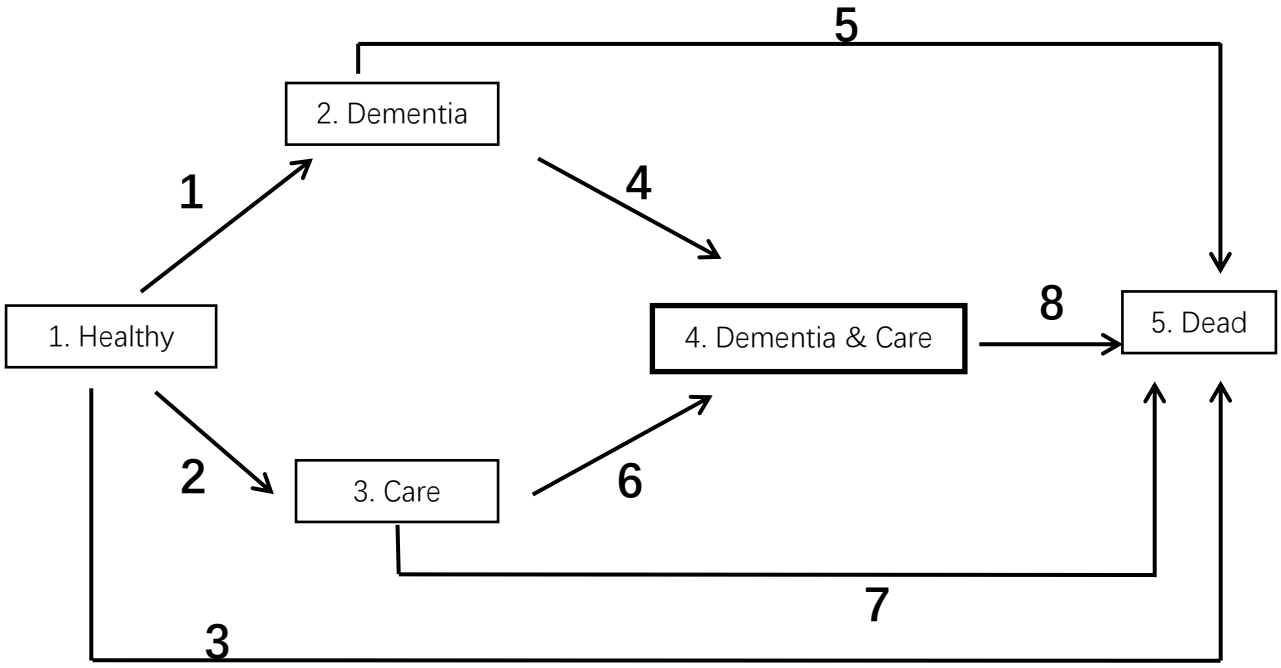

Figure 4: Multi-state model of the stages of healthy, dementia, care and dead
The boxes represent five states: (1) *Healthy* refers to no dementia, no care need. (2) *Dementia* includes incident and prevalent dementia, but without care need. (3) *Care* includes incident and prevalent care need, but without dementia (4) *Dementia & Care* refers to both dementia and care need. (5) *Dead* refers to a dead state, the only absorbing stage in our model. The other four states are transient states. The arrows represent the eight transitions from the ORIGIN STATE to the DESTINATION STATE.

Stratified Cox proportional hazards models were estimated. In the models, LEI was used as a time-dependent and transition-specific explanatory variable, sex as a stratification factor, and age as process time, taking into account right censoring and left truncation (132). Right censoring was defined as changing to another health insurance company, reaching the age of 95 during the follow-up and being in one of the transient states on 31 December 2010. For each person, the date of birth was given; the date of death was recorded if he/she died during the study period; the date of diagnosis of dementia and LEI was also available, which was collected quarterly; and the data on care needs were also available for each quarter of the year between 2007 and 2010. The age on 1 January 2005 was used for the left truncation. In addition, the age of entry into the origin state of each transition was used as the left truncation for that transition. The variables dementia, care need, and LEI were treated as “ever”-variables. For these variables, the value was assigned as one for the first time they

were recorded in the data and thereafter; otherwise these variables have a value of zero. As the care need was only recorded annually before 2007, it was assumed to occur in the middle of the year if the persons survived to the end of that year; for persons who died in that year it was assumed to be occur in the middle of the survival period. In addition, given our quarterly data, we assumed that all the transitions and LEI occurred at the midpoint of each quarter with the following exceptions: if a person experienced multiple transitions and/or LEI in the same quarter of the year, then dementia, need for care and LEI occurred before death; dementia occurred before need for care; LEI occurred before the need for care and before dementia. Sensitivity analyses were performed under different order assumptions, which did not affect our results. Proportional hazard assumptions in the Cox models were also checked and were generally met.

In our multistate model, the hazard ratios and 95 percent confidence intervals (CIs) of the LEI for each transition hazard were obtained. The transition probability was defined as

$$P_{hj}(s,t) = P(X(t) = j|X(s) = h),$$

which denoted the probability of transition from state h to state j in the time (age) interval (s,t] (133). That is, the probability that the subject is in state j at age t, given that he/she is in state h at age s. Estimates of the transition probabilities were obtained from the estimated transition hazards by means of the Aalen-Johansen formula (132, 134). The age-specific transition probabilities for men and women were estimated and plotted by LEI in the age range 75-95, starting at the individual's 75th birthday with different initial states. Furthermore, the state-specific rLE for a 75-year-old individual was estimated by calculating the state-specific expected length of stay for a 75-year-old individual with different initial states. In addition, the composite measure YLL due to LEI was used to compare the state-specific rLE under LEI exposure and under no-LEI exposure. In line with the age range of our study population,

the state-specific rLE was restricted between 75 and 95 years of age. 95% confidence intervals for the state-specific rLEI and YLL were bootstrapped using a thousand replications to resample the sample data with replacement.

All analysis was performed using the software R 3.0. The multi-state analysis was performed using the “mstate” package in R 3.0 (133).

5. Results

5.1 Study 1: Development over Time in Cognitive Function in Europe

The sample consisted of 40689 subjects with an average age of about 62 years, of whom about 54% were female and 46% male. From Wave 2 to Wave 6, scores for Recall and Verbal Fluency increased on average.

Descriptive analysis shows a consistent increase in Verbal Fluency over time for each European region. For Recall, a consistent increase over time was found in central Europe, whereas a less consistent trend of increase was also observed in northern and southern Europe. Overall, northern Europe had the highest scores of cognitive function, central Europe ranked as the second, and southern Europe had the lowest scores of cognitive function. However, the differences between the regions were shrinking since the increase had different rates over time among regions. The overall model of linear regression also confirmed that southern and central Europe experienced statistically significant faster improvements in Recall and Verbal Fluency than northern Europe.

Table 1 shows the results of the models for the association of cognitive function and time, stratified by region and education.

Region: There was a general improvement in cognitive function over time in southern and Central Europe, but not in Northern Europe. Concretely, cognitive function improved significantly in southern and central Europe ($p<0.0001$ for both Recall and Verbal Fluency in both southern and central Europe), whereas such a statistically significant improvement was not found in Northern Europe.

Gender: Females had statistically significantly better Recall than males consistently in Southern, Central and Northern Europe, whereas no such consistent significant

gender effects for Verbal Fluency were observed among regions. In southern Europe, the interaction of time-by-gender revealed that males tended to benefit more from improving cognitive function than females (Recall: p=0.003; Verbal fluency: p = 0.081). In the low education group in southern Europe, a statistically significant interaction of time and gender favoring males was observed. (Recall: p=0.002; Verbal fluency: p=0.039).

Education: Compared to those with relative low levels of education, people with middle and higher levels of education had statistically significantly higher cognitive function. This was true for all regions of Europe and for both Recall and Verbal Fluency. However, in southern and central Europe, those with lower education levels tended to improve their cognitive function fastest among the three educational groups, as most of the coefficients for the time-by-education interaction were statistically significantly negative values, and none of these coefficients were positive values.

The sensitivity analysis confirmed that the results were stable, after the data of Wave 7 was included, or using other covariance structures, or using the conventional classification of education by ISCED. However, when the conventional classification of education was used, we were unable to show the interaction of survey year and educational level consistently.

Table 1: GEE models for the association between cognitive function and time in SHARE, stratified by region and education

		Recall [a]				Verbal Fluency[a]			
		Overall *(I)*	Low Edu.[c] *(II)*	Middle Edu.[c] *(III)*	High Edu.[c] *(IV)*	Overall *(V)*	Low Edu.[c] *(VI)*	Middle Edu.[c] *(VII)*	High Edu.[c] *(VIII)*
Southern Europe[b]	Intercept	5.67***	6.42***	5.87***	6.52***	5.55***	5.59***	5.60***	8.15***
	Gender (Female)[d]	0.27***	0.27***	0.23**	0.35*	-0.13**	-0.16**	-0.04	-0.24
	Survey year	0.08***	0.08***	0.04***	0.02	0.07***	0.07***	0.05***	0.05***
	Survey year * Gender[d]	-0.02***	-0.03***	-0.01	-0.01	-0.01*	-0.02**	-0.01	0.00
	Middle Edu.[c]	1.01***				0.58***			
	High Edu.[c]	1.69***				1.00***			
	Survey year * Middle Edu.[c]	-0.03***				-0.01			
	Survey year * High Edu.[c]	-0.05***				0.00			
Central Europe[b]	Intercept	6.81***	7.57***	7.28***	7.75***	7.30***	7.44***	8.02***	8.71***
	Gender (Female)[d]	0.46***	0.40***	0.49***	0.42***	0.05	0.06	0.05	0.05
	Survey year	0.09***	0.10***	0.07***	0.08***	0.06***	0.07***	0.05***	0.03***
	Survey year * Gender[d]	0.00	-0.01	0.00	0.01	0.01**	0.00	0.01*	0.02**
	Middle Edu.[c]	0.54***				0.72***			
	High Edu.[c]	1.12***				1.41***			
	Survey year *Middle Edu.[c]	-0.01**				-0.01**			
	Survey year *High Edu.[c]	0.00				-0.03***			
Northern Europe[b]	Intercept	7.01***	7.16***	7.49***	7.61***	8.42***	9.60***	8.65***	9.07***
	Gender (Female)[d]	0.59***	0.54***	0.47***	0.73***	0.01	-0.06	0.07	0.00
	Survey year	-0.02	-0.03	0.00	0.03***	0.02*	0.03	0.04***	0.03***
	Survey year *Gender[d]	0.01	0.03	0.02	-0.01	0.01	0.01	-0.01	0.02
	Middle Edu.[c]	0.43***				0.41***			
	High Edu.[c]	0.78***				0.91***			
	Survey year * Middle Edu.[c]	0.02*				0.01			
	Survey year * High Edu.[c]	0.04***				0.02			

[a] *** p<=0.01; ** p<=0.05; *p<=0.1. Models are further adjusted by age and whether the subject participated in the SHARE survey for the first time.
[b] Region: Southern Europe: Italy, Spain; Central Europe: Austria, Belgium, Czech Republic, France, Germany, Switzerland; Northern Europe: Denmark, Sweden.
[c] Adjusted educational level: low: lowest–Q1 (reference group); Middle: Q1–Q3; High: Q3–highest. Abbreviation: Edu.: Education.
[d] Male is the reference group for gender.

5.2 Study 2: Association between Starting Age of ECEC and Psycho-Social Problems in Adolescence in West and East Germany

The children in our sample were on average 14.4 (±0.03) years old at wave 2, and approximately 50% were girls and 50% were boys. 41.1% of our sample started ECEC at the age of 2-3 years, followed by 22.4% who started ECEC older than 3 years but before starting school. All other ECEC-age-groups accounted for about 10%. The majority of children in West Germany started ECEC at the age of 2-3 years (44.3%), while the majority of children in East Germany started ECEC at the age of 1-2 years (43.9%). Only 7.3% of children in West Germany started ECEC before the age of 1 year, while 22.9% of children in East Germany started before the age of 1 year.

Most other baseline characters were similar for West and East Germany, except for mother's employment status, SES, family structures and migrant status. In East Germany, more mothers with 3-4 year old children were in full-time employment (East vs. West: 34.7% vs. 8.1%), and fewer were unemployed (East vs. West: 31.4% vs. 51.6%); more children from low SES families (East vs. West: 20.8% vs. 15.4%), and fewer children from high SES families (East vs. West: 22.6% vs. 25.9%); there were less family structure as natural parents in a joint household (East vs. West: 76.6% vs. 88.6%), and less migrant (East vs. West: 8.5% vs. 17.8%). SES and family structure differed significantly among ECEC-start-age groups in West Germany, whereas such significant difference was not found in East Germany. Mother's employment status differed significantly among ECEC-start-age groups in both West and East Germany. Children starting ECEC younger than 1 year old in the West Germany tended to be more likely in a one-parent family with high SES and with a full-time employed mother.

Among ECEC-start-age groups, those who started ECEC between the ages of 2 and 3 had the least psycho-social problems in adolescence with lowest SDQ scores. Those

who started ECEC younger than 1 had the highest total SDQ score and the highest score for externalizing psycho-social problems. Those who started ECEC older than 3 (but before school entry) had the highest score for internalizing psycho-social problems.

By region, West Germany had a similar pattern as to the whole Germany, whereas the East Germany didn't. In East Germany, for externalizing psycho-social problems, those who started ECEC younger than 1 had lower scores than those who started ECEC at the age 1-2; for internalizing psycho-social problems, the later the children started ECEC, the higher scores the children had in adolescence generally.

The linear regression (Table 2) shows that the total SDQ score was statistically significantly higher for ECEC-start-age groups "Below age 1" (p=0.002), "Age 1-2" (p=0.036) and "Age 3+ and before schooling" (p=0.020) compared to ECEC-start-age group "Age 2-3". Those starting ECEC younger than 2 years had statistically significant higher scores for externalizing psycho-social problems (p=0.001 for Group "Below age 1"; p=0.005 for "Age 1-2"). The group "Age 3+ and before schooling" had statistically significantly higher scores for internalizing psycho-social problems (p=0.017).

The stratified linear regression by region shows that results in West Germany were comparable to the findings for whole Germany (Table 2). However, the analysis in East Germany revealed no statistically significant differences depending on ECEC starting age. Those who started ECEC at the age of 1-2 years tended to have higher scores for externalizing psycho-social problems in East Germany (p=0.062). The beta of "Age 3+ and before schooling" for SDQ total score and for internalizing psycho-social problems were relatively high (2.1 and 1.2), with relatively a small sample size (n=20) and statistically insignificant p-values (p=0.363 and p=0.394).

The linear regression with an interaction factor of ECEC-start-age by region shows an unfavorable effect of ECEC younger than 1 year in West Germany but not East Germany.

Sensitivity analysis confirmed that our results remained robust after dropping outliers (n for outliers = 76). The assumptions of linear regression have been checked by plots, which are also provided in the Supplemental Materials of Study 2.

Table 2: Linear regression models for the association between ECEC-start-age and psycho-social problems in adolescence, and stratified by Region (West/East Germany)

	ECEC-start-age groups		SDQ Total Score		Externalizing Psycho-social Problems		Internalizing Psycho-social Problems	
		n	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Whole Germany (n=1022)	Below age 1	144	**1.8 (0.6,2.9)**	**0.002***	**1.3 (0.6,2.0)**	**0.001***	0.5 (-0.3,1.2)	0.245
	Age 1-2	214	**1.4 (0.1,2.8)**	**0.036***	**1.2 (0.4,2.1)**	**0.005***	0.2 (-0.5,0.9)	0.586
	Age 2-3 (Reference group)	366						
	Age 3+ and before schooling	205	**1.0 (0.2,1.9)**	**0.020***	0.4 (-0.1,0.9)	0.149	**0.7 (0.1,1.2)**	**0.017***
	Only cared in Family before schooling	93	0.8 (-0.6,2.1)	0.255	0.7 (-0.1,1.6)	0.099	0.0 (-0.7,0.8)	0.930
West Germany (n=621)	Below age 1	45	**2.9 (1.3,4.6)**	**<0.001***	**1.9 (0.9,3.0)**	**<0.001***	1.0 (-0.2,2.1)	0.088
	Age 1-2	41	2.3 (-0.1,4.6)	0.055	**1.7 (0.2,3.3)**	**0.029***	0.6 (-0.5,1.6)	0.300
	Age 2-3 (Reference group)	261						
	Age 3+ and before schooling	185	**1.2 (0.4,2.1)**	**0.006***	0.4 (-0.1,1.0)	0.094	**0.8 (0.2,1.4)**	**0.005***
	Only cared in Family before schooling	89	0.9 (-0.5,2.3)	0.214	0.8 (-0.2,1.7)	0.108	0.1 (-0.6,0.9)	0.731
East Germany (n=401)	Below age 1	99	0.3 (-1.3,1.9)	0.714	0.3 (-0.5,1.1)	0.514	0.0 (-1.1,1.1)	0.971
	Age 1-2	173	0.4 (-1.0,1.8)	0.589	0.6 (-0.03,1.3)	0.062	-0.3 (-1.3,0.7)	0.609
	Age 2-3 (Reference group)	105						
	Age 3+ and before schooling	20	2.1 (-2.4,6.6)	0.363	0.8 (-1.2,2.8)	0.406	1.2 (-1.6,4.1)	0.394
	Only cared in Family before schooling	4	-1.4 (-5.1,2.4)	0.462	-0.6 (-2.0,0.7)	0.341	-0.7 (-4.0,2.5)	0.648

* p<0.05.

Covariates: age in adolescence, gender, schooling type, parents' divorce by wave 2, and other baseline characters including region (East/West Germany), social economic status, migrant status, number of older siblings, family situation, family cohesion, birth weight, obesity/overweight, age of mother at childbirth, and employment status of mother.

5.3 Study 3: Years of Life Lost due to Lower Extremity Injury in Association with Dementia, and Care Need

The insured persons in our sample were on average 81.5 years old (with standard deviation as 4.8 years) in the first quarter of 2005, and 71.2% of our sample was female. In that quarter as the baseline, the majority (approximately 75%) of the sample were in the state *Healthy*; the other states *Dementia*, *Care*, *Dementia & Care* have 5%, 13% and 9% of the samples respectively.

During the follow up from 2005 to 2010, 25730 persons died, 1538 persons moved to other health insurance companies, and 6651 persons reached the age of 95 or more. Of the 45758 individuals in the risk of transitioning from the state *Healthy*, 7699 (17%) transited to the state *Dementia*, 12302 (27%) to *Care*, 5446 (12%) to *Dead*, and 20311 (44%) kept in state *Healthy* till the end of the study or the time point of right censoring. Of the 10587 individuals who were at the risk of transiting from the state *Dementia*, 6977 individuals (66%) changed to the state *Dementia & Care*, 1349 (13%) to the state *Dead*, and 2261 (21%) had no change.

LEI significantly increased the risk of each transition and accelerated health deterioration. In particular, LEI increased the risk of the majority of the transitions from the states *Healthy* or *Dementia* by about 50% or more. As the largest risk among the eight transitions, it was 70% higher risk for those with LEI than for those without LEI (Hazard Ratio: 1.70, 95%CI: 1.63-1.77) to transit from *Healthy* to *Care*. In addition, LEI increased the risk of the majority of the transitions to the states *Dead* by about 20%.

Figure 5 shows the age-specific estimated probabilities of the transitions of states regarding Health, Dementia, Care, and Dead from age 75 to 95, stratified by the presence of LEI and sex. For example, Figure 5A shows the transition probabilities for a synthetic cohort starting in the *Healthy* state at age 75. Figure 5B, C, and D show the transition probabilities starting in the states *Dementia*, *Care*, and *Dementia & Care*

at age 75 respectively. For most transitions, the age-specific probability of entering a state of decline was greater for those with LEI than for those without LEI. For the transitions to transient states, the transition probabilities peaked at younger ages for those with LEI than for those without LEI. For the transitions to the absorbing state *death*, those with LEI had higher age-specific probability of dying than those without LEI. All of above were observed for both males and females. Regarding the sex difference, men had higher age-specific probability to die, whereas women had generally higher age-specific probability to transit to *Care* State (from *Healthy* to *Care*, or, from *Healthy* to *Dementia & Care*, or from *Dementia* to *Dementia & Care*).

The remaining life expectancy at age 75 is higher for those without LEI than those with LEI in each transient state, and this was true for both sexes. At the age of 75, women who started out in *Healthy* state but experienced an LEI lost 2.10 years of rLE, and men lost 1.97 years. The majority of these lost years were years without dementia or long-term care need (women 2.00 years, men 1.79 years). Dementia patients lost about 1.5 years, and more than 60% of these lost years are years free of long-term care need. For the majority of the transitions, the YLL due to LEI were statistically significantly different from zero.

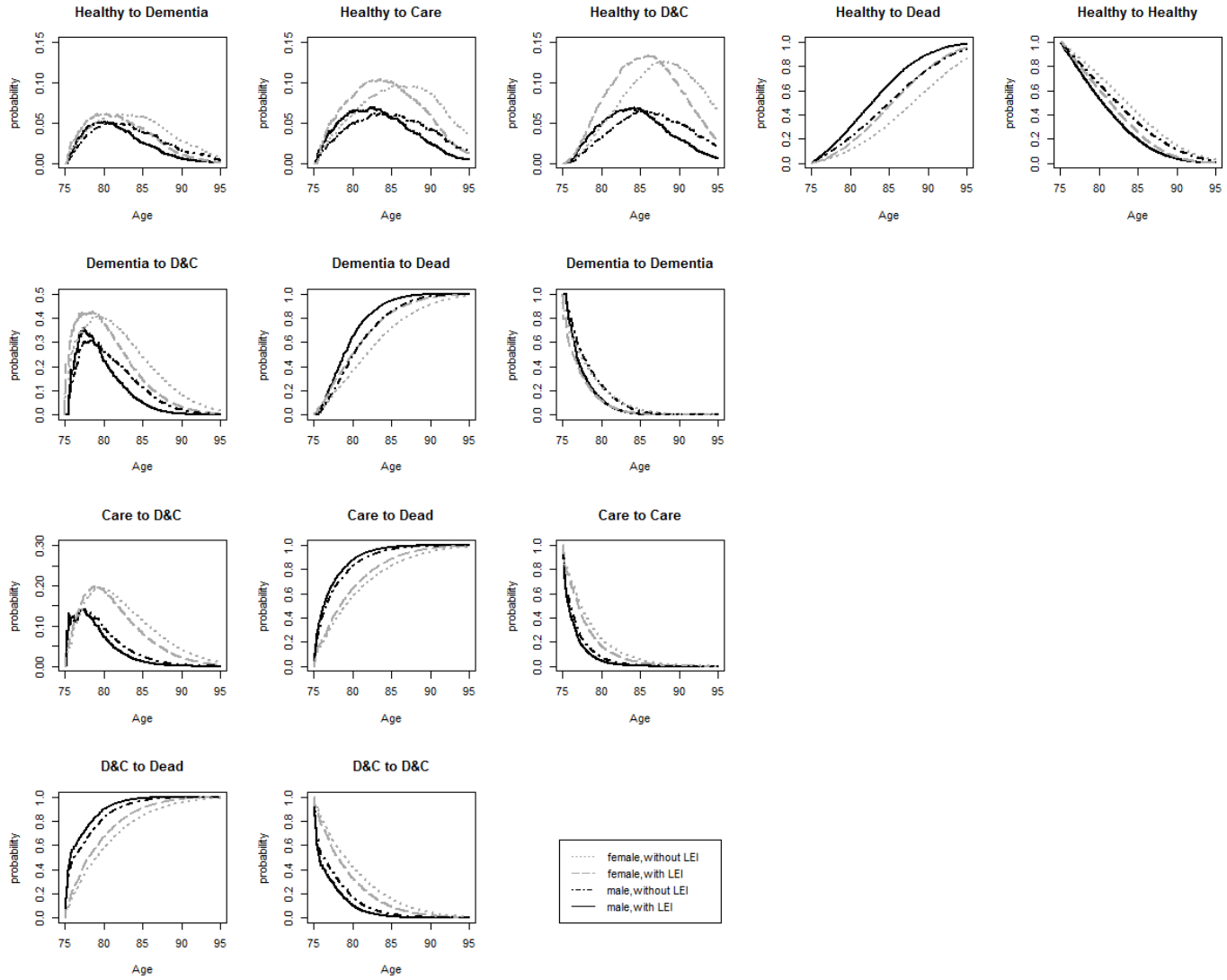

Figure 5: Estimated transition probabilities in the age interval 75-95, stratified by sex and LEI for the populations with different initial states on the 75th birthday.
(1st row: from Healthy as the initial state (5A); 2nd row: from Dementia as the initial state (5B); 3rd row: from Care as the initial state (5C); 4th row: from Dementia & Care as the initial state (5D)). "Without LEI" refers to individuals who do not experience LEI during the whole period. "With LEI" refers to individuals who start out with LEI in their initial state. Abbreviation: D&C: Dementia & Care.

6. Discussion

The aim of the thesis is the investigation of the mental health and cognitive function of people and their influence factors or trends at three key stages in their lives, namely first five years of life, late working age, and old old age. To achieve this aim, three examples with concrete exposures and outcomes of interest have been used. In addition, education is investigated as a factor of special interest, and will be discussed in particular together with accumulation of risk model.

Below, the findings of the three studies are discussed in respect to their reflection on the hypotheses, strengths, limitations, implications, and additional research needs.

6.1 Reflection on the Hypotheses

In the following, the hypotheses of the studies are reflected on and briefly discussed.

6.1.1 Study 1: Development over Time in Cognitive Function in Europe

Hypothesis 1.1: Cognitive performance became better over time among 55-69-year-old adults in Europe from 2006 to 2015.

This hypothesis can be confirmed partly by Study 1. Cognitive function among 55-69-year-old adults improved significantly from 2006 to 2015 in southern and central Europe, whereas it did not in northern Europe.

Hypothesis 1.2: There existed differences of changes in cognitive function over time linked to region, gender and education for 55-69-year-old adults in Europe from 2006 to 2015.

This hypothesis can be confirmed. Cognitive function of 55-69 year olds improved significantly between 2006 and 2015 in southern and central Europe. However, this improvement was not observed in northern Europe. In southern and central Europe, the relatively low educated group tended to improve their cognitive functions faster

than the medium and higher educated groups. Among people with a lower level of education in southern Europe, men improved their cognitive functions faster than women.

The results of Study 1 added to the knowledge of differences in changes in cognitive function over time in relation to region, gender and education. I will now briefly discuss them.

Regional Disparities

The results of this study suggest that 55-69-year-old adults in southern and central Europe remained in the Flynn effect phase, whereas the same age group in northern Europe stayed at the anti-Flynn effect phase from 2006 to 2015. Flynn et al. have summarized that some Scandinavian nations had robust intelligence gains in the twentieth century, but these peaked around 1990 and may have been in slight decline since then (58). Looking dynamically at trends in cognitive function, the Flynn effect in southern and central Europe suggests that these countries may have the potential for further improvements in cognitive function from one generation to the next, whereas the anti-Flynn effect in northern Europe suggests that these countries may have reached or are approaching the maximum plateau.

Educational Disparities

The association between education and the rates of cognitive change may be explained by a threshold for benefits of education on cognitive health. According to a review published in 2000, the majority of the studies between 1985 and 1999 reported protective effects of education on the rate of cognitive decline (135). In contrast, another review paper published in 2015 found that most studies between 2000 and 2015 reported no such protective effect (74). The beneficial effect of education on cognitive decline may no longer be observed once education levels exceed a certain threshold, such as an eight years (74, 136). It was reported that having eight years or

less of formal education was associated with a greater degree of cognitive decline. However, there was no further reduction in cognitive decline associated with having nine or more years of education (136).

Consistent with this threshold explanation, Study 1 suggests that most of the benefits of the Flynn effect among the least educated is probably due to the fact that those with the lowest levels of education had the lowest baseline levels of cognitive function, and these remained below the threshold throughout the analysis period in southern and central Europe. This means that the less educated in these regions have improved their cognitive function disproportionally over time. In contrast, this was not the case in northern Europe. One possible explanation is that the majority of the northern Europeans have reached maximum cognitive reserve capacity with increasing levels of education as the norm (74).

It was recommended that education-based interventions should be target at less educated and other disadvantaged groups (137). In a review paper, Lenehan et al. pointed out that less educated groups were an under-researched subgroup regarding the effect of education on the rate of cognitive function, and they assumed that this subgroup could get most benefits from education-based interventions (74).

Gender Disparities

One explanation for the greater improvement in cognitive function in men in southern Europe may be the greater age-related decline in men than women, regardless of whether men or women outperform on the cognitive function parameter (138). In other words, 55-69-year-old men may have a greater potential for improvement, particularly in those groups in southern Europe with the lowest levels of education.

Bank et al. found that school reform in England improved executive function in old age only for men with less education (47). Similarly, Schneeweis et al. found that educational reforms in Europe had stronger protective effects on cognitive decline in

men (139). Both studies explained this by the positive financial returns and longer labor force participation only for men after the education reforms (47, 139). This may also explain the present study's finding of greater increases in cognitive function favoring men in the group with lower education in southern Europe.

6.1.2 Study 2: Association between Starting Age of ECEC and Psycho-Social Problems in Adolescence in West and East Germany

Hypothesis 2.1: There is an association between ECEC-start-age and psycho-social problems in adolescence.

This hypothesis can be confirmed by Study 2, at least to some extent. There is an association between starting ECEC later than 3 years of age and higher parent-reported scores of internalizing psycho-social problems in adolescence in West Germany with statistically significant results. A similar association is observed in the East Germany as well, but with a relatively larger effect size but statistically insignificant results. Children starting ECEC between the ages of 1 and 2 tend to have a higher possibility of externalizing psycho-social problems in both West and East Germany. I shall now discuss them briefly.

Starting ECEC at 3+ years old: increased probability of internalizing psycho-social problems

We observed an increased probability of internalizing psycho-social problems if children start ECEC older than 3 years old in both West Germany (with statistically significant results) and East Germany (with a relatively larger effect size but statistically insignificant results). The lack of statistical significance in East Germany may be explained by the small sample size (n=20). Interestingly, a descriptive analysis in the Study 2 shows a "dosage effect" of ECEC-start-age on the increased probability of internalizing psycho-social problems from ECEC-start-age group <1 to 3+ in East Germany. The later the children started ECEC, the more likely they are to have

internalizing psycho-social problems in adolescence.

This observation underscores the importance of participating in ECEC no later than the age of 3. The association may be explained by the importance of peer play in the pre-school age group, from three years of age onwards. Playing with others is children's main activity at these ages (140, 141). Playing and interacting with their peers at these ages helps children explore and develop their social, emotional, language and cognitive skills. In particular, social and cooperative play with peers helps children to develop and improve their ability to make decisions, solve problems and influence others (140, 141). Participation in ECEC provides good opportunities to play and interact with peers. In addition, the risk of internalizing psycho-social problems may be increased by having no close friends (86). Therefore, if a child doesn't start ECEC at the age of 3, more attention should be given to preventing internalizing psycho-social symptoms, for example by providing more chances for peer play.

Starting ECEC between 1-2 years old: increased probability of externalizing psycho-social problems

In both West and East Germany there is a trend towards increased externalizing psycho-social problems for those starting ECEC between the ages of 1 and 2. More attention needs to be paid by teachers and parents to preventing these children from developing externalizing psycho-social problems. Previous studies have reported that a higher risk of behavioral problems and long-term insecure attachment was associated with prolonged exposure to ECEC before the age of 2; However, such negative effects were not observed if the exposure to ECEC was short (50, 142). Therefore, for parents who wish to work when the child is very young, part-time participation in ECEC may be a compromised but a better option. The quality of ECEC and the qualifications of early childhood educators need to be monitored carefully and regularly, in order to maintain a good teacher to child ratio and to provide a stable, continuous and sensitive care for the children, which can help prevent early insecure

attachment and subsequent externalizing psycho-social problems (50, 83).

Hypothesis 2.2: There is no difference in West versus East Germany regarding the association between ECEC-start-age and psycho-social problems in adolescence.

This hypothesis cannot be confirmed by the Study 2. Instead, we found some differences between West and East Germany for the association in the group of children starting ECEC before the age of 1 year.

Children starting ECEC before age 1 were more likely to have psycho-social problems in West Germany, but not in East Germany. Selection processes may be at work that leads to this disadvantage in terms of psycho-social development for children starting ECEC before the age of 1 year in West Germany. Our data show that children starting ECEC in West Germany before age 1 were more likely to come from a high-SES single-parent family with a mother in full-time employment.

Regional cultural differences in the role of women, and consequently in attitudes to ECEC, are worth discussing. In West Germany, mothers who take their children to ECEC earlier may experience stress or even blame from relatives or neighbors; in East Germany, children who are looked after by their parents at home may feel strange if the majority of their peers go to an ECEC. This cultural difference may be one of the sources of the possible selection effects for the children starting ECEC under 1 year in West Germany. Concretely, in West Germany, families with “problems” (e.g. work overload, partnership problems, lack of social support from grandparents or friends, economic problems) may be more or less forced to send their children to non-parental ECEC in the first year of life; and the real reason(s) for more psycho-social difficulties in children’s development may be these “problems”. In East Germany, in contrast, it is more accepted or normal to send children to non-parental ECEC at this early age, even in “non-problematic” families.

There is a need for further research to identify the sources of this possible selection process.

However, for children starting ECEC over the age of 1, similarities were observed between West and East Germany in the association between ECEC-start-age and psycho-social problems in adolescence.

6.1.3 Study 3: Years of Life Lost due to Lower Extremity Injury in Association with Dementia, and Care Need

Hypothesis 3.1: LEI increases the risk of getting dementia, care need and dying in the elderly aged 75+.

This hypothesis can be confirmed by Study 3. The results of Study 3 show that LEI in older people significantly increases the risk of the whole chain of adverse outcomes, from health over dementia and care need to death. I shall now discuss them briefly.

Association between LEI and care need

Study 3 shows that LEI increases the risk of needing long-term care in both healthy older people and people with dementia. It is well known that fractures or fall-induced injuries in older people are associated with poor functional outcomes and a high burden of care (22, 143). The presence of dementia exacerbates these negative effects (144). The underlying mechanisms may be as follows: LEI may accelerate the progression of dementia (145); or dementia may slow the rate of functional recovery following LEI, thus increasing the need for care in patients with dementia (27, 146).

Association between LEI and dementia

Study 3 shows that in both healthy people and people with care needs, LEI is a risk factor or predictor of dementia. The following mechanisms may explain the link between LEI and dementia. First, LEI in older people is associated with an increased risk of cognitive impairment (44, 103), which increases the risk of developing dementia

(104, 147–149), and makes dementia worse and more likely to progress (150, 151). Second, LEI limits physical activity, mobility and participation in social life (24, 25), thus limiting these potential preventive factors of dementia (45, 105). Third, there are common risk factors for LEI and dementia. These include age, ApoE4, diabetes and vascular dysfunction, executive dysfunction and gait disturbance (26, 99).

However, the observed association must be interpreted with caution. The possibility of reverse causality must be considered. LEI may occur as a pre-symptom or an early symptom of undiagnosed dementia.

Association between LEI and mortality

Study 3 found that LEI was associated with an increased risk of dying in general. This was particularly true for people with dementia. Higher mortality has been observed in several previous studies of fractures or falls (23, 24, 107–110). However, the underlying mechanism is still unclear. Some studies suggest that fracture and trauma-related post-fracture alone are mainly responsible for the excess mortality (23, 152), while others claimed that underlying health conditions or comorbidities accounted for much of the association (153). In line with our findings, several previous studies have also suggested that dementia is an independent risk factor or predictor of mortality after fracture (24, 107, 108, 112).

Hypothesis 3.2: There exist years of life lost due to LEI for the elderly aged 75+.

This hypothesis can be confirmed by Study 3. The results of the study show that LEI in older people resulted in a large loss of years of life. LEI was generally associated with a reduction in life expectancy, but with relatively prolonged life with dementia and needing care.

6.2 Methodological Strengths and Limitations

6.2.1 Methodological Strengths

The studies have several methodological strengths.

First, the longitudinal data was used to evaluate the associations and time trends from a perspective of life course. Study 1 investigated the development over time in cognitive function among European 55-69-year-olds in ten years and differences of region, gender and education. This fulfils the life course perspective over time or cohorts. Study 2 explored and found the association between ECEC-start-age at early childhood and psycho-social problem in adolescence. In the Study 3, the longitudinal data with a 6-year follow-up allowed us to analyze multiple transitions between different states. These fulfil the life course perspective over various life stages.

Second, large and representative population-based datasets were used to answer research questions. Study 1 used SHARE datasets with large sample sizes covering numerous European countries with harmonized design and data. Study 2 used a national representative and adequately large sample of children and their parents in Germany (i.e. KiGGS). Study 3 used a large population-based sample of community dwelling and institutionalized elderly. Large and representative sample sizes can grant a high statistical power and generalize the results of the studies to the target populations well.

Third, some approaches have been used to reduce attrition bias and selection bias, which usually exists in the longitudinal analysis. In Study 1, education was defined by quantiles, which decreased selection bias and increased comparability. In Study 2, longitudinal weights were applied to minimize the attrition bias. In Study 3, right censoring has been considered and controlled carefully.

Fourth, claims data and performance-based measures were used in Studies 1 and 3,

which are free of recall bias or interview bias. In Study 2, the parents-reported values of SDQ were used, which may be different from self or teacher-reported ones. However, German parent SDQ has been shown to possess reliable and useful psychometric properties (154).

Finally, specific strengths of the three studies need to be mentioned.

Study 1 looked at adults aged 55-69, whose cognitive development over time is important for sustained productive work in old age and pension policies, but who have been relatively little studied.

In Study 2, there is considerable variation in the starting age of ECEC in Germany, which provides good opportunities to explore the association between ECEC-start-age and psycho-social problems. In some other countries such as the United States, there is less variation in the starting age of ECEC, making it difficult to answer such a research question thoroughly (79, 155). We also provide more socio-political variation and contribute to the external validity of this area of research. In addition, most previous studies have used discrete categories to analyse psycho-social problems (i.e. creating groups such as “normal”, “borderline” and “abnormal”) (78). Study 2 used a continuous score, which may provide a more valid and reliable assessment to analyse psycho-social problems (78). However, there is still a need for further research into the use of discrete categories for the analysis of these associations in order to support the clinical relevance of these associations.

A particular strength of Study 3 was a holistic analysis of LEI effects. To our knowledge, this is the first study to examine the effect of LEI on the risk of dementia, care need, and death simultaneously in a multi-state model. Previous studies have mainly looked at individual endpoints and have not derived composite measures at the population level, such as life expectancy and years of life lost. Such a life table, as applied in Study 3, has been recommended to provide a synthetic life course measure of

successful aging by integrating the effects on mortality and functional declines across ages (156). The results of Study 3 provide insight into the effects of LEI on both the functional outcomes (dementia, care need) and the survival outcomes holistically. This is valuable for two reasons. First, all forms of dementia, the need for long-term care and premature mortality add to the health burden in a society with an aging population. Second, LEI and dementia, as well as mobility and cognitive dysfunction, may interact and particularly exacerbate each other, leading to a profound combined effect on care needs and mortality (26, 27).

6.2.2 Methodological Limitations

Besides the strengths mentioned, several weaknesses also emerged in the analysis.

First, the associations have been found, but the associations are not necessarily the causal ones. This is a general limitation of observational studies. Therefore, results need to be interpreted with caution. In particular, the potential reverse causality should be paid attention to. For example, in Study 3, dementia may have already existed ahead of LEI, and LEI simply brought the dementia to clinical attention. More research is needed to understand the underlying mechanisms of the observed associations.

Second, the operationalization for parameters of interest has limitations. In Study 1, the two parameters (recall and verbal fluency) only partially cover the overall concept of cognitive function. Further studies are needed to investigate other parameters of cognitive function. However, recall and verbal fluency can be regarded as two key dimensions of intelligence, i.e. fluid intelligence/working memory, and crystallized intelligence/knowledge (72, 120, 121). In Study 2, regarding ECEC exposure, not only beginning age of ECEC but also quality and intensity of ECEC exposure matters (155). But neither data of quality nor of intensity regarding ECEC exposure is available in KiGGS. Further research is needed to take these different aspects into analysis. In Study 3, the dementia was defined by a doctor's ICD diagnosis, which is prone to

imperfect sensitivity and specificity. Underreporting cannot be avoided, although an internal validation procedure was used to minimize the probability of false positive dementia diagnoses.

Third, not all of potential (known or unknown) confounders have been controlled for, because of lack of data (for known confounders) or because of limited knowledge (for unknown confounders). For example, in Study 2, some other factors may also influence the association, such as later school experience and relationship between parents and children. But these data are not captured in details in the KiGGS. However, we have controlled for some of the potential confounders, such as type of schooling and family cohesion, in our analysis to reduce this kind of bias. The natural experimental design of the study also helps to reveal potential unmeasured or unknown biases. Yet, not all of these biases can be fully controlled for by the statistical adjustment. In Study 3, no information is available about other potential confounders such as education, family status, or life style factors such as smoking, obesity, or alcohol consumption. The multistate model does not control for polypharmacy or multimorbidity, either. However, in sensitivity analyses of the hazard models several further available variables were controlled for, including the Charlsonmorbidity-index, brain injuries, osteoporosis, depression, Parkinson and Down-Syndrom at baseline, which did not alter the findings. These factors should be investigated in a more detailed way in further studies.

Fourth, some exposure variables or confounders are time-varying, but were treated as time-constant, which is a common limitation in life course models (14). For example, in Study 3, to evaluate the long-term effect, LEI was defined as an ever-variable, although some LEIs may be apparently or actually cured. However, LEI can influence a patient in the long-term, even after recovery. A relationship has been observed linking fall and subsequently fear-related avoidance of activity (157).

Finally, specific limitations of the three studies must be mentioned. To begin, in Study 1,

the retest effect may have an impact on cognitive parameters (158). An adjustment for first-time participation was included in the statistical models to minimize this effect. Furthermore, the overall effect sizes appear to be small. However, the true effect size might be larger than it appears since some values were divided in the parameters to get a comparable range. Moreover, the difficulty of establishing criteria of clinical relevance for effect size is a general limitation of research using cognitive tests (159). In Study 2, the small sample of 93 children who did not attend ECEC before school shows no statistically significant difference in the risk of psycho-social problems in adolescence. Due to the small sample size, the statistical power for this group may be limited. In Study 3, given the crude nature of the quarterly data, the order of occurrence of LEI, dementia, need for care and death must be assumed if more than one event occurred within a quarter. Sensitivity analysis changing these orders still found a significantly increased risk of LEI for most transitions, albeit with smaller effect sizes.

6.3 Implications for Theory, Research, and Policy

6.3.1 Implications for Theory – about Sensitive Period Model

The studies in this thesis have confirmed the sensitive period model in the life course perspective. The age under 5 years old and the age over 75 years old are sensitive periods for mental health development and mental disorders; the age between 55 to 69 is a sensitive period for decline of cognitive function. In addition to these, the studies in the thesis also had some further implications for sensitive period model.

Study 2 shows that first several life years may be sensitive to different factors, and may be differently sensitive to the same factor at different ages. For example, the first three life years are not so sensitive to peer play whereas from the three years and up are sensitive to peer play in general. First two life years may be particularly sensitive to get attachment connection with parents, and to have separate anxiety in children.

Study 3 suggests that time periods with LEI of older people may be regarded as

sensitive periods during which individuals are more prone to develop dementia, or to get in care need, or to die. Sensitive periods can be defined not only by age, but also by some characteristics/exposure or by particular functional transitions (14).

6.3.2 Implications for Theory – about Accumulation of Risk Model

I investigated the education as a special factor of interest for the mental health and cognitive function, and aimed to understand whether the education fulfills the accumulation of risk model.

Study 1 shows that the cumulative positive effect of education may disappear once the length of education or the beneficial effect of education arrives the threshold. This study helps to understand how the trajectories of functional decline differ with person, place and time among European 55-69-year-olds. It shows that hypotheses of "*success of success*" or "*failure of success*" alone may not explain the complete picture of time trends in cognitive function. Instead, *threshold theory* may be able to explain the various rates of cognitive improvement throughout all Europe by region, education, and gender. Southern and central Europeans, people with lower education, and males may have larger potentials to improve their cognitive function than the corresponding comparison groups, thus also showing quicker improvements in the data. Conversely, the cognitive function of the corresponding comparison groups (for example, people with higher education) may be closer to biological limits (saturation), hence improvements happen more slowly, if at all.

Study 2 shows that the starting age of early education before school has a relationship (but not a linear relationship) with the risk of psycho-social problems in adolescence. This study also provides evidence that early education before school is neither a simple risk factor nor a simple preventive factor. The assumption "*earlier is better*" or "*earlier is worse*" alone is not enough to explain our observed associations. Instead, the association is much more complex than accumulation of risk factor model, and highly

dependent on the ECEC-start-age. Therefore, such a factor ideally should be adapted to the age during children's developments.

Interestingly, some other researchers have also pointed out that there is something beyond risk and protective factors (160). For example, Ellis et al. have mentioned an adaption-based approach to resilience (161). The authors have argued that the cumulative risk model is incomplete because it doesn't include the scenarios that individuals adapt to their environments by fine-tuning their cognitive abilities to solve recurrent problems and consequently specialize their cognitive abilities (such as attention, learning, memory, problem-solving and decision-making strategies) to match high-adversity contexts (161). In addition, more generally speaking, Overton and Lerner have proposed a theoretical construct which is called "relational developmental systems theory (RDST)" (162, 163). RDST suggests that individuals adaptively respond to different biological, social, cultural, and physical environment which they influence and are also influenced by (160).

These theories may add another perspective to the results of Study 2. The effect of ECEC on mental development of children may be also influenced by the adaption of children to the ECEC. This adaption ability may be highly dependent on the age of children. This adaption may be also dependent on other factors such as children's personal characteristics, teachers' quality, quantity and characteristics, intensity of ECEC visits, parents and families' situations, and adaption process. In Germany, the adaption period to the new ECEC with parents' support may be a helpful approach to support a smooth adaption into the new ECEC. Moreover, teachers or managers of some good ECECs hear the feedback and opinions from children and parents, adapt themselves to children and provide better children' adapted education and care. This also helps the adaption of children to ECEC.

More research is needed to understand the association between ECEC-start-age and children's psycho-social development, in particular from the perspective of adaption of

children to the ECEC.

6.3.3 Implications for Research

Study 2 suggests that the long-term association between ECEC-start-age and psycho-social problems is not linear. This indicates that the pattern of ECEC-start-ages is valuable to investigate in the future research, instead of just using one cut-off point for ECEC-start-ages. Previous studies often looked at one cut-off point in terms of ECEC-start-age only. For example, among the rare studies investigating the long-term effect of ECEC on psycho-social problems, an American study has reported that more exposure of ECEC from birth to 4.5 years predicts more teacher-reported externalizing problems at age 12 (164). However, our study brings more insight of the ECEC-start-age for the ECEC exposure, and thus also reveals the beneficial effects of ECEC on the long-term psycho-social development.

In addition, Study 2 uses a natural experiment with similar family policies and a number of other similarities such as the education system and language within Germany, but with a different cultural context regarding the role of women and consequently different use and availability of ECEC in West and East Germany. Thus, Study 2 is able to reveal the selection effect which most observational studies with conventional statistical approaches are not able to do. A previous study from Norway has also successfully applied the natural experiment study design by using birth month as an additional factor of interest when exploring the association between ECEC and aggression (165). Such a natural experiment design is recommended for future studies.

Study 3 suggests that expressing the detrimental effect of LEI in terms of the composite measure years of life lost helps to holistically appreciate the scale of the problem and the substantial benefits of preventive and rehabilitative measures. This approach is worthwhile being applied in the future studies.

6.3.4 Implications for Policy

The findings of Study 1 indicate that increases of the retirement age may be reasonable in southern and central European countries from the perspective of cognitive health. Because cognitive health is a key prerequisite for deciding the age at which people retire, although the decision of when to retire is complex and often based on many factors including macroeconomic, family, work-related, and individual factors (31, 32). Moreover, the findings of this study regarding the educational disparities provide evidence that in the context of limited resources, it may be worth prioritizing those with relatively low educational levels when it comes to education-based intervention approaches in southern and central Europe. This would also hold true for developing countries, since a continuing Flynn effect has been observed or has begun to be observed in the developing world (58, 122).

The findings of Study 2 suggest that if a child begins ECEC before age 2, more attention needs to be given to the externalizing psycho-social problems, especially for children with longer exposure of ECEC. The quality of ECEC and qualification of nursery teachers need to be monitored carefully and regularly, to ensure a stable, continuous and sensitive child care. Knowledge of children's emotional and cognitive needs should also be provided and emphasized to parents, so as to ensure a secure parent-child relations (38). For the parents who want to work at child's earlier ages, part-time participating ECEC may be a compromised option. Furthermore, if a child doesn't begin with ECEC at age 3, more attention should be given to prevent internalizing psycho-social symptoms, for example by providing more opportunities to play with peers.

In particular, some previous studies have also shown that children in the low SES group benefit more regarding social, cognitive, language and academic skills from ECEC, particularly for the children over age 3 (79, 166). This is of public health relevance because in Germany it is still more difficult for some children from low SES

families or other disadvantaged backgrounds to get access to ECEC (167). A study in Berlin has revealed that almost all the children over age 3 without migrant background have access to ECEC, whereas less than 85% of children over age 3 with migrant background are able to visit ECEC (167). For children below age 3, 55% of the children without migrant background but only 33% of the children with migrant background had a nursery place of ECEC (167). Widening access to ECEC for children over age 3 and setting priority to children from low SES families may help to increase health equity and to reduce socio-economic disparities (168). Reducing health inequalities is the central in the life-course perspective, and increasing the level and equitable distribution of health and social determinants in the early life is very important.

The findings of Study 3 suggest that prevention and timely treatment of LEI as well as rehabilitative care after LEI may be of utmost importance in delaying or reducing the onset of care need and death, not only among cognitive intact elderly but also among dementia patients. These measures will not only help to save years of life, but also to increase the quality of life of the elderly and reduce the burden for families, public health, and the care system.

6.4 Future Research Directions and Prospects

For the late working age, more research is needed to regularly monitor and analyse cognitive development over time.

For the first five years, research on ECEC and children's mental development needs more data to provide a complete picture. More data on the quality and intensity of ECEC are needed so that the association between ECEC-start-age and psycho-social problems can be examined in a more detailed way. In addition, further research is needed to better understand why children starting ECEC before the age of one are particularly disadvantaged in West Germany and not in East Germany.

For the old old age, more research is needed to provide a holistic view of the impact

of risk factors on both functional and survival outcomes (156), for example by using the multi-state model.

Education is a key factor for the mental development and cognitive function. The accumulation of risk model and sensitive period model alone cannot fully explain the association between education and mental health and cognitive function. Threshold theory and RSTD may add another dimension to life course thinking for education. In addition, the life-long learning and adult education is more and more popular. This may add a further question on the effect of education with potential threshold theory. More research is needed for education, in particular regarding the adaption of children to the early education institute and the life-long learning.

7. Conclusion

The thesis provides insights into the mental health and cognitive functions during three key periods of life (late working age, first five years, and old old age) from a life course perspective.

Regarding late working age, the thesis has extended the literature on the development of cognitive function over time in older people near retirement in Europe by region, gender and education, and suggested that future increases in the retirement age in southern and central European countries may be appropriate from the perspective of cognitive function.

Regarding first five years, the thesis provides evidence that ECEC-start-age older than 3 years old is associated with a higher risk of internalizing psycho-social problems in adolescence; and that ECEC-start-age between 1-2 years of age tended to have higher scores of externalizing psychological problems in adolescence. Therefore, the thesis suggests that for those starting ECEC after the age of 3, more attention may be needed to prevent potential internalizing psycho-social problems, for example by providing more opportunities for social interaction through peer play. For those who start ECEC before the age of 2, more attention is needed from parents and nursery teachers to prevent potential externalizing psycho-social problems. It could be useful if a stable and continuous relationships is stablished between nursery teachers and children and if the daily care period is not too long. For parents who want to work earlier in the child's life, part-time participation in ECEC may be a compromise but a better option.

Regarding old old age of 75+, the thesis reveals that LEI in older people significantly increases the whole adverse chain from health to dementia, care need and death, and results in a large loss of years of life. Therefore, prevention and timely treatment of LEI, as well as rehabilitative care after LEI, may be very important in delaying or reducing

the onset of long-term care and death, not only in cognitively intact older people, but also in those with dementia. These measures will not only help to save years of life, but will also improve the quality of life of older people and reduce the burden on families, public health and the care system.

Last but not least, the thesis helps to understand and deepen the knowledge of the life course approach. The results of the thesis provide evidence for associations between risk or protective factors in earlier life stages and mental health at later life stages. Moreover, in terms of the sensitive period model in the life course approach, periods of LEI in older people can be seen as sensitive periods when people are more likely to develop dementia, become dependent on care, or die. This may add to the knowledge of the theory of sensitive periods in adulthood. In addition, the analysis of the association between ECEC-start-age and psycho-social problems shows that ECEC-exposure is more than a risk or preventive factor. The earlier begin of non-parental education doesn't always predict a better or poorer mental development in children. Moreover, the threshold effect may exist, and consequently the longer education doesn't always predict a better mental health or cognitive function. Therefore, the accumulation models of risk factor and sensitive period model alone cannot explain the effect of education on mental health and cognitive function. Instead, the relationship is more complex and depends on the age of children and length of education to a large extent. For such kind of relationship, an adaption-based approach or a relational developmental systems theory can add another dimension to life course thinking.

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9. Appendix: Original Publications and Indication of Own Contribution for Collaborative Work with Multiple Authors

Comparative Population Studies
Vol. 47 (2022): 119-142 (Date of release: 29.03.2022)

Development over Time in Cognitive Function among European 55-69-Year-Olds from 2006 to 2015, and Differences of Region, Gender, and Education

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Abstract: With populations rapidly aging, the development over time in the cognitive function among the elderly approaching or reaching retirement is important for successful aging at work and planning pension policies. However, few studies in this field focus on this age group. This study characterizes time trends in cognitive function among 55-69-year-old Europeans from 2006 to 2015, and compares these trends by region, gender, and education. This study analyzes 40,689 subjects in Waves 2, 4, 5 and 6 of the Survey of Health, Aging and Retirement in Europe (SHARE) covering ten countries. Cognitive function was measured by Recall and Verbal Fluency. Educational levels were classified by quartiles. A Generalized Estimating Equation (GEE) model was used to explore the association between cognitive function and development over time after controlling for confounders. Further stratification analysis using GEE models was conducted, stratified by region, gender and education. Cognitive function improved significantly in southern and central Europe over the observed timeframe, whereas it did not in northern Europe. Those with relative low levels of formal education displayed the most rapid increases in cognitive function in southern and central Europe. Among those with lower education in southern Europe, males' cognitive function improved more quickly than females'. The improvement of cognitive function at ages 55-69 in southern and central Europe may contribute to continuing engagement with productive activities in old age. Educational interventions for people with lower levels of education may be most effective in achieving such engagement. This paper extends the literature on the development over time in the cognitive function among the elderly close to retirement age in Europe by analysing southern, central and northern Europe, as well as differences by region, gender and education. The results may provide evidence for planning pension policies and educational interventions.

Keywords: Aging · Cognitive function · Education · Flynn effect

URL: www.comparativepopulationstudies.de
DOI: https://doi.org/10.12765/CPoS-2022-04
URN: urn:nbn:de:bib-cpos-2022-04en0

1 Introduction and review

As populations rapidly age, public policies in many countries now encourage working into increasingly higher ages, so as to help manage the increased costs of government retirement pension and health care (*Fisher et al.* 2016, 2017). By legislation, about half of the OECD countries will increase their retirement age to approximately 66 years on average by 2060 (*OECD* 2017). Moreover, financial incentives are now widely provided to delay retirement (*Fisher et al.* 2016).

However, poor health – including cognitive health – is one of the leading causes of early and unplanned retirement (*Fisher et al.* 2016). Although age-related cognitive decline begins in early adulthood (*Salthouse* 2010b), a study of the United States found that between the ages of 55 and 69, approximately 10 percent of workers experienced steep cognitive decline (*Belbase et al.* 2015). These workers experiencing steep cognitive decline were more likely to have lower performance at work, to "downshift" to a less cognitively demanding job, or to retire earlier than workers not experiencing cognitive decline (*Belbase et al.* 2015; *Fisher et al.* 2017). The cognitive functioning among older adults at work, particularly during periods approaching or reaching retirement, is a critical factor to successfully aging at work, especially in cognitively-demanding jobs, such as professional, managerial, technical and other cognitively complex jobs (*Fisher et al.* 2017).

Therefore, the development of cognitive function over time is a public health concern, particularly for the 55-69 age group.

1.1 Current research on trends in cognitive function

Past research analysing the trends of cognitive function remains inconsistent regarding the theory ("success of success" hypothesis versus "failure of success" hypothesis, "Flynn-effect" versus "Anti-Flynn-effect"), as well as in study results and conclusions.

On the one hand, the "success of success" hypothesis states that there exist factors which may improve the cognitive function of a population over time, postpone the onset of disability, and thereby result in more people living longer and healthier lives (*Fries* 1980). These positive factors for younger generations include higher education, better cardiovascular risk factor profiles (i.e. lower blood pressure and total cholesterol levels, less smoking, and more physical activity), better nutrition, and the improved treatment of cardiovascular diseases and diabetes (*Pietschnig/Voracek* 2015; *Ahrenfeldt et al.* 2018). Moreover, according to the "cognitive reserve" hypothesis, more recent generations have also more experience in jobs that require considerable cognitive investment, which leads to increases in neuronal development and consequently serves as a buffer against cognitive decline (*Fisher et al.* 2017). Recent studies have shown more recent birth years are associated with better cognitive function in Europe (*Ahrenfeldt et al.* 2018), and with slower rates of age-related cognitive decline and a lower risk of incident cognitive impairment in the United States (*Downer et al.* 2019; *Vonk et al.* 2019). The Berlin Aging Study reports that later-born cohort (in 2013-14, mean age of 75 years

old) showed higher levels of cognitive performance than their counterparts born 20 years earlier (*Gerstorf et al.* 2015). In addition, the tendency toward a cumulation of advantages or disadvantages, the so-called "Matthew effect", is observed in human aging and life-course patterns within cohorts, as well as between cohorts (*Dannefer* 1987, 2003). If a larger proportion of younger generations is exposed to more factors beneficial to cognitive function, taking the "Matthew effect" into consideration, their cognitive development over time at older ages may also develop positively.

The increase of cognitive abilities from one generation to the next, the so called "Flynn effect", has been reported in both developed countries (including the United States, 15 European nations, Japan, South Korea, Australia, Canada, and New Zealand) and developing countries (including China, India, Brazil, Dominica, Saudi Arabia, and Sudan) (*Flynn* 2012, 1987; *Pietschnig/Voracek* 2015). A meta-analysis has estimated a global increase of 3 IQ points per decade on average from 1909 to 2013 (*Pietschnig/Voracek* 2015).

On the other hand, according to the "failure of success" hypothesis, reduced age-specific mortality and longer lifespans might increase the prevalence of chronic conditions including cognitive impairment, leading to worse overall cognitive health of the elderly population (*Fries* 1980). Studies examining trends in cognitive function showed an increase over time in prevalent cognitive impairment in the Netherlands (*van den Kommer et al.* 2018) and the United States (*Downer et al.* 2019), and in prevalence of dementia in Japan (*Sekita et al.* 2010) and Sweden (*Mathillas et al.* 2011). These studies investigating cognitive impairment and dementia usually focus on the population aged 65+, 75+, or 85+. However, little is known about the cognitive functioning and its development over time for the elderly approaching or reaching retirement (55-69 years old), despite research revealing that some workers experience steep cognitive decline over this period (*Belbase et al.* 2015).

The plateauing or decline of cognitive abilities from one generation to the next, the so-called "negative Flynn effect" or "anti-Flynn effect", has been reported in European countries including Norway (*Sundet et al.* 2004), Denmark (*Teasdale/Owen* 2008), the Netherlands (*Woodley/Meisenberg* 2013), Finland (*Dutton/Lynn* 2013), France (*Dutton/Lynn* 2015), and Britain (*Shayer/Ginsburg* 2009). However, the majority of research on the negative Flynn effect used samples of under-20-year-olds (*Dutton et al.* 2016; *Sundet et al.* 2004; *Teasdale/Owen* 2008; *Shayer/Ginsburg* 2009; *Woodley/Meisenberg* 2013; *Dutton/Lynn* 2013, 2015).

Taking dynamic time periods, geographic areas, and gender into consideration, the trends in the cognitive function studies are more complicated, since development over time in cognitive function may vary among different population subgroups of geographic regions, genders, and further potential factors (*Prince et al.* 2016; *Dutton et al.* 2016; *Vonk et al.* 2019). Studies of both Denmark and Norway found early gains of the Flynn effect, followed by stagnation through the 1990s in both countries, and a slight decline since the late 1990s in Denmark (*Teasdale/Owen* 2005; *Sundet et al.* 2004). A recent study indicated greater increases in cognitive performance for southern Europeans (compared to central and northern Europe) and for females (compared to males) (*Weber et al.* 2017). However, the authors noted that further research is required for the inconclusive and statistically insignificant

findings, namely that males had larger gains than females in southern Europe, whereas females had larger gains in northern and central Europe (*Weber et al.* 2017). Moreover, the study did not analyse nor adjust for educational levels explicitly.

However, in addition to region and gender, education appears to be one of the key factors for time trends in cognitive ability in some countries, while not appearing influential in others (*Neisser* 1998; *Teasdale/Owen* 2005). More education in Europe may help cognitive levels, with a long-term effect through the pathways of occupation, social interaction, and lifestyle choices (*Bennett et al.* 2014; *Banks/Mazzonna* 2012; *Alley et al.* 2007; *Pavlova/Silbereisen* 2012; *Schneeweis et al.* 2014). Well-educated people are more likely to achieve higher earnings and income, to engage in greater social and cultural participation, and to have more healthy habits and lifestyles, which may prevent the age-related cognitive decline (*Banks/Mazzonna* 2012; *Rowe/Kahn* 1997). Moreover, people with higher education have more opportunities to work jobs demanding higher cognitive ability, and the "use it or lose it" hypothesis seems to be supported by results across studies (*Fisher et al.* 2017). Yet it remains unclear whether and how education moderates the trajectory of cognitive change (*Lenehan et al.* 2015; *Alley et al.* 2007). Some of the inconsistency in previous evidence may lie in the threshold of education for its effect (*Lenehan et al.* 2015).

1.2 Novel contributions of this study

First, this study focuses on the age group of 55-69. As mentioned above, the cognitive ability and its trends for this age group has a considerable influence on sustained productive work in old age and desired retirement timing. Moreover, this age group is less affected by sample attrition related to death or other health conditions than older adults. However, most research examining time trends in cognitive limitations or dementia focuses on persons 70 years of age or older (*Langa* 2015; *Choi et al.* 2018); while the majority studies which found the anti-Flynn effect examined those younger than 20 years old (*Larson et al.* 2013; *Alley et al.* 2007; *Dutton/Lynn* 2013; *Teasdale/Owen* 2005).

Second, this study investigates trends in cognitive function considering region, gender, and education by using a large representative European sample covering a total of ten countries in three European regions over nine years. The countries are Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, Spain, Sweden, and Switzerland.

Third, this study applies a new approach to operationalising education, which elsewhere has been successfully applied to time trend investigation by examining the relative rank of educational attainment or socio-economic status in proportion to the overall distribution (*Choi et al.* 2018; *Bound et al.* 2015). In contrast, the conventional classification of educational attainment by credentials or International Standard Classification of Education (ISCED) may lead to less comparable subgroups in the study of time trends, because the high educational group (ISCED $\geq$ 5) has grown over time, and the low educational group (ISCED $\leq$ 2) has shrunk and is becoming an increasingly vulnerable segment of the population (*Bound et al.* 2015).

Insufficient numbers of participants with low or high education levels may limit statistical power and lead to bias (*Lenehan et al.* 2015). Furthermore, relying only on years of education may cloud international comparisons, as each country has its own system with varying programme durations and differing types of certification, such as vocational and academic degrees.

1.3 Research question

This study aims to investigate changes in cognitive function over time at ages 55-69 in Europe and the differences linked to region, gender, and education. This study seeks to provide evidence whether and how cognitive performance becomes better over time at the population level for the elderly close to retirement ages in Europe. These results may contribute to the maintenance of productive activities in old age.

2 Data and methods

2.1 Sample

This study uses data of people between the ages of 55 and 69 in Waves 2, 4, 5, and 6 of the SHARE survey, a longitudinal, nationally representative, population-based, international, and harmonized survey (*Börsch-Supan et al.* 2013). Wave 1 was excluded because education was measured differently than in subsequent waves. Wave 3 was also excluded because it focused on respondents' life histories. Wave 7 was excluded because it was designed to focus on both life history and panel information, and the panel information was collected by a shorter, condensed set of questions from the regular panel questionnaire. Thus, Verbal Fluency in Wave 7, one of the key variables in this study, has a great deal of missing values because it was only asked for respondents who participated in SHARELIFE in Wave 3. This study included only those countries which participated in all selected waves, except for the Netherlands due to differences in its mixed mode experiment in Wave 6 compared to the regular SHARE waves for other countries. Thus, ten countries were included in the analysis: Austria, Belgium, Czech Republic, Denmark, France, Germany, Italy, Spain, Sweden, and Switzerland. Although some waves covered two calendar years, the first calendar year was used as the survey year, namely the years 2006, 2011, 2013, and 2015 for Waves 2, 4, 5, and 6, respectively. Italy and Spain were assigned to the category of southern Europe; Austria, Belgium, Czech Republic, France, Germany, and Switzerland were grouped together as central Europe; Denmark and Sweden were listed as northern Europe.

2.2 Cognitive function measures

SHARE uses temporal orientation, numeracy, immediate and delayed recall testing, and verbal fluency to measure cognitive function. This study focuses on recall tests and verbal fluency for four reasons. First, episodic recall tests and semantic

verbal fluency are sensitive to cognitive aging (*Souchay et al.* 2000; *Tomer/Levin* 1993). Second, recall and verbal fluency reflect two key dimensions of cognitive performance separately, namely fluid intelligence/working memory and crystallized intelligence/knowledge (*Arpino/Bordone* 2014; *Salthouse* 2006; *Weber et al.* 2017). Crystallized intelligence refers to an individual's store of knowledge and learned operation; fluid intelligence refers to the ability to think logically and solve novel problems independently of acquired knowledge, and is highly related to working memory (*Nisbett et al.* 2012; *Arpino/Bordone* 2014; *Salthouse* 2006; *Horn/Cattell* 1967; *Jaeggi et al.* 2008). Third, the temporal orientation in SHARE had a skewed distribution and thus was strongly affected by ceiling and floor effects. Fourth, the ordinal variable resulting from the numeracy test had limited variability, and the numeracy tests had a high number of missing values in Wave 6 (*Adam et al.* 2013; *Mehrbrodt et al.* 2019).

The recall test was used to assess episodic memory performance. The respondent listened to a list of ten words, and immediately did a recall test (immediate recall test), followed by another after a delay (delayed recall test). The number of words the respondent recalled correctly was recorded, ranging from 0 to 10 for both tests. The Recall variable is the average score of the immediate and delayed recall tests.

Verbal fluency was used to assess executive function. Respondents were asked to list animals, and the number of animals the respondent said correctly in one minute was counted and stored as the raw variable of verbal fluency. Outliers were defined as the values more than 2.5 standard deviations away from the mean per wave. These outliers were replaced by the wave-specific maximum values within 2.5 standard deviations. Thus, the verbal fluency without outliers ranged from 0 to approximately 40. Additionally, the variable was multiplied by 0.25, so that it had a comparable scale of 0 to approximately 10, similar to the Recall variable.

2.3 Educational level

For an international comparison of education, the ISCED 1997 was used with categories ranging from 0 to 6, with higher categories indicating higher levels of formal education. In order to improve comparability across groups over time, the ISCED 1997 grades were multiplied by years of education and further categorized into groups of "low", "middle", and "high" Adjusted Educational Levels for each survey wave. These three groups are made up of the bottom 25 percent (lowest to first quartile Q1), middle 50 percent (first quartile Q1 to third quartile Q3), and top 25 percent (third quartile Q3 to highest) for each survey wave.

2.4 Modelling strategies and statistical analysis

Generalized Estimating Equation (GEE) models were estimated using a linear link function with normally distributed error terms and an unstructured covariance matrix to account for the dependency of observations between waves. The GEE model is also capable of handling missing values and unbalanced cases and is fairly robust with large sample sizes in particular.

Separate GEE models for Recall and Verbal Fluency were run to explore their association with the time trend measured by the numeric survey year, adjusting for gender, region, education, and the interactions of gender-by-survey year, education-by-survey year, and region-by-survey year. The adjustment was conducted further for age at interview and whether the subject had participated in SHARE for the first time. In subsequent stratification analyses the association between cognitive function and time was further investigated by GEE models stratified by region, gender, and education.

A sensitivity analysis was conducted for the other common correlation structures (autoregressive, exchangeable, and independent). The goodness of fit statistic Quasilikelihood under the Independence Model Information Criterion (QIC) was used for the GEE model comparison (*Hardin/Hilbe* 2013). Moreover, a sensitivity analysis was conducted to include Wave 7. Finally, in order to investigate differences and similarities between the two operationalizations of education, the conventional classification of education by ISCED (ISCED-97 = 0-2, 3-4, 5-6 as low, middle, and high levels of education) was additionally applied in a separate analysis.

All analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

3 Results

The sample comprised 40,689 subjects with a mean age of approximately 62; roughly 54 percent of whom were female and 46 percent were male (see Table 1). From Wave 2 to Wave 6, the scores for Recall and Verbal Fluency increased on average. The proportions of low, middle, and high Adjusted Educational Level were approximately 25 percent, 50 percent, and 25 percent for each survey wave as defined, although these were not as precise as defined due to the tied values. The proportion of subjects who participated in the SHARE survey for the first time decreased over time (see Table 1).

Figure 1 illustrates the mean values and 95 percent confidence intervals for Recall and Verbal Fluency, showing a consistent increase of Verbal Fluency over time for each European region, and of Recall over time in central Europe. A less consistent trend of increase of Recall can also be found in northern and southern Europe. Overall, central Europe shows higher cognitive function than southern Europe, while northern Europe has the highest values. However, the differences between regions are shrinking due to different speeds of increase over time.

Table 2 shows the results of the two overall models for the association of cognitive function and time after controlling for age, gender, region, education, their interaction, and whether the subject had participated in SHARE for the first time.

Gender: Females had statistically significantly better Recall than males (ß = 0.44, $p < 0.0001$). There was a general improvement in cognitive function over time (Recall: ß = 0.02, $p < 0.0001$; Verbal Fluency: ß = 0.04, $p < 0.0001$). However, there was no significant overall difference in the trend between the two genders (Recall: ß = 0.00, $p = 0.322$; Verbal Fluency: ß = 0.01, $p = 0.176$).

Tab. 1: Demography, cognitive function, educational level, and other characteristics for the sample in SHARE

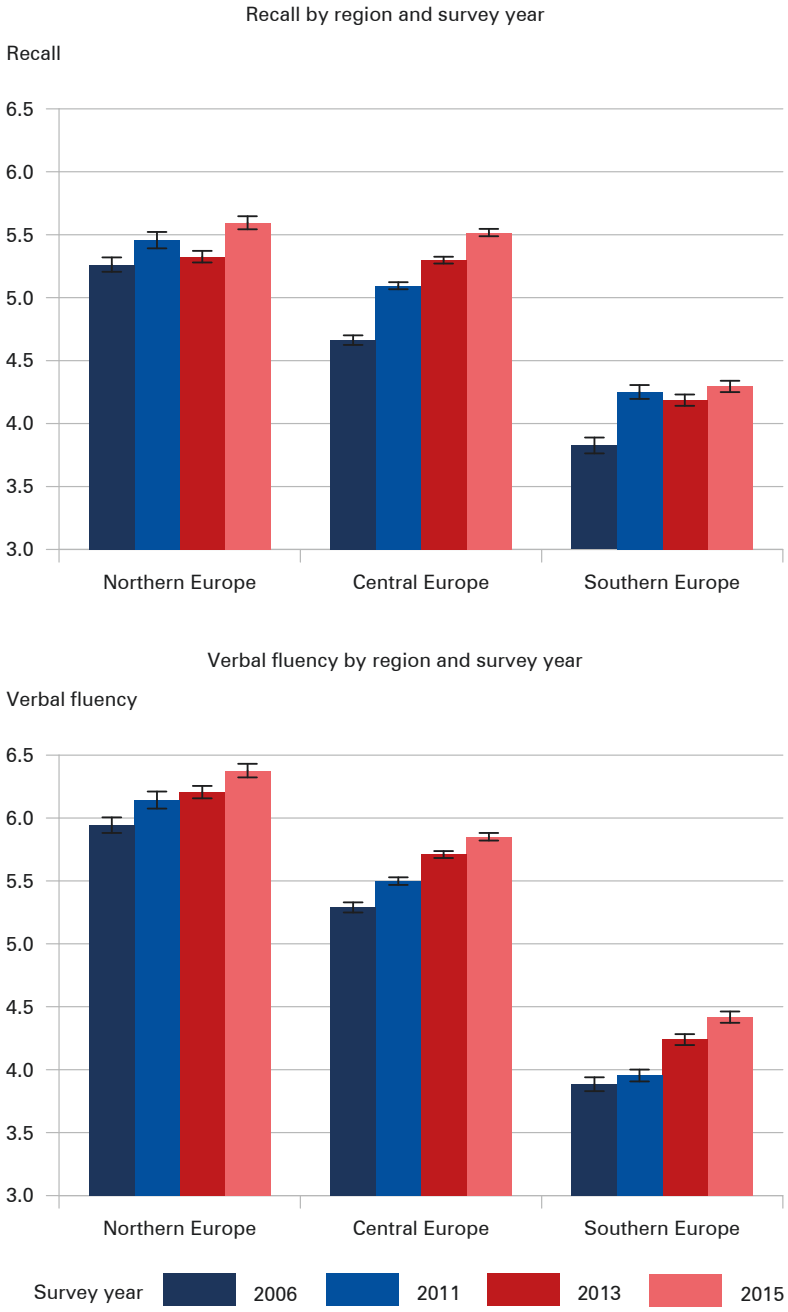
	Wave 2		Wave 4		Wave 5		Wave 6	
	n	(%)	n	(%)	n	(%)	n	(%)
N	12556		19338		24464		21151	
Age	61.7	(4.27)	61.9	(4.22)	62.2	(4.21)	62.4	(4.25)
Gender								
Female	6778	(54.0)	10562	(54.6)	13268	(54.2)	11666	(55.2)
Male	5778	(46.0)	8776	(45.4)	11196	(45.8)	9485	(44.8)
Country								
Austria	649	(5.2)	2549	(13.2)	2128	(8.7)	1578	(7.5)
Belgium	1553	(12.4)	2597	(13.4)	2814	(11.5)	2883	(13.6)
Czech Republic	1442	(11.5)	3067	(15.9)	3094	(12.6)	2515	(11.9)
Denmark	1233	(9.8)	1122	(5.8)	2162	(8.8)	1932	(9.1)
France	1361	(10.8)	2767	(14.3)	2322	(9.5)	1905	(9.0)
Germany	1429	(11.4)	886	(4.6)	2731	(11.2)	2181	(10.3)
Italy	1591	(12.7)	1789	(9.3)	2280	(9.3)	2489	(11.8)
Spain	1048	(8.3)	1629	(8.4)	3018	(12.3)	2483	(11.7)
Sweden	1536	(12.2)	1026	(5.3)	2308	(9.4)	1705	(8.1)
Switzerland	714	(5.7)	1906	(9.9)	1607	(6.6)	1480	(7.0)
Recall	4.6	(1.67)	5.0	(1.69)	5.1	(1.71)	5.2	(1.70)
Verbal fluency	5.1	(1.79)	5.3	(1.80)	5.5	(1.82)	5.6	(1.82)
Adjusted Educational Level								
Low	3179	(26.0)	4001	(25.6)	5214	(26.9)	3889	(26.5)
Middle	5895	(48.3)	7697	(49.2)	9267	(47.9)	7098	(48.3)
High	3143	(25.7)	3946	(25.2)	4879	(25.2)	3707	(25.2)
Participate in SHARE-survey								
First time	5786	(46.1)	13175	(68.1)	10664	(43.6)	3827	(18.1)
Not the first time	6770	(53.9)	6163	(31.9)	13800	(56.4)	17324	(81.9)

Source: Own calculations, based on data from SHARE

Region: There were statistically significant regional differences, with northern Europe showing higher cognitive function than southern and central Europe (central vs. northern Europe: Recall: ß = -0.56, $p < 0.0001$; Verbal Fluency: ß = -0.57, $p < 0.0001$; southern vs. northern Europe: Recall: ß = -0.97, $p < 0.0001$; Verbal Fluency: ß = -1.73, $p < 0.0001$). However, southern Europe experienced faster improvements in Recall (ß = 0.03, $p < 0.0001$) and Verbal Fluency (ß = 0.02, $p = 0.0009$) than northern Europe; in central Europe Recall and Verbal Fluency also improved more quickly than in northern Europe (Recall: ß = 0.07, $p < 0.0001$; Verbal Fluency: ß = 0.02, $p = 0.0006$).

Education: In comparison to those with relative low levels of education, people with middle and higher levels of education had higher cognitive function (Middle vs. Low educational levels: Recall: ß = 0.65, $p < 0.0001$; Verbal Fluency: ß = 0.61, $p < 0.0001$; High vs. Low educational level: Recall: ß = 1.18, $p < 0.0001$; Verbal Fluency: ß = 1.22, $p < 0.0001$). Nevertheless, those with lower levels of education

Fig. 1: Bar chart for mean values of cognitive function with 95 percent confidence interval by region and survey year



Source: Own calculations, based on data from SHARE

Tab. 2: Overall models: Association of the cognitive function and time after controlling for gender, region, education, their interactions, and potential confounders in SHARE by GEE models[1]

	Recall	Verbal Fluency
Intercept	7.14***	7.84***
Gender (Female)[2]	0.44***	0.00
Survey year	0.02***	0.04***
Survey year*Gender (Female)[2]	0.00	0.01
Region (Central Europe)[3]	-0.56***	-0.57***
Region (Southern Europe)[3]	-0.97***	-1.73***
Survey year * Region (Central Europe)[3]	0.07***	0.02***
Survey year * Region (Southern Europe)[3]	0.03***	0.02***
Adjusted educational level (Middle)[4]	0.65***	0.61***
Adjusted educational level (High)[4]	1.18***	1.22***
Survey year * Adjusted educational level (Middle)[4]	-0.01***	-0.01
Survey year * Adjusted educational level (High)[4]	0.00	-0.02***
Age	-0.05***	-0.04***
Participate in SHARE-survey for the 1st time	-0.18***	-0.13***

[1] *** p<=0.01; ** p<=0.05; *p<=0.1.

[2] Male is the reference group for gender.

[3] Regions: Southern Europe: Italy, Spain; Central Europe: Austria, Belgium, Czech Republic, France, Germany, Switzerland; Northern Europe: Denmark, Sweden (reference group).

[4] Adjusted educational level: low: lowest-Q1 (reference group); Middle: Q1-Q3; High: Q3-highest.

Source: Own calculations, based on data from SHARE

improved their Recall faster than those with middle educational levels did (ß = -0.01, p = 0.005), and improved their Verbal Fluency more quickly than the highly-educated (ß = -0.02, p = 0.006).

The models are stratified by regions in Table 3 (Columns I and IV), permitting us to study the differences in regional time trends. The models reveal that cognitive function improved significantly in southern and central Europe (southern Europe: Recall: ß = 0.08, p < 0.0001; Verbal fluency: ß = 0.07, p < 0.0001; central Europe: Recall: ß = 0.09, p < 0.0001; Verbal fluency: ß = 0.06, p < 0.0001), whereas in northern Europe Recall has stagnated (ß = -0.02, p = 0.145) and Verbal Fluency improved somewhat, but not statistically significantly according to a significance level of 0.05 (ß = 0.02, p = 0.066). Moreover, in southern Europe, the interaction of time-by-gender showed that males tended to benefit more from improving cognitive function than females (Recall: ß = -0.02, p = 0.003; Verbal fluency: ß = -0.01, p = 0.081). Additionally, in southern and central Europe, those with lower education levels tended to improve their cognitive function faster than the other educational groups, as most of the coefficients for the time-by-education interaction

Tab. 3: Stratification analyses: Association of cognitive function and time in SHARE by GEE models, stratified by region, and further stratified by gender[1]

	Recall			Verbal Fluency		
	Overall (I)	Female (II)	Male (III)	Overall (IV)	Female (V)	Male (VI)
Southern Europe[2]						
Intercept	5.67***	6.22***	5.32***	5.55***	5.66***	5.25***
Middle Education[3]	1.01***	0.95***	1.06***	0.58***	0.61***	0.55***
High Education[3]	1.69***	1.71***	1.69***	1.00***	0.94***	1.04***
Survey year	0.08***	0.05***	0.09***	0.07***	0.05***	0.07***
Survey year * Middle Education[3]	-0.03***	-0.02*	-0.04***	-0.01	0.00	-0.01
Survey year * High Education[3]	-0.05***	-0.04**	-0.07***	0.00	0.01	-0.02
Gender (Female)[4]	0.27***			-0.13**		
Survey year * Gender (Female)[4]	-0.02***			-0.01*		
Central Europe[2]						
Intercept	6.81***	7.31***	6.77***	7.30***	7.51***	7.10***
Middle Education[3]	0.54***	0.56***	0.50***	0.72***	0.71***	0.74***
High Education[3]	1.12***	1.12***	1.12***	1.41***	1.39***	1.43***
Survey year	0.09***	0.08***	0.10***	0.06***	0.07***	0.07***
Survey year * Middle Education[3]	-0.01**	-0.01	-0.02**	-0.01**	-0.01	-0.02**
Survey year * High Education[3]	0.00	0.00	-0.01	-0.03***	-0.02*	-0.05***
Gender (Female)[4]	0.46***			0.05		
Survey year * Gender (Female)[4]	0.00			0.01**		
Northern Europe[2]						
Intercept	7.01***	7.80***	6.74***	8.42***	8.99***	7.76***
Middle Education[3]	0.43***	0.40***	0.46***	0.41***	0.46***	0.36***
High Education[3]	0.78***	0.86***	0.67***	0.91***	0.91***	0.91***

Tab. 3: Continuation

	Recall			Verbal Fluency		
	Overall (I)	Female (II)	Male (III)	Overall (IV)	Female (V)	Male (VI)
Survey year	-0.02	0.00	-0.03**	0.02*	0.03*	0.02
Survey year * Middle Education[3]	0.02*	0.01	0.03*	0.01	0.00	0.01
Survey year * High Education[3]	0.04***	0.01	0.06***	0.02	0.02	0.01
Gender (Female)[4]	0.59***			0.01		
Survey year * Gender (Female)[4]	0.01			0.01		

[1] *** p<=0.01; ** p<=0.05; *p<=0.1. Models are further adjusted by age and whether the subject participated in the SHARE survey for the first time.

[2] Regions: Southern Europe: Italy, Spain; Central Europe: Austria, Belgium, Czech Republic, France, Germany, Switzerland; Northern Europe: Denmark, Sweden.

[3] Adjusted educational level: low: lowest-Q1 (reference group); Middle: Q1-Q3; High: Q3-highest.

[4] Male is the reference group for gender.

Source: Own calculations, based on data from SHARE

Tab. 4: Stratification analysis: Association of the cognitive function and time in SHARE by GEE models, stratified by region and education[1]

	Recall				Verbal Fluency			
	Overall[2]	Low Education[3]	Middle Education[3]	High Education[3]	Overall[2]	Low Education[3]	Middle Education[3]	High Education[3]
	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)
Southern Europe[4]								
Intercept	5.67***	6.42***	5.87***	6.52***	5.55***	5.59***	5.60***	8.15***
Gender (Female)[5]	0.27***	0.27***	0.23**	0.35*	-0.13**	-0.16**	-0.04	-0.24
Survey year	0.08***	0.08***	0.04***	0.02	0.07***	0.07***	0.05***	0.05***
Survey year * Gender[5]	-0.02***	-0.03***	-0.01	-0.01	-0.01*	-0.02**	-0.01	0.00
Middle Education[3]	1.01***				0.58***			
High Education[3]	1.69***				1.00***			
Survey year * Middle Education[3]	-0.03***				-0.01			
Survey year * High Education[3]	-0.05***				0.00			
Central Europe[4]								
Intercept	6.81***	7.57***	7.28***	7.75***	7.30***	7.44***	8.02***	8.71***
Gender (Female)[5]	0.46***	0.40***	0.49***	0.42***	0.05	0.06	0.05	0.05
Survey year	0.09***	0.10***	0.07***	0.08***	0.06***	0.07***	0.05***	0.03***
Survey year * Gender[5]	0.00	-0.01	0.00	0.01	0.01**	0.00	0.01*	0.02**
Middle Education[3]	0.54***				0.72***			
High Education[3]	1.12***				1.41***			
Survey year * Middle Education[3]	-0.01**				-0.01**			
Survey year * High Education[3]	0.00				-0.03***			
Northern Europe[4]								
Intercept	7.01***	7.16***	7.49***	7.61***	8.42***	9.60***	8.65***	9.07***
Gender (Female)[5]	0.59***	0.54***	0.47***	0.73***	0.01	-0.06	0.07	0.00
Survey year	-0.02	-0.03	0.00	0.03***	0.02*	0.03	0.04***	0.03***
Survey year * Gender[5]	0.01	0.03	0.02	-0.01	0.01	0.01	-0.01	0.02

Tab. 4: Continuation

	Recall				Verbal Fluency			
	Overall[2]	Low Education[3]	Middle Education[3]	High Education[3]	Overall[2]	Low Education[3]	Middle Education[3]	High Education[3]
	(I)	(II)	(III)	(IV)	(V)	(VI)	(VII)	(VIII)
Middle Education[3]	0.43***				0.41***			
High Education[3]	0.78***				0.91***			
Survey year * Middle Education[3]	0.02*				0.01			
Survey year * High Education[3]	0.04***				0.02			

[1] *** p<=0.01; ** p<=0.05; *p<=0.1. Models are further adjusted by age and whether the subject participated in the SHARE survey for the first time.

[2] The overall model is the same as that in the Table 3. It is listed here again for easier comparison with other models.

[3] Adjusted educational level: low: lowest-Q1 (reference group); Middle: Q1-Q3; High: Q3-highest.

[4] Region: Southern Europe: Italy, Spain; Central Europe: Austria, Belgium, Czech Republic, France, Germany, Switzerland; Northern Europe: Denmark, Sweden.

[5] Male is the reference group for gender.

Source: Own calculations, based on data from SHARE

were statistically significantly negative values, and none of these coefficients were statistically significantly positive values.

Further stratification analysis by region and education, shown in Table 4, confirmed a statistically significant interaction of time and gender favoring males with lower education levels in southern Europe (Table 4). (Column II, interaction time-by-gender for Recall: ß = -0.03, p = 0.002; Column VI, for Verbal fluency: ß = -0.02, p = 0.039).

The sensitivity analysis regarding the correlation structures (autoregressive, exchangeable, and independent correlation structures) resulted in consistent parameter estimations and inference p-values, as well as similar goodness of fit statistics (QICs). Results remained stable when the data of Wave 7 was included, despite a large number of missing values for Verbal Fluency. The sensitivity analysis using the conventional classification of education by ISCED produced similar results, but was not able to show the interaction of survey year and educational level consistently (data not shown).

4 Discussion

This study has three important results. First, cognitive function among 55-69-year-olds improved significantly from 2006 to 2015 in southern and central Europe, whereas it did not in northern Europe, although there was already a generally higher level in northern Europe to begin with. Thus, the gap between European regions is getting smaller. Second, in southern and central Europe, the group with relative low education, starting from the lowest level of cognitive function, tended to improve its cognitive functions more quickly than the middle and higher educational groups did. Thus, the gap between the relative low educational group and other educational groups is growing smaller. Third, among those with lower education in southern Europe, males improved their cognitive functions more quickly than females. More generally, in southern Europe, males seemed to benefit more than females in terms of improvement of cognitive function after controlling for education.

The disparity of regions, education, and genders over time may be explained by the threshold theory, as *Lyketsos et al*. tried to interpret the benefit of education for preventing cognitive decline in adulthood (i.e. beyond a certain "dose" of education, such as 8 years of schooling, additional years of education are no longer associated with less cognitive decline) (*Lenehan et al.* 2015; *Lyketsos et al.* 1999). Once the biological limits or environmental threshold on the improvement of cognitive function are reached or approaching, gains of cognitive ability might arrive at or get close to saturation and the improvements may yield diminishing returns, cease, or even reverse (*Weede* 2006; *Rindermann* 2008; *Pietschnig/Voracek* 2015; *Dutton et al.* 2016). In other words, the "success of success" or "failure of success" hypotheses alone may not explain the complete picture of time trends in cognitive function.

4.1 Regional disparities

The findings of this study suggest that 55-69-year-old adults in southern and central Europe stay at the Flynn effect phase, whereas the same age group in northern Europe stays at the anti-Flynn effect phase. *Flynn et al.* have summarized that some Scandinavian nations had robust intelligence gains in the twentieth century but peaked around 1990 and may have gone into mild decline since then (*Flynn* 2012). If we look at the trends in cognitive function dynamically, the Flynn effect in southern and central Europe indicates that these countries may have the potential for further improvement on cognitive function from one generation to the next, whereas the anti-effect in northern Europe suggests that these countries may have arrived at or be approaching the maximum plateau. A recent study showed improvements in cognitive function for those aged 50+ in all European regions (*Ahrenfeldt et al.* 2018). However, more closely examining those aged 55-69 in that study, southern and central Europeans had considerable improvements of cognitive function, whereas northern Europeans didn't (*Ahrenfeldt et al.* 2018). The mortality selection and different survival patterns for the oldest among the old (*Hülür et al.* 2013; *Gerstorf et al*. 2015) may explain the inconsistency between the present study and theirs. Furthermore, the finding of the present study is consistent with some previous studies on trends in cognitive function (*Pietschnig/Voracek* 2015; *Sundet et al.* 2004), but inconsistent with others (*Dutton/Lynn* 2015; *Weber et al.* 2017). The inconsistency may result from the age groups of the samples, the measures and analysis of cognitive function, and other potential influencing factors. Nonetheless, a major strength of the present study is that it provides evidence from three European regions with internationally comparable data and approaches.

Cognitive health is a key prerequisite for deciding the age at which people retire, although the decision of when to retire is complex and often based on many factors including macroeconomic, family, work-related, and individual factors (*Fisher et al.* 2016, 2017). This study indicates that increases of the retirement age may be reasonable in southern and central European countries from the perspective of cognitive health.

4.2 Educational disparities

A threshold for the cognitive health benefits of education may explain the association between education and the rates of cognitive change. According to a review paper published in 2000, the majority of the studies between 1985 and 1999 reported protective effects of education on the rate of cognitive decline (*Anstey/Christensen* 2000). In contrast, another review paper published in 2015 indicated that the majority of the studies from 2000 to 2015 reported no such protective effects (*Lenehan et al.* 2015). The beneficial impact of education on cognitive decline may no longer be observable as education levels extend beyond a certain threshold, such as an eight-year threshold (*Lyketsos et al.* 1999; *Lenehan et al.* 2015). Having eight years or less of formal education was reported to be associated with greater cognitive

decline. However, having nine years of education or more was unrelated to any further reduction of cognitive decline (*Lyketsos et al.* 1999).

In line with this threshold explanation, this study indicates that most benefits of the Flynn effect in those with the least education are probably due to the fact that those people with the lowest education levels had the lowest baseline values for cognitive function, and these remained lower than the threshold throughout the analysis period in southern and central Europe. Consequently, those with low education in these regions have disproportionally improved their cognitive function over time. On the other hand, this was not observed in northern Europe. A possible explanation is that the majority of the northern Europeans attained the maximum cognitive reserve capacity with increasing levels of education as the norm (*Lenehan et al*. 2015).

Interestingly, previous studies have revealed that school reform in England led to improvements in old-age memory of people with less education (*Banks/Mazzonna* 2012). Other studies also found that the early gains of the Flynn effect in Denmark and Norway were primarily at the low end of the cognitive test score distributions, which were attributed to the developments of educational system (e.g. improved pre-school care, starting school earlier and leaving later, and improved special education for physically or mentally disabled children) (*Teasdale/Owen* 2005; *Sundet et al.* 2004). Support for active aging was recommended to target less-educated and other disadvantaged groups in Germany (*Pavlova/Silbereisen* 2012). In a review paper, *Lenehan et al.* suggested that less-educated groups were an under-researched subgroup for the effect of education on the rate of cognitive function, and they assumed that this subgroup could benefit most from education-based intervention approaches (*Lenehan et al.* 2015).

Consistently, the findings of this study provide further evidence that in the context of limited resources, it may be worth prioritizing those with relative low educational levels when it comes to education-based intervention approaches in southern and central Europe. This would also hold true for developing countries, since a continuing Flynn effect has been observed or has begun to be observed in the developing world (*Flynn* 2012; *Nisbett et al.* 2012).

4.3 Gender disparities

An explanation for the greater improvement of cognitive function in males in southern Europe may be the larger biological vulnerability, variability, and flexibility of cognitive function for males (*Halpern* 2012). Some types of mental retardation are X-linked and are therefore more prevalent in males (*Halpern* 2012). Moreover, previous studies have found that males show greater age-related decline than females, independent of whether males or females outperform for the parameter of cognitive function (*Maylor et al.* 2007). In other words, 55-69-year-old males may have lower baselines, and a larger potential to improve, particularly in those groups in southern Europe with the lowest educational levels.

Banks et al. found that school reform in England improved executive function at old age only for males with less education (*Banks/Mazzonna* 2012). Schneeweis et

al. similarly observed that the educational reforms in Europe had stronger protective effects on cognitive function and decline for males (*Schneeweis et al.* 2014). Both of these studies explained this as the positive financial returns and prolonged labor force participation only for males from the educational reforms (*Banks/Mazzonna* 2012; *Schneeweis et al.* 2014). This may also explain the present study's finding of greater increases in cognitive function favoring males in the group with lower education in southern Europe. Additionally, this study's analysis of education gives further insights into the regional gender differences based on *Weber's* papers (*Weber et al.* 2017). The larger gain for males in southern Europe which was observed by Weber et al. (*Weber et al.* 2017) may be attributed to the improvement in the lower educational group.

4.4 A more complete picture of disparity by region, gender, and education

On the whole, threshold theory may be able to explain the various rates of cognitive improvement throughout all Europe by region, education, and gender. Southern and central Europeans, people with lower education, and males may have larger potentials to improve their cognitive function than the corresponding comparison groups, thus also showing quicker improvements in the data. Conversely, the cognitive function of the corresponding comparison groups may be closer to biological limits (saturation), hence improvements happen more slowly, if at all. In addition, threshold theory may also cover other factors, such as living conditions and heathy behaviors, which may influence cognitive improvements over time as well. Further research is needed to investigate and further support this explanation.

4.5 Strengths and limitations

One of the major strengths of this study is that it investigated 55-69-year-olds, whose cognitive development over time is important for sustained productive work in old age and pension policies, but who have relatively rarely been investigated to date. Second, this study used SHARE datasets with large sample sizes covering numerous European countries with harmonized design and data (*Börsch-Supan et al.* 2013). Third, this study used a definition of education by quantiles, which decreased selection bias and increased comparability. Fourth, this study used the data of Waves 2, 4, 5 and 6, and considered the correlation of the same subject in its modelling strategy. This longitudinal approach can show a more precise picture than cross-sectional studies or studies with only two time points (*Lenehan et al.* 2015). Fifth, recall and verbal fluency are performance-based measures, thus avoiding the biases which may occur in self-reported measures.

This study also has limitations. First, the retest effect may influence the cognitive parameters (*Salthouse* 2010a). In order to minimize it, an adjustment for first-time participation was included in the statistical models. Second, the two parameters only partially cover the overall concept of cognitive function. Further studies are needed to investigate other parameters of cognitive function. However, our

assessments of recall and verbal fluency can be regarded as two key dimensions of intelligence, fluid intelligence/working memory, and crystallized intelligence/knowledge (*Arpino/Bordone* 2014; *Salthouse* 2006; *Weber et al.* 2017). Third, as an observational study without a causal identification strategy, no causal relationship can be provided. Moreover, it is difficult to clearly distinguish the aging and cohort effects. Consideration must be taken when interpreting the results. Fourth, the overall effect sizes seem to be small. However, due to the division of values in our parameters for a comparable range, the true effect size might be larger than it seems to be. Moreover, the difficulty of setting criteria of clinical meaningfulness for the effect size is a general limitation in research using cognitive tests (*Halpern* 2012). Fifth, the relative rank of educational attainment is used to minimize the selection bias of educational groups over time. However, it is difficult to use another golden standard measurement to validate this approach. A sensitivity analysis using conventional classification of educational attainment was conducted to investigate the differences and similarities between the two operationalizations of education.

4.6 Conclusions

Older adults close to retirement age (55-69-year-olds) in southern and central Europe improved their cognitive function significantly from 2006 to 2015, whereas adults of the same age in northern Europe did not. Those with relative low levels of education in southern and central Europe improved their cognitive function most rapidly. Among those with lower education in southern Europe, males improved in cognitive function more quickly than females did. These results can be interpreted in line with threshold theory. Despite the complexity of the decisions about the retirement age, future increases of the retirement age may be reasonable in southern and central European countries from the perspective of cognitive function. It also may be worth prioritizing people with lower levels of formal education when it comes to education-based intervention approaches.

Acknowledgements

I would like to express my sincere thanks to Gabriele Doblhammer for her very valuable comments on this manuscript, and Renee Lueskow for her English editing service. This paper uses data from SHARE Waves 2, 4, 5, and 6, see *Börsch-Supan et al.* (2013) for methodological details. The SHARE data collection has been funded by the European Commission, DG RTD through FP5 (QLK6-CT-2001-00360), FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-2006-028812), FP7 (SHARE-PREP: GA N°211909, SHARE-LEAP: GA N°227822, SHARE M4: GA N°261982, DASISH: GA N°283646) and Horizon 2020 (SHARE-DEV3: GA N°676536, SHARE-COHESION: GA N°870628, SERISS: GA N°654221, SSHOC: GA N°823782, SHARE-COVID19: GA N°101015924) and by DG Employment, Social Affairs & Inclusion through VS 2015/0195, VS 2016/0135, VS 2018/0285, VS 2019/0332, and VS 2020/0313. Additional funding from the German

Ministry of Education and Research, the Max Planck Society for the Advancement of Science, the U.S. National Institute on Aging (U01_AG09740-13S2, P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11, OGHA_04-064, HHSN271201300071C, RAG052527A) and from various national funding sources is gratefully acknowledged (see www.share-project.org).

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Date of submission: 05.02.2020 *Date of acceptance: 05.11.2021*

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Comparative Population Studies

www.comparativepopulationstudies.de

ISSN: 1869-8980 (Print) – 1869-8999 (Internet)

Published by
Federal Institute for Population Research (BiB)
D-65180 Wiesbaden / Germany

Managing Publisher
Dr. Nikola Sander

E-mail: cpos@bib.bund.de

BMC Psychology

RESEARCH Open Access

Association between the starting age of non-parental Early Childhood Education and Care (ECEC), and psycho-social problems in adolescence in West and East Germany – a natural experiment using data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)

Ying Zhou[1], Annelene Wengler[2] and Gabriele Doblhammer[1,3*]

Abstract

Introduction The study aimed to investigate the association between the start age of non-parental Early Childhood Education and Care (ECEC) and psycho-social problems in adolescence. The similarities and differences between West and East Germany were also investigated in a natural experiment.

Methods Our sample consisted of 1022 children (621 from West Germany, 401 from East Germany) aged 3–4 years at wave 2003–2006 that were followed up to wave 2014–2017 as adolescents (mean ± SD age = 14.4 ± 0.03 years) in the KiGGS study. The psycho-social problems were measured by the parent-reported Strengths and Difficulties Questionnaire (SDQ) at wave 2014–2017. Linear regression was used to explore the relationship between ECEC-start-age and psycho-social problems in adolescence in Germany, and stratified by West and East Germany.

Results Those who started ECEC between 2 and 3 years old (reference) had the lowest scores of psycho-social problems in the whole Germany and in West Germany in adolescence. In comparison, those who started ECEC older than 3 years old had higher scores of internalizing psycho-social problems in both West Germany (with statistically significant results) and East Germany (with a relatively larger effect size but insignificant results). Those who started ECEC younger than 1 year old had statistically significant higher scores for externalizing psycho-social problems in West Germany, even though less children started ECEC younger than 1 in West Germany compared to East Germany. This significant association was not found in East Germany. Those who started ECEC between 1 and 2 years old tended to have higher scores of externalizing psycho-social problems in both West and East Germany.

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Conclusion The results suggest that if children start ECEC older than 3 years or younger than 2 years, more attention needs to be given to internalizing or externalizing psycho-social problems respectively. The regional differences for children younger than 1 year old may suggest a selection effect in West Germany where only fewer parents bring babies to ECEC, while the regional similarities for children over 3 years old indicate the importance of providing access to ECEC for children over 3 years old.

Keywords Early childhood education and care (ECEC), ECEC-start-age, Psycho-social problems

Background

The request for and use of non-parental Early Childhood Education and Care (ECEC) at a young age has increased in Germany and other high- and middle-income countries in recent years [1]. ECEC refers to any regulated non-parental arrangement that provides education and care for children from birth to compulsory primary school age [2]. It includes center-based ECEC and family-based non-parental daycare. In Germany, the use of non-parental ECEC for children under 3 years of age increased remarkably between 2002 and 2019 from 9 to 34%; and for children over 3 years of age from 90 to 93% [3, 4].

Germany was divided into German Democratic Republic (GDR) and Federal Republic of Germany (FRG) from 1949 to 1990. The different historical background resulted in distinct cultural and societal norms regarding women's employment and family roles which continues to today. In GDR women were encouraged to work by emphasizing the principle of equal pay for equal work, providing a generous maternity leave policy, and available free non-parental ECEC. Housewives were devalued by being described as "parasites" in an environment where soviet-ordained gender equality was popular. On the other hand, in FRG women were discouraged to work because of tax and benefit system for dual-earner families and scarce non-parental ECEC. Working mothers were devalued and described as "raven mothers" in an environment where more traditional gender-role attitude were apparent [5]. Therefore, regional difference between West and East Germany affects the proportions of women in employment (56% women in West Germany and 89% women in East Germany worked in 1989; 12% mothers in West Germany and 30% mothers in East Germany worked full-time in 2017), and for the amount of ECEC available and its use (8% of children 0–3 year old in West Germany and 40% of 0–3 year old children in East Germany attended ECEC in 2006) [3, 5, 6]. The cultural difference regarding the role of women still exists today, several decades after the reunification [5]. Mothers in East Germany still behave according to the more egalitarian gender norms in which they grew up, and return back to work earlier and tend to work more hours after childbirth than mothers in West Germany [5]. However, with reunification, the GDR adopted the political, economic and legal institutions of West Germany since 1990. This included 1 year paid parental leave from 2005 with 36 months of parental leave in total available per child. The different development in the two parts of Germany provides an opportunity to study the effect of ECEC on psycho-social problems in adolescence as a sort of *natural experiment*, which, similarly to twin studies, can control for unmeasured or unknown confounders to some extent.

Psycho-social problems are major health problems with a prevalence of around 17 −20% in children and adolescents in Germany [7]. They have a significant impact on their performance potential, quality of life, social participation, and lead to significant medical costs for society [8]. Psycho-social problems can be differentiated as externalizing and internalizing problems. Externalizing problems includes aggressive and oppositional behavior, high impulsivity and hyperactivity; Internalizing problems includes high social anxiety, depressive symptoms and withdrawal [8].

So far, the association between ECEC attendance and children's psycho-social development is inconclusive. There is evidence of the benefits of ECEC on social and emotional functioning [2, 9] and, conversely, evidence of negative outcomes of ECEC, including insecure attachment, behavioral disorders and aggression [10–12]. In addition, some studies showed few or missing effects of ECEC [13, 14]. These inconsistencies of the findings may be due to the differences in the age at which ECEC started, as well as the intensity and quality of ECEC [2, 15].

Particular attention should be paid to the age at which ECEC begins. Previous studies reported early ECEC as a risk factor for insecure attachment and externalizing psycho-social problems, especially in the case of extensive, unstable, or low quality of ECEC exposure [10, 16]. However, other studies showed that the early childhood years are a sensitive period for social and language development [16]. Attending ECEC early is likely to provide more opportunities to play and interact with peers, to acquire social, language skills and to have close friends, which can reduce the risk of internalizing problems [17].

In addition, it remains questionable whether and to what extent the influence of ECEC on psycho-social problems continues beyond early childhood. Most studies investigating the effects of ECEC on psycho-social problems had a short-term follow-up, such as up to

primary school [1, 2]; or are limited to investigating long-term effects on academic achievements or on secure attachment states of mind only [18, 19]. Among the few studies investigating the long-term effects of ECEC on psycho-social problems, an American study has reported that greater exposure to ECEC from birth to 4.5 years predicted more teacher-reported externalizing problems at age 12 [20].

Furthermore, in the literature there are also concerns about the internal and external validity of the studies regarding child-care and children's psycho-social problems. One major concern regarding the internal validity is the potential selection bias, which is difficult to well control by using conventional statistical approaches such as covariate-adjusted correlations in observational studies [21]. For example, parental and family interaction outside ECEC, as an important factor for psycho-social development [22], is difficult to be fully controlled for by using conventional statistical approaches in the analysis of the association between ECEC and children's psycho-social problems. Another critical limitation of previous studies is the heavy reliance on samples from the United States of America, which has limited the external validity [21]. Yet, in recent years there has been a growing body of research in this area in Europe [13].

Data from the KiGGS study (German Health Interview and Examination Survey for Children and Adolescents) allows us to investigate the long-term association between ECEC-start-age and psycho-social problems in adolescence, and its similarities and differences between West and East Germany in a natural experiment. Our study can contribute to this field of research, in particular regarding the following three points: First, we assess psycho-social development long time after ECEC started. Second, the natural experiment comparing the regional differences and similarities between West and East Germany may help control some unmeasured or unobserved confounders, thus reducing the selection bias and improving the internal validity. Third, our study attempts to provide more socio-political variations by using German samples and by even categorizing the samples into West and East Germany, to contribute to the external validity in this area of research.

Methods

Data source

We used data from the KiGGS study, a prospective cohort study [23, 24] of 17,640 children who were first interviewed in 2003–2006 (baseline wave) and followed up in two waves until 2014–2017 (wave 2). Since telephone interviews were used in wave 1, whereas self-administered questionnaires were used in the baseline wave and wave 2, wave 1 was excluded from our analysis. Wave 1 data were only used for the classification of the age at which ECEC started, because this age could only be clearly defined by using the data from baseline wave and wave 1 together (described below).

Analysis sample

Our analysis sample included children who were 3 and 4 years old at the baseline wave and those who were younger than 18 years old and participated in wave 2. In addition, only children with complete SDQ (Strengths and Difficulties Questionnaire) and ECEC-start-age were included, resulting in an analysis sample of 1022 children (Fig. 1).

We selected children ≥ 3 years old at the baseline wave to ensure a clear classification of ECEC-start-age based on the data from the baseline wave and wave 1. We excluded children aged 5 and older, as they may be preparing to start school or may even be in school in Germany.

Instruments

Psycho-social problems

We used the total difficulties score and four subscales of the SDQ at wave 2 to measure psycho-social problems in adolescence [25]. The score for externalizing psycho-social problems was obtained by summing up the scores for conduct problems and hyperactivity. The score for internalizing psycho-social problems was obtained by summing up the scores for emotional symptoms and peer problems. Each score (for externalizing or internalizing psycho-social problems) ranged from 0 to 20. The sum of the scores for externalizing and internalizing psycho-social problems made up the total score of SDQ, which accordingly ranged from 0 to 40. The higher the scores are, the larger psycho-social problems the children may have.

ECEC-start-age

The age at which ECEC started (ECEC-start-age) was derived from the data of the baseline wave and wave 1, based on the following two questions: "Was or is your child only cared for in the family before starting school?". If the answer was no, then parents were asked about the ECEC-start-age. The specific rules for deriving the ECEC-start-age can be found in Supplementary Material 1.

Potential confounders

All potential confounding variables – SES (Socioeconomic Status), migration status, number of older siblings (order of birth), family situation and family cohesion, birth weight, obesity/overweight, maternal age at birth, maternal employment status and region (West/East Germany) - were collected at the baseline wave, except for the age, type of schooling, and parental divorce, which

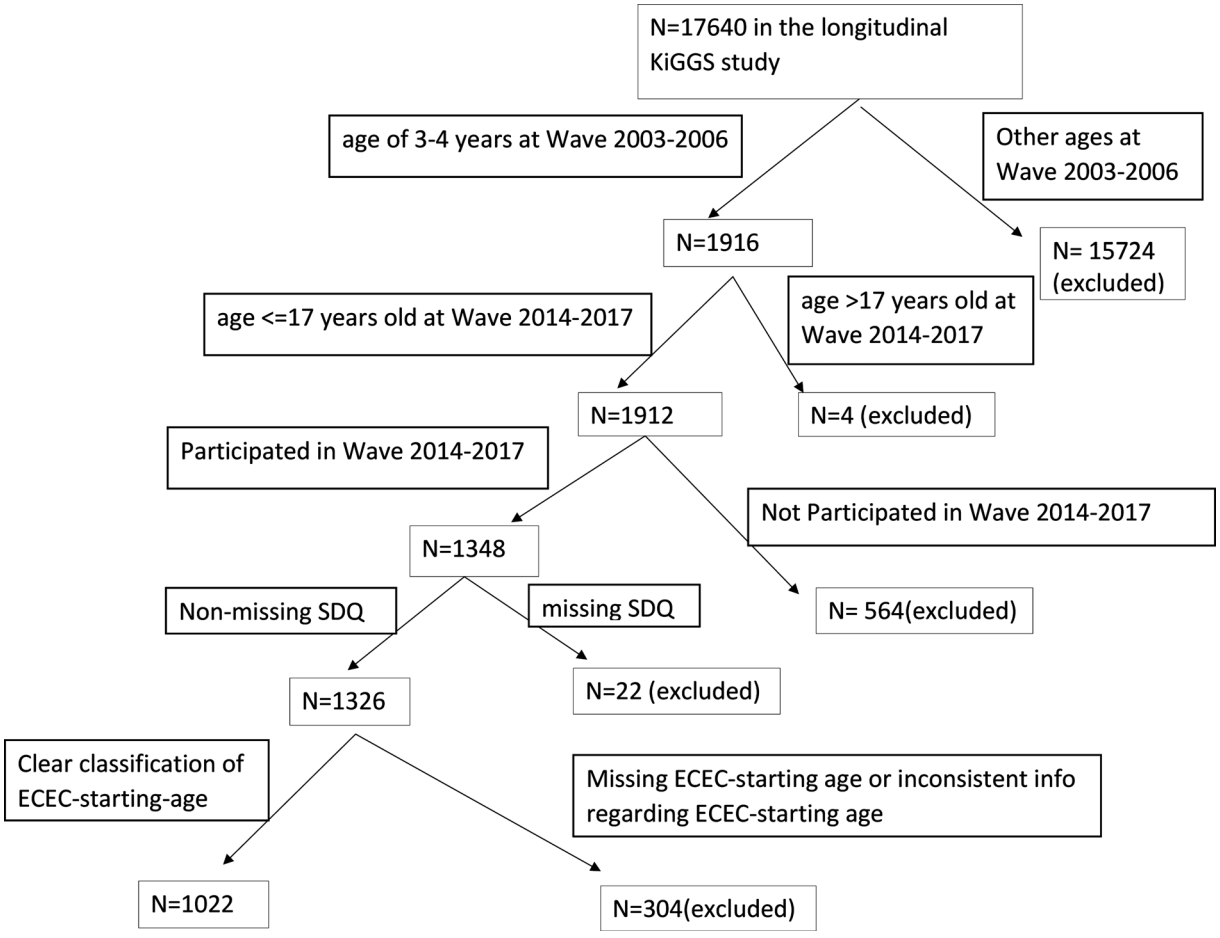

Fig. 1 Flow chart for the sample

were collected or derived at wave 2. Exact operationalizations and some previous findings on these confounders can be found in the Supplementary Materials 2 and 3.

Statistical analysis

We described the characteristics of the sample by using means and standard deviations for continuous variables and percentages for categorical variables for Germany as a whole, and by region (i.e. West or East Germany). In the bar charts, the mean values and 95% confidence intervals (CIs) of psycho-social problems in adolescence were presented by ECEC-start-age group. In an additional analysis, we used the Chi-square tests to analyze the distribution of SES and other baseline variables of interest by ECEC-start-age in West and East Germany separately. To ensure the representation of data at a national level, a cross-sectional weighting factor was applied to the baseline data, which was calculated to correct for deviations between the net sample (baseline data) and the population structure (as of 31 December 2004). The weighing factor is based on age, gender, region (West or East Germany) and nationality [23]. A longitudinal weight was applied to the wave 2 data to compensate for possible sample bias due to selective re-participation in the follow-up study [26].

We used linear regression to explore the relationship between ECEC-start-age and psycho-social problems in adolescence in the whole Germany, controlling for age, gender and other potential confounders as mentioned above. We also ran a similar linear regression, but stratified by West and East Germany. In an additional analysis, we added an interaction variable of region (West/East Germany) and ECEC-start-age in the linear regression of the whole Germany. In all linear regressions, we used the longitudinal weight, and the category "Age 2–3" as the reference group for the ECEC-start-age. Furthermore, linear regression assumptions, including normality and homoscedasticity, were checked using standardized residual graphics including histograms, normal quantile-quantile (QQ) plots and scatterplots of standardized residuals versus predicted values. We used the "PROC SURVEYREG" procedure in the SAS for a robust variance estimation method (Taylor series linearization method) to address the deviation from linear regression

assumptions. A sensitivity analysis was performed to compare the results with and without outliers, which were defined as values more than 2 standardized residuals away from zero in the linear regression. All analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

Results

The children in our sample were on average 14.4 (±0.03) years old at wave 2 (see Table 1). The sample was almost equally divided between girls and boys; 41.1% of our sample started ECEC at the age of 2–3 years, followed by 22.4% who started ECEC older than 3 years but before starting school. All other ECEC-age-groups accounted for about 10% of the children. At baseline wave 57.3% of the families belonged to the middle SES group, 16.5% to the low SES group and 25.2% to the high SES group; 16.0% of the children had a migrant background. The children were mostly (37.3%) the second child in the household and at baseline wave, 86.3% of the children lived with their natural parents in the same household. 16.7% of the parents were divorced by wave 2. Based on the data collected at baseline wave, most children were born with a birth weight of 2500-4000 g (78.8%) and were neither obese nor overweight (89.5%) when they were 3–4 years old. Most mothers gave birth at the age of 25–34 years (60.7%) and were unemployed (including housewife, or on parental leave etc.) (47.7%) when their child was 3–4 years old.

Most of the descriptive variables for baseline characters were similar for West and East Germany, with the exception of ECEC-start-age, mother's employment status, SES, family structures and migrant status. More mothers with 3–4 year old children in East Germany were in full-time employment (34.7%) than in West Germany (8.1%), and fewer mothers in East Germany were unemployed (31.4%) than in West Germany (51.6%). The majority of children in West Germany started ECEC at the age of 2–3 years (44.3%), whereas the majority of children in East Germany started ECEC at the age of 1–2 years (43.9%). Only 7.3% of children in West Germany started ECEC younger than 1 year, while 22.9% of children in East Germany started younger than 1 year. In terms of SES, 15.4% of children in West Germany and 20.8% of children in East Germany came from low SES families, while 25.9% of children in West Germany and 22.6% of children in East Germany came from high SES families. In West Germany there were more family structure as natural parents in a joint household (88.6%) and more migrant (17.8%) than in East Germany (76.6% and 8.5% respectively).

Additional analysis showed that SES and family structure differed significantly among ECEC-start-age groups in West Germany whereas it didn't in East Germany (Supplementary Material 7). Mother's employment status when the child was 3–4 years old differed significantly among ECEC-start-age groups in both West and East Germany. Regarding children starting ECEC younger than 1 year in the West Germany, they tended to be more likely in a one-parent family with high SES and with a full-time employed mother.

Figure 2 illustrates the mean values and 95% confidence intervals of psycho-social problems in adolescence by ECEC-start-age group in the whole sample. Compared to the other ECEC-start-age groups, those who started ECEC between the ages of 2 and 3 had the lowest SDQ scores, indicating the least psycho-social problems in adolescence (mean SDQ total score=6.81; mean score of externalizing psycho-social problems=3.96; mean score of internalizing psycho-social problems=2.85). Those who started ECEC before 2 years of age had higher SDQ scores than children in the reference group (ECEC-start-age = "Age 2–3"), and the earlier the child started ECEC, the higher the SDQ scores were. Among them, those who started ECEC within the first year after birth had the highest total SDQ score (8.10) and the highest score for externalizing psycho-social problems (4.99). Those who started ECEC after the age of 3 (but before school entry) had the highest score for internalizing psycho-social problems (3.50).

By region, the pattern in West Germany is similar to that for the whole Germany, whereas only externalizing psycho-social problems (except for the ECEC-start-age group<1 year old) in East Germany is similar to that for the whole Germany (Fig. 3). In East Germany, the ECEC-start-age group<1 year had lower scores for externalizing psycho-social problems than the group of "Age 1–2"; for internalizing psycho-social problems, the later children started the ECEC, the higher their scores in adolescence in general.

Our multivariate results (Table 2) show that, compared to the reference group (ECEC-start-age between the ages of 2–3), the total SDQ score was on average 1.8 units higher for those who started ECEC younger than 1 year (p=0.002), 1.4 units higher for those who started ECEC between the ages of 1–2 (p=0.036), and 1.0 unit higher for those who started ECEC older than 3 years old but before starting school (p=0.020). Those starting ECEC younger than 2 years had statistically significant higher scores for externalizing psycho-social problems (beta=1.3, p=0.001 for "Below age 1"; beta=1.2, p=0.005 for "Age 1–2"). Those who started ECEC older than 3 years old (but before starting school) had statistically significantly higher scores for internalizing psycho-social problems (beta=0.7, p=0.017).

In West Germany, overall, results were comparable to the findings for whole Germany (Table 3). The only exception was the ECEC-start-age group of "Age 1–2". While this ECEC-start-age group showed statistically

Table 1 Descriptive data for sample regarding baseline characters, and other potential confounders[a]

Character/Confounder	Category	Mean (Standard Deviation) / Number (%)		
		Total (n = 1022)	West Germany (n = 621)	East Germany (n = 401)
Age		14.4 (0.03)	14.4 (0.03)	14.4 (0.06)
Gender	Female	542 (47.6)	329 (47.4)	213 (48.2)
	Male	480 (52.4)	292 (52.6)	188 (51.8)
ECEC-start-age group	Below age 1	144 (10.3)	45 (7.3)	99 (22.9)
	Age 1–2	214 (13.4)	41 (6.1)	173 (43.9)
	Age 2–3	366 (41.1)	261 (44.3)	105 (27.9)
	Age 3 + and before schooling	205 (22.4)	185 (26.7)	20 (4.2)
	Only cared in Family before schooling	93 (12.8)	89 (15.6)	4 (1.1)
Psycho-social problems	SDQ Total Score	7.4 (0.20)	7.4 (0.24)	7.5 (0.27)
	Externalizing psycho-social problems	4.4 (0.14)	4.4 (0.17)	4.3 (0.15)
	Internalizing psycho-social problems	3.1 (0.11)	3.1 (0.13)	3.1 (0.18)
Social Economic Status	Low	93 (16.5)	47 (15.4)	46 (20.8)
	Middle	608 (57.3)	365 (57.5)	243 (56.3)
	High	314 (25.2)	203 (25.9)	111 (22.6)
	Missing	7 (1.0)	6 (1.2)	1 (0.4)
Migrant Status	Non-migrant	927 (83.3)	540 (81.6)	387 (90.1)
	Migrant	88 (16.0)	78 (17.8)	10 (8.5)
	Missing	7 (0.7)	3 (0.5)	4 (1.3)
Number of older siblings	0	206 (20.7)	132 (21.4)	74 (17.7)
	1	384 (37.3)	252 (38.4)	132 (32.7)
	2	127 (14.0)	86 (15.0)	41 (10.2)
	3 and more	45 (3.9)	26 (4.0)	19 (3.6)
	Missing	260 (24.1)	125 (21.3)	135 (35.8)
Family situation (With whom the child live together primarily?)	Natural parents in a joint household	910 (86.3)	572 (88.6)	338 (76.6)
	Mother or father with their own partner	25 (2.2)	9 (1.6)	16 (4.9)
	Mother or father without partner	73 (10.4)	36 (9.2)	37 (15.4)
	Others (grandparents etc.)	6 (0.3)	0 (0.0)	6 (1.7)
	Missing	8 (0.8)	4 (0.7)	4 (1.3)
Family cohesion	Min-<=20th Percentile	203 (21.0)	125 (20.4)	78 (23.1)
	20th - <=40th Percentile	205 (20.5)	134 (21.5)	71 (16.3)
	40th - <=60th Percentile	249 (23.6)	149 (24.0)	100 (21.8)
	60th - <=80th Percentile	189 (15.6)	109 (14.6)	80 (19.8)
	80th Percentile-Max	139 (14.1)	77 (13.7)	62 (15.7)
	Missing	37 (5.3)	27 (5.7)	10 (3.2)
Parents' Divorce	Did	165 (16.7)	83 (15.0)	82 (23.0)
Birth weight	< 2500 g	57 (5.2)	28 (4.8)	29 (6.8)
	>=2500 g and < 4000 g	811 (78.8)	488 (78.0)	323 (81.8)
	>=4000 g	136 (12.9)	90 (13.5)	46 (10.6)
	Missing	18 (3.1)	15 (3.7)	3 (0.8)
Obesity/Overweight	Obesity	22 (2.0)	14 (2.2)	8 (1.4)
	Overweight but not obesity	59 (6.4)	37 (6.8)	22 (4.8)
	Neither obesity nor overweight	927 (89.5)	559 (88.7)	368 (92.6)
	Missing	14 (2.1)	11 (2.3)	3 (1.2)
Age of mother at childbirth	Till 24 years old	134 (17.1)	68 (15.4)	66 (23.8)

Table 1 (continued)

Character/Confounder	Category	Mean (Standard Deviation) / Number (%)		
		Total (n = 1022)	West Germany (n = 621)	East Germany (n = 401)
	25–29 years old	279 (25.2)	136 (23.5)	143 (32.1)
	30–34 years old	374 (35.5)	247 (36.8)	127 (30.1)
	35 + years old	212 (19.9)	158 (22.1)	54 (10.8)
	Missing	23 (2.3)	12 (2.1)	11 (3.2)
Employment status of mother	Full-time employed	194 (13.2)	53 (8.1)	141 (34.7)
	Part-time employed	382 (36.8)	253 (37.7)	129 (33.0)
	Unemployed	432 (47.7)	304 (51.6)	128 (31.4)
	Missing	14 (2.3)	11 (2.7)	3 (0.9)
Region (East/West Germany)	West Germany	621 (80.7)		
	East Germany (including Berlin)	401 (19.3)		
Schooling type[b]	Academic secondary school preparing for university	467 (38.0)	270 (36.3)	197 (45.3)
	Secondary school preparing for vocational training in trade	235 (24.0)	157 (25.4)	78 (18.4)
	Secondary general school preparing for vocational training in crafts	36 (5.9)	29 (7.0)	7 (1.5)
	Comprehensive school	133 (16.4)	88 (16.6)	45 (15.6)
	Secondary school preparing for vocational training in trade and crafts	98 (8.7)	39 (7.4)	59 (13.8)
	Others	35 (4.9)	23 (4.9)	12 (4.5)
	Missing	18 (2.1)	15 (2.4)	3 (0.8)

[a]The weighted means and percentages have been listed. Data of age, type of schooling, and parental divorce were assessed at wave 2; ECEC-start-age was derived using data from Baseline wave and wave 1; all the other data in this table were collected at baseline wave

[b]Schooling type in Germany:

Academic secondary school preparing for university (*Gymnasium*) is the highest form of secondary education and aims to prepare students for continued university education. The curriculum at a *Gymnasium* has an academic focus, with a minimum of two foreign languages, higher math, and science courses, with the goal to reach the university level

Secondary school preparing for vocational training in trade (*Realschule*) offers mid-level education. It is more challenging than the *Hauptschule*, but a step lower than the *Gymnasium*. The *Realschule* prepares students with practical and theoretical knowledge for their future professional life. Students usually have the option to choose a focus area, such as an additional foreign language or science subject

Secondary general school preparing for vocational training in crafts (*Hauptschule*) offers the lowest, least demanding learning level in the German education system. It is a choice for pupils who want to continue their education with an apprenticeship in crafts

Comprehensive school (*Gesamtschule*) combines all three tracks of school education (*Gymnasium*, *Realschule* and *Hauptschule*) in one comprehensive school, making it easier to switch tracks if necessary

Secondary school preparing for vocational training in trade and crafts (*Haupt-und Realschule*) combines *Realschule* and *Hauptschule* in one school

significant increased SDQ score (beta = 1.4, p = 0.036) in the whole Germany, this group showed a tendency of increased SDQ score (beta = 2.3, but statistically insignificant with p = 0.055) in West Germany. However, for the externalizing psycho-social problems, children starting ECEC younger than 2 years had statistically significant higher scores in the whole Germany and in West Germany as well.

In East Germany, in contrast, the analysis revealed no statistically significant differences depending on ECEC starting age (Table 3). Those who started ECEC at the age of 1–2 years tended to have higher scores for externalizing psycho-social problems in East Germany, but these association was statistically insignificant at the conventional significance level p = 0.05 (beta = 0.6, p = 0.062). The beta of "Age 3 + and before schooling" for SDQ total score and for internalizing psycho-social problems were relatively high (2.1 and 1.2), and the sample size for this group of ECEC-start-age was relatively small (n = 20). The p-values for these two betas were statistically insignificant (p = 0.363 and p = 0.394).

The linear regression with an interaction factor of ECEC-start-age by region shows a statistically significant interaction of ECEC-start-age younger than 1 year by region on SDQ total score (p = 0.001), on externalizing psycho-social problems (p = 0.016) and on the internalizing psycho-social problems (p = 0.018) (see Supplementary Material 4). There was an unfavorable effect of ECEC

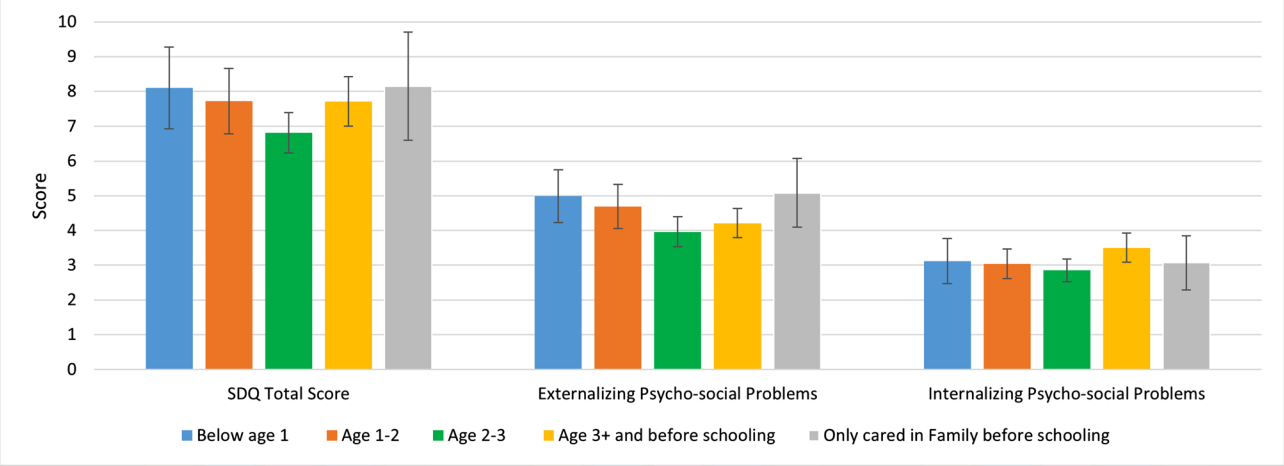

Fig. 2 Mean values and 95% CI of psycho-social problems in adolescence by ECEC-start-age group (n=1022)

Table 2 Linear regression of the association between ECEC-start-age and psycho-social problems in adolescence after controlling for confounders (n = 1022)

	ECEC-start-age groups	SDQ Total Score			Externalizing Psycho-social Problems		Internalizing Psycho-social Problems	
		n	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Germany (n = 1022)	Below age 1	144	**1.8 (0.6,2.9)**	**0.002***	**1.3 (0.6,2.0)**	**0.001***	0.5 (-0.3,1.2)	0.245
	Age 1–2	214	**1.4 (0.1,2.8)**	**0.036***	**1.2 (0.4,2.1)**	**0.005***	0.2 (-0.5,0.9)	0.586
	Age 2–3 (Reference group)	366						
	Age 3 + and before schooling	205	**1.0 (0.2,1.9)**	**0.020***	0.4 (-0.1,0.9)	0.149	**0.7 (0.1,1.2)**	**0.017***
	Only cared in Family before schooling	93	0.8 (-0.6,2.1)	0.255	0.7 (-0.1,1.6)	0.099	0.0 (-0.7,0.8)	0.930

Covariates: age in adolescence, gender, schooling type, parents' divorce by wave 2, and other baseline characters including region (East/West Germany), social economic status, migrant status, number of older siblings, family situation, family cohesion, birth weight, obesity/overweight, age of mother at childbirth, and employment status of mother

* p < 0.05

Table 3 Stratified Linear regression of the association between ECEC-start-age and psycho-social problems in adolescence after controlling for confounders by region (West/East Germany) (n = 1022)

	ECEC-start-age groups	SDQ Total Score			Externalizing Psycho-social Problems		Internalizing Psycho-social Problems	
		n	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
West Germany (n = 621)	Below age 1	45	**2.9 (1.3,4.6)**	**< 0.001***	**1.9 (0.9,3.0)**	**< 0.001***	1.0 (-0.2,2.1)	0.088
	Age 1–2	41	2.3 (-0.1,4.6)	0.055	**1.7 (0.2,3.3)**	**0.029***	0.6 (-0.5,1.6)	0.300
	Age 2–3 (Reference group)	261						
	Age 3 + and before schooling	185	**1.2 (0.4,2.1)**	**0.006***	0.4 (-0.1,1.0)	0.094	**0.8 (0.2,1.4)**	**0.005***
	Only cared in Family before schooling	89	0.9 (-0.5,2.3)	0.214	0.8 (-0.2,1.7)	0.108	0.1 (-0.6,0.9)	0.731
East Germany (n = 401)	Below age 1	99	0.3 (-1.3,1.9)	0.714	0.3 (-0.5,1.1)	0.514	0.0 (-1.1,1.1)	0.971
	Age 1–2	173	0.4 (-1.0,1.8)	0.589	0.6 (-0.03,1.3)	0.062	-0.3 (-1.3,0.7)	0.609
	Age 2–3 (Reference group)	105						
	Age 3 + and before schooling	20	2.1 (-2.4,6.6)	0.363	0.8 (-1.2,2.8)	0.406	1.2 (-1.6,4.1)	0.394
	Only cared in Family before schooling	4	-1.4 (-5.1,2.4)	0.462	-0.6 (-2.0,0.7)	0.341	-0.7 (-4.0,2.5)	0.648

Covariates: age in adolescence, gender, schooling type, parents' divorce by wave 2, and other baseline characters including social economic status, migrant status, number of older siblings, family situation, family cohesion, birth weight, obesity/overweight, age of mother at childbirth, and employment status of mother

* p < 0.05

younger than 1 year in West Germany but not East Germany. No such statistically significant interaction was observed for other ECEC-start-ages by region at the conventional significance level p=0.05 (see Supplementary Material 4).

Sensitivity analysis confirmed our results which remained robust after dropping outliers (n for outliers=76) (Supplementary Material 5). The plots to check the assumptions of linear regression are also provided in Supplementary Material 6.

Discussion

Starting ECEC later than 3 years of age is associated with higher parent-reported scores of internalizing psycho-social problems in adolescence in both West Germany (with statistically significant results) and East Germany (with a relatively larger effect size but statistically insignificant results). For externalizing psycho-social problems, starting ECEC between the ages of 2 and 3 is associated with the lowest score; in West Germany, those who start before the age of 2 have more externalizing psycho-social problems, and this disadvantage increases with an even younger starting age. However, in East Germany only those who start ECEC between 1 and 2 years old tend to have higher scores of externalizing psycho-social problems. This association does not hold in East Germany for the children starting ECEC younger than 1 year old. The regional difference in the results for children under 1 year of age may suggest a selection effect in West Germany where only fewer parents use this option.

A major limitation of previous observational studies investigating the effect of ECEC is the possibility of a selection bias due to unmeasured or unknown potential confounders which cannot be fully addressed by conventional statistical approaches [27, 28]. Our study uses a natural experiment with similar family policies and a number of other similarities such as the education system and language within Germany, but with a different cultural context regarding the role of women and consequently different use and availability of ECEC in West and East Germany. Thus, our study is able to reveal the selection effect which most observational studies with conventional statistical approach are not able to do. A previous study from Norway has also successfully applied the natural experiment study design by using birth month as an additional factor of interest when exploring the association between ECEC and aggression [29].

Starting ECEC younger than 1 year old: inconsistent association in West and East Germany

Children starting ECEC younger than 1 year old had a higher possibility of psycho-social problems in West Germany, but not in East Germany. Selection processes may be at work that leads to this disadvantage for children starting ECEC younger than 1 in terms of psycho-social developments in West Germany. Our data showed that the children starting ECEC younger than 1 in the West Germany were more likely from a one-parent high-SES family with a full-time employed mother.

The regional culture difference regarding the role of women and consequently regarding the attitude to the ECEC is worth discussing. In West Germany, the mothers who bring the children to the ECEC earlier may get stress or even blame from relatives or neighbours; in East Germany, the children who get parental care at home may regard themselves strange if the majority of their peer friends go to an ECEC. This culture difference may be one of the sources of the possible selection effects for the children starting ECEC younger than 1 year in West Germany. Concretely, in West Germany, families with "problems" (e.g., job overload, partnership problems, lack of social support by grandparents or friends, economic problems) may be more or less forced to bring children to non-parental ECEC in the first life year; and these "problems" might be the actual reason(s) for more psycho-social difficulties in children's development. In East Germany, in contrast, it is more accepted or normal to bring children to non-parental ECEC at this young age, even in "non-problematic" families.

Further research is needed to identify the sources of this possible selection process.

Starting ECEC between 1 and 2 years old: increased probability of externalizing psycho-social problems

It is interesting to note that in both West and East Germany there is a tendency towards increased externalizing psycho-social problems for those who start ECEC between the ages of 1 and 2. Teachers and parents therefore need to pay more attention to preventing children in this group of ECEC-start-age from developing externalizing psycho-social problems. Previous studies have reported that prolonged exposure to ECEC before age 2 was associated with a higher risk of behavioral problems and long-term insecure attachment, but short exposure to ECEC did not have such negative effects [10, 30]. Therefore, participation in ECEC on a part-time basis may be a compromise but better option for parents who wish to work at an earlier stage in the child's life. The quality of ECEC and the qualifications of nursery teachers need to be carefully and regularly monitored, in order to maintain a good teacher-child ratio, and to provide stable, continuous and sensitive care for children, which may help to prevent early insecure attachment and, consequently, externalizing psycho-social problems [10, 16].

Starting ECEC at 3 + years old: increased probability of internalizing psycho-social problems

We observed an increased probability of internalizing psycho-social problems in the group of children starting ECEC over the age of 3 years in both West Germany (with statistically significant results) and East Germany (with a relatively larger effect size but statistically insignificant results). The small sample size (n = 20) in East Germany may explain the lack of statistical significance. This observation underlines the importance of participating in ECEC at the age of 3 years at the latest. Interestingly, Fig. 3 shows a "dosage effect" of ECEC-start-age on the increased probability of internalizing psycho-social problems from ECEC-start-age < 1 to 3 + in East Germany. The later the children started ECEC, the higher the probability that the children will have internalizing psycho-social problems in adolescence.

The importance of playing with peers in the preschool age group, from three years of age onwards, may explain this association. At these ages, playing with others is the central activity of children [31, 32]. Playing and interacting with their peers at these ages is a good way to explore and develop their social, emotional, language and cognitive skills. Social and cooperative play helps children develop a sense of initiative and confidence in their ability to make decisions, solve problems and influence others [31, 32]. Participating in ECEC provides good opportunities to play and interact with peers. In addition, having no close friends may increase the risk of internalizing psycho-social problems [17]. Therefore, if a child doesn't start ECEC at the age of 3, more attention should be paid to preventing internalizing psycho-social symptoms, for example by providing more opportunities to play with peers.

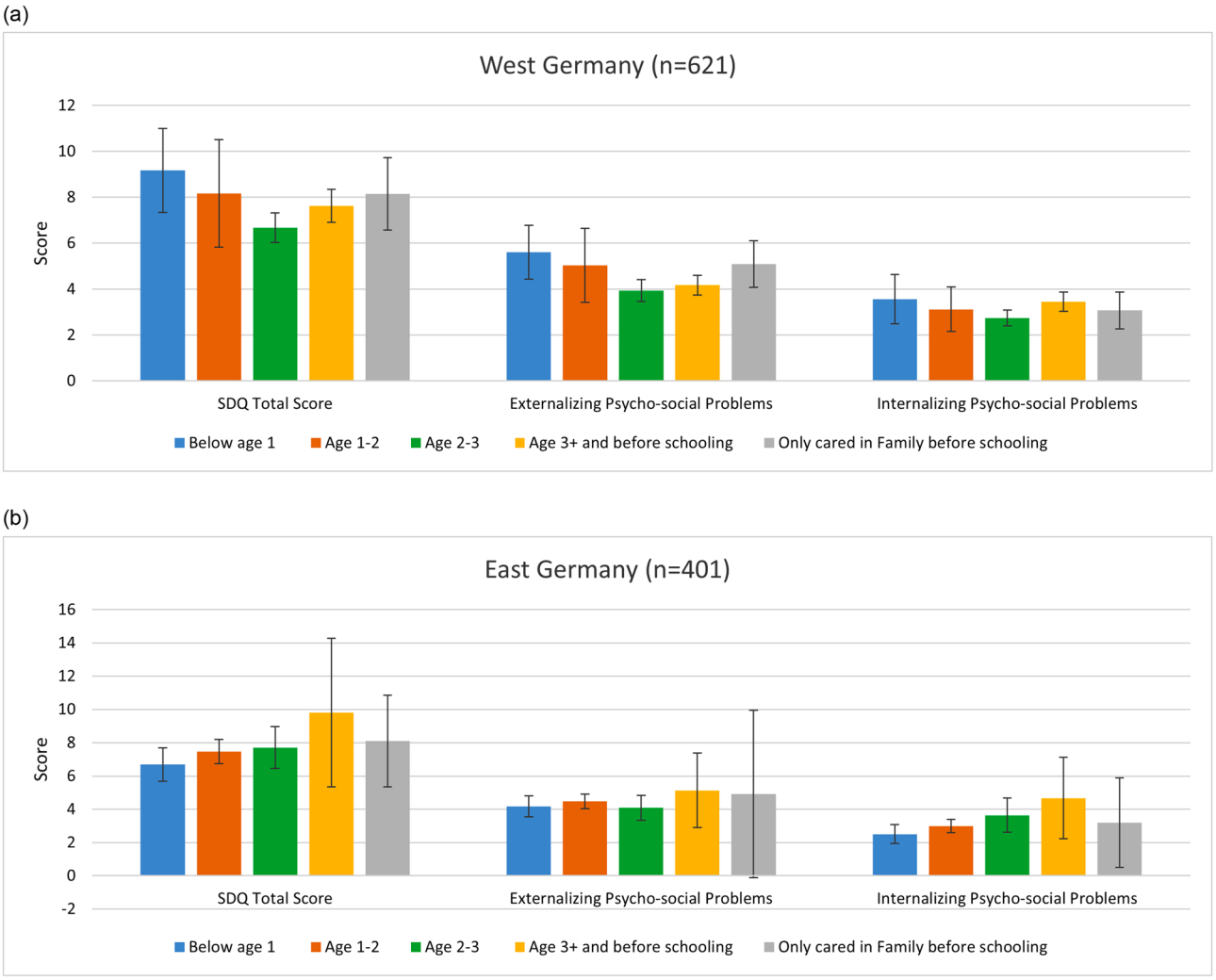

Fig. 3 Mean values and 95% CI of psycho-social problems in adolescence by ECEC-start-age group and region. (**a**) Mean values and 95% CI of psycho-social problems in adolescence by ECEC-start-age group in West Germany. (**b**) Mean values and 95% CI of psycho-social problems in adolescence by ECEC-start-age group in East Germany

Strengths and limitations

Our study has several strengths. Our study has used a nationally representative and adequately large sample of children and their parents in Germany. We have considerable variations of ECEC-start-age in the data, and explored the similarity and difference of the association between West and East Germany in a natural experiment. Thus, we provide more socio-political variations and contribute to the external validity in this research field. Furthermore, by using the natural experiment, we have found the potential selection effect to interpret the negative association between ECEC and psycho-social development for the children starting ECEC younger than 1 in West Germany. Moreover, we have examined the pattern of ECEC-start-age rather than just using a cut-off point for ECEC-start-age. By doing so, we are able to show that the association is not linear, and to reveal both the beneficial and unfavourable association between ECEC-start-age and psycho-social development in adolescence. Furthermore, most previous studies used discrete categories to analyse psycho-social problems [8]. Our study analyses psycho-social problems using a continuous score, which may provide a more valid and reliable assessment [8]. However, further research is still needed to use discrete categories to analyse these associations, to support the clinical relevance of these associations. Last but not least, we have found the association between ECEC-start-age and psycho-social problems in adolescence. There is at least 10 years between the exposure of interest and the outcome of interest. We are helping to provide evidence to fill the gap in the literature.

Our study also has some limitations. Firstly, the quality and intensity of ECEC exposure influences the association [33]. However, neither quality nor intensity data on ECEC exposure are available in KiGGS. Further research is needed to include these different aspects in the analysis. Secondly, some factors which may influence the association have not been considered, such as later school experience and the relationship between parents and child. However, we have controlled for some of the potential confounders, such as type of schooling and family cohesion, in our analysis to reduce this kind of bias. The natural experimental design of the study also helps to reveal potential unmeasured or unknown biases. However, not all of these biases can be fully controlled for. These factors should be investigated in more detail in further studies. Thirdly, there may be an attrition bias. However, we have used longitudinal weights to minimize this bias. Furthermore, we have used parent-reported SDQ scores in our analysis, which may differ from self or teacher-reported scores. However, the German parent SDQ has been shown to have reliable and useful psychometric properties [34]. Further analysis using self or teacher-reported measures in the future may provide more insight into this research question. Moreover, as a general limitation of observational studies, our results are associations rather than causalities. Therefore, the results should be interpreted with caution. However, our findings remain valuable because our findings suggest that more attentions from teachers and parents should be given to some particular psycho-social problems for some particular ECEC-start-age groups. Finally, the sample size for the ECEC-start-age group of 'only cared for in family before schooling' is relatively small (n=93), which may limit the statistical power for this group.

Conclusion

The regional similarities between West and East Germany with regard to the increased probability of internalizing psycho-social problems among those starting ECEC at the age of 3 or older indicate the importance of providing access to ECEC for these children, while the regional difference with regard to the probability of psycho-social problems among those starting ECEC at the age of 1 year or younger suggests a possible selection effect for the observed association in West Germany, where fewer parents use this option. However, in both West and East Germany, children starting ECEC between the ages of 1 and 2 tend to have a higher possibility of externalizing psycho-social problems. In conclusion, for those who start ECEC older than 3 years old, more attention may be needed to prevent potential internalizing psycho-social problems, for example by providing more opportunities for social interaction through peer play. For those who start ECEC younger than 2 years old, more attention by parents and nursery teachers is needed to prevent potential externalizing psycho-social problems. A stable and continuous relationship with nursery teachers as well as a not too long hours of daily care could be helpful. For those who start ECEC younger than 1 year old, more research is needed to better understand why children in West Germany are particularly disadvantaged and those in East Germany are not.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40359-023-01447-1.

Additional file 1: **1**. Operationalization of ECEC-start-age. **2**. Operationalization of potential confounders. **3**. Potential confounders: association with exposure and outcome of interest. **4**. Linear Regression with Interaction Factor Region*ECEC-start-age. **5**. Sensitivity analysis for the outliers. **6**. Diagnostics for linear regression. **7**. Distribution of SES and other Covariates by ECEC-start-age in West and East Germany. **8**. Table to support Figures 2 and 3 in the main paper

Acknowledgements

We would like to express our sincere thanks to Elvira Mauz for her support providing advising on the data. We would also like to thank Amal Dietrich for her proofreading and English improvement.

Author Contributions
YZ and GD provided research proposal. YZ has done the data collection, analysis, and manuscript provision. GD and AW participated in manuscript provision, reviewed and edited the manuscript. YZ, AW and GD read and approved the final manuscript.

Funding
Open Access funding enabled and organized by Projekt DEAL. The KiGGS study was funded by the German Federal Ministry of Health, the Ministry of Education and Research, and the Robert Koch Institute. For this concrete project, no extra funding has been provided.
Open Access funding enabled and organized by Projekt DEAL.

Data Availability
The authors confirm that some access restrictions apply to the data underlying the findings. The data set cannot be made publicly available because informed consent from study participants did not cover public deposition of data. However, the minimal data set underlying the findings is archived in the 'Health Monitoring' Research Data Centre at the Robert Koch Institute (RKI) and can be accessed by researchers on reasonable request. On-site access to the data set is possible at the Secure Data Center of the RKI's 'Health Monitoring' Research Data Centre. Requests should be submitted to the 'Health Monitoring' Research Data Centre, Robert Koch Institute, Berlin, Germany (e-mail: fdz@rki.de).

Declarations

Ethics approval and consent to participate
The KiGGS study was approved by the Charité/Universitätsmedizin Berlin ethics committee and the Federal Office for the Protection of Data. All methods of KiGGS study were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all study participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 12 July 2023 / Accepted: 13 November 2023
Published online: 20 November 2023

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Publisher's Note

SUPPLEMENTARY TO STUDY 2

Contents

1. Operationalization of ECEC-start-age

ECEC-start-age was derived through the following rules:

a. If the age for beginning ECEC at wave 2003-2006 was available, then ECEC-start-age = age for beginning ECEC at wave 2003-2006.

b. Else if the age for beginning ECEC was available at wave 2009-2012, then ECEC-start-age = age for beginning ECEC from wave 2009-2012.

c. Else if the children were only cared for in the family in both waves (baseline and wave 1), then ECEC-start-age = “Care only in family before schooling”.

d. Else if the answers to the question “Was or is your child only be cared for in the family before schooling” at the two waves were inconsistent, then children were excluded from the analysis to ensure high validity of the exposure variable.

2. Operationalization of potential confounders

SES

The scores of education, occupation and income per household were summed up at first, and then the sum was classified by quintiles into low SES (first quintile), medium SES (second to fourth quintile) and high SES (fifth quintile) (see (1) for details).

Migration status

The migration status was categorized as non-migrant and migrant. A child was defined as migrant if she/he immigrated from another country and at least one of her/his parents was not born in Germany, or if both of her/his parents had a foreign citizenship or immigrated from another country (2).

Number of older siblings (Order of birth)

Number of older siblings presented how many brothers or sisters were older than the child who participated in KiGGS. That number plus 1 reflected the order of birth for the child participating in KiGGS among siblings in the family.

Family situation and family cohesion

The family situation was categorized as: natural parents in a joint household, mother or father with their own partner, mother or father without partner and others. Additionally, a variable is included that indicates whether the parents experienced divorce by the survey time of wave 2.

As an indicator for the extent of emotional support from the family members, the subscale “family cohesion” was used from the family climate scale (3). The subscale “family cohesion” comprises four items by using 4-stage options from “definitely no” to “definitely yes”. In the analysis, the sum value over the four items is categorized by using 20 percentile, so that the subjects with missing values can remain in the analysis.

Birth weight

Birth weight was categorized as <2500g, >=2500g and <4000g, and >=4000g (4).

Obesity/overweight

Obesity/Overweight of the child was categorized as obese, overweight without obesity, neither obese nor overweight. Normal weight (⩽90th percentile, P90), overweight (>P90 to ⩽P97) and obesity (>P97) were defined using the national German percentiles (5).

Age of mother at childbirth

Age of mother at childbirth was categorized as the group till 24 years of age, 25-29 years old, 30-34 years old and 35 years old and older (35+).

Employment status of mother

Employment status of mother was categorized as full-time employed, part-time employed (including mini-job) and unemployed (including housewife, or due to study, retirement or parental leave etc.).

Region (east/west Germany)

To account for the varying cultural context and supply of ECEC in east and west Germany, a regional variable differentiating between east (including Berlin) and west Germany was included.

Schooling type

Schooling type was categorized as “ Academic secondary school preparing for university“, “Secondary school preparing for vocational training in

trade“, “Secondary general school preparing for vocational training in crafts“, “Comprehensive school“, “Secondary school preparing for vocational training in trade and crafts “ and others at wave 2. Academic Secondary School preparing for university (*Gymnasium*) is the highest form of secondary education and aims to prepare students for continued university education. The curriculum at a *Gymnasium* has an academic focus, with a minimum of two foreign languages, higher math, and science courses, with the goal to reach the university level. Secondary School preparing for vocational training in trade (*Realschule*) offers mid-level education. It is more challenging than the *Hauptschule*, but a step lower than the *Gymnasium*. The *Realschule* prepares students with practical and theoretical knowledge for their future professional life. Students usually have the option to choose a focus area, such as an additional foreign language or science subject. Secondary General School preparing for vocational training in crafts (*Hauptschule*) offers the lowest, least demanding learning level in the German education system. It is a choice for pupils who want to continue their education with an apprenticeship in craft or industrial trades. Comprehensive School (*Gesamtschule*) combines all three tracks of school education (i.e. *Gymnasium, Realschule* and *Hauptschule*) in one comprehensive school, making it easier to switch tracks if necessary. Secondary School preparing for vocational training in trade and crafts (*Haupt-u. Realschule*) combines Realschule and Hauptschule in one school.

3. Potential confounders: association with exposure and outcome of interest

Table S1. Previous findings regarding potential confounders and their association with ECEC-participation and psycho-social problems

Potential confounder	**Associated with ECEC-participation**		**Risk or predictor factors for psycho-social problems**	
	Previous findings	**Reference**	**Previous findings**	**Reference**
SES	Household income, education and employment biography (of the mother) are associated with ECEC-participation	(6)	Social-demographic factors (low SES) is such a factor	(7, 8)
Migration Status	Migrant background is associated with ECEC-participation	(9)	Migrant background is such a factor	(2)
Number of Older Siblings (Order of birth)	Subsequent siblings within one family have a higher priority for an ECEC place compared to the first or single child in Germany when demand of ECEC places exceeds supply.	(10)	Birth order is such a factor	(11)
Family Situation	Household structure (single-parent or two-	(12)	Single-parent family is such a factor	(8)

	parent families etc.) is associated with ECEC-participation			
Family Cohesion	Family cohesion has a positive association with school belonging, mediated by security and achievement goals. Moreover, family cohesion is associated with household structure.	(13)	Lack of family cohesion is such a factor	(8)
Parents' Divorce	Household structure (single-parent or two-parent families etc.) is associated with ECEC-participation	(12)	Parents' divorce results in psycho-social and mental problems among their children	(14)
Birth Weight	A factor influencing ECEC-participation may be the birth weight, because parents of children with low birth weight return to work less or later or work less than parents with a normal birthweight child	(15)	Low birth weight is such a factor	(16)
Obesity/Overweight	It could be hypothesized that children in ECEC profit from more physical activities and healthier food and hence have a lower likelihood of being overweight/obese. An evidence is that school closure during COVID-19 pandemic promotes childhood obesity	(17)	Obesity or overweight is such a factor	(18)
Age of mother at childbirth	Advanced maternal age may be associated with low birth weight, which may influence ECEC-participation	(19, 15)	Advanced maternal age may be associated with low birth weight, which may be a risk/predictor factor for psycho-social problems	(19, 16)
Employment status of mother	Employment biography (of the mother) is associated with ECEC-participation	(6)	Parental unemployment is such a factor	(8)
Region (East/West Germany)	Belonging to east ("new" federal states) or west Germany ("old" federal states) is associated with ECEC-participation. Concretely, from 2002 to 2019 the use of	(20, 21)	Some social changes (e.g. economic stability, unemployment rate) may influence psycho-social problems. In Germany, these social	(7, 22)

	ECEC for children under 3 years old increased from 37% to 52% in east Germany, and from 3% to 30% in west Germany		changes differ in east and west Germany.	
Schooling Type	Schooling type at the school age is associated with ECEC-participation	(6)	Schooling type is such a factor	(8, 23)

4. Linear Regression with Interaction Factor Region*ECEC-start-age

Table S2. With interaction factor Region*ECEC-start-age: linear regression of the association between ECEC-start-age and psycho-social problems in adolescence after controlling for confounders (n=1022)

	ECEC-start-age groups	SDQ Total Score		Externalizing Psycho-social Problems		Internalizing Psycho-social Problems	
		Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Germany (n=1022)	Below age 1	**2.9 (1.4, 4.4)**	**<0.001***	**1.8 (0.8, 2.8)**	**<0.001***	1.1 (-0.02, 2.1)	0.054
	Age 1-2	**2.3 (0.004, 4.6)**	**0.0496***	**1.7 (0.2, 3.2)**	**0.030***	0.6 (-0.4, 1.7)	0.238
	Age 2-3 (Reference group)						
	Age 3+ and before schooling	**1.1 (0.2, 2.0)**	**0.013***	0.4 (-0.1, 0.9)	0.124	**0.7 (0.2, 1.3)**	**0.011***
	Only cared in Family before schooling	1.0 (-0.4, 2,4)	0.178	0.8 (-0.1, 1.7)	0.080	0.1 (-0.6, 0.9)	0.736
	East Germany	0.9 (-0.5, 2.3)	0.204	0.1 (-0.8, 1.0)	0.799	0.8 (-0.2, 1.8)	0.128
	West Germany (Reference group)						
	Below age 1 * East	**-3.6 (-5.7, -1.4)**	**0.001***	**-1.7 (-3.0, -0.3)**	**0.016***	**-1.9 (-3.4, -0.3)**	**0.018***
	Age 1-2 * East	-2.5 (-5.2, 0.2)	0.064	-1.2 (-3.0, 0.5)	0.167	-1.3 (-2.7, 0.1)	0.078
	Age 2-3 (Reference group) * East						
	Age 3+ and before schooling * East	1.2 (-3.2, 5.6)	0.595	0.7 (-1.4, 2.8)	0.518	0.5 (-2.3, 3.3)	0.724
	Only cared in Family before schooling* East	-3.1 (-6.8, 0.7)	0.108	-1.2 (-3.6, 1.2)	0.312	-1.8 (-4.9, 1.2)	0.227

'* p<0.05, Age 2-3 and West Germany are the reference group. Covariates: age in adolescence, gender, schooling type, parents' divorce by wave 2, and other baseline characters including region (East/West Germany), social economic status, migrant status, number of older siblings, family situation, family cohesion, birth weight, obesity/overweight, age of mother at childbirth, employment status of mother. Interaction factor: region*ECEC-start-age

5. Sensitivity analysis for the outliers

Table S3.1. Without outliers: linear regression of the association between ECEC-start-age and psycho-social problems in adolescence after controlling for confounders (n=946)[1]

	ECEC-start-age groups		SDQ Total Score		Externalizing Psycho-social Problems		Internalizing Psycho-social Problems	
		n	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Germany (n=946)	Below age 1	130	**1.2 (0.3,2.2)**	**0.012***	**1.0 (0.3,1.7)**	**0.005***	0.2 (-0.5,0.9)	0.570
	Age 1-2	200	**1.0 (0.1,1.8)**	**0.036***	**0.7 (0.2,1.2)**	**0.007***	0.2 (-0.3,0.8)	0.398
	Age 2-3 (Reference group)	340						
	Age 3+ and before schooling	189	**0.8 (0.1,1.5)**	**0.033***	0.2 (-0.2,0.6)	0.371	**0.6 (0.2,1.0)**	**0.009***
	Only cared in Family before schooling	87	0.7 (-0.3,1.7)	0.176	0.6 (-0.02,1.3)	0.059	0.0 (-0.6,0.7)	0.913

[1] '* p<0.05, Outlier is defined as "values more than 2 standardized residuals away from zero in the linear regression". Covariates: age in adolescence, gender, schooling type, parents' divorce by wave 2, and other baseline characters including region (East/West Germany), social economic status, migrant status, number of older siblings, family situation, family cohesion, birth weight, obesity/overweight, age of mother at childbirth, and employment status of mother.

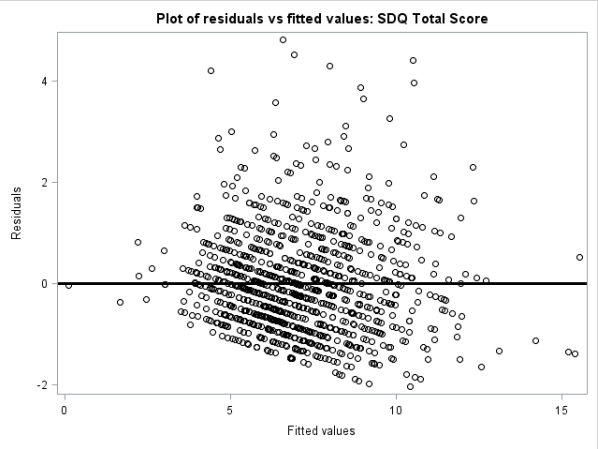
Table S3.2. Without outliers: Stratified Linear regression of the association between ECEC-start-age and psycho-social problems in adolescence after controlling for confounders by Region (West/East Germany) (n=946)[1]

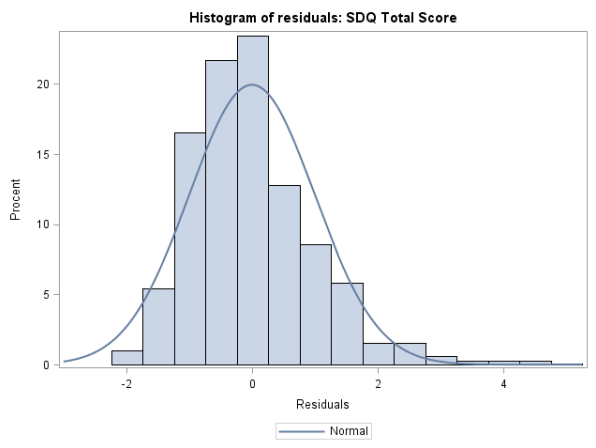
	ECEC-start-age groups		SDQ Total Score		Externalizing Psycho-social Problems		Internalizing Psycho-social Problems	
		n	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
West Germany (n=571)	Below age 1	38	**2.0 (0.7,3.4)**	**0.003***	**1.7 (0.7,2.7)**	**0.001***	0.3 (-0.7,1.3)	0.504
	Age 1-2	35	0.5 (-0.9,2.0)	0.466	0.5 (-0.3,1.4)	0.190	0.0 (-0.9,0.9)	0.986
	Age 2-3 (Reference group)	245						
	Age 3+ and before schooling	170	**0.8 (0.03,1.6)**	**0.043***	0.2 (-0.3,0.7)	0.371	**0.6 (0.1,1.1)**	**0.013***
	Only cared in Family before schooling	83	0.6 (-0.4,1.7)	0.239	0.6 (-0.1,1.3)	0.083	0.0 (-0.6,0.7)	0.955
East Germany (n=375)	Below age 1	92	0.4 (-0.9,1.7)	0.572	0.1 (-0.7,1.0)	0.740	0.2 (-0.6,1.1)	0.587
	Age 1-2	165	1.0 (-0.3,2.2)	0.131	**0.7 (0.05,1.4)**	**0.036***	0.2 (-0.6,1.1)	0.549
	Age 2-3 (Reference group)	95						
	Age 3+ and before schooling	19	2.1 (-0.7,4.9)	0.140	0.7 (-1.0,2.4)	0.434	1.5 (-0.1,3.0)	0.059
	Only cared in Family before schooling	4	0.7 (-1.3,2.8)	0.480	-0.1 (-1.2,1.0)	0.819	0.8 (-1.2,2.8)	0.399

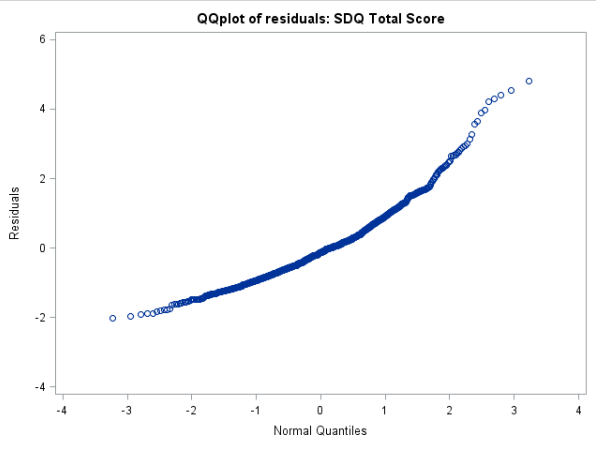
[1] '* p<0.05, Outlier is defined as "values more than 2 standardized residuals away from zero in the linear regression". Covariates: age in adolescence, gender, schooling type, parents' divorce by wave 2, and other baseline characters including social economic status, migrant status, number of older siblings, family situation, family cohesion, birth weight, obesity/overweight, age of mother at childbirth, and employment status of mother.

6. Diagnostics for linear regression

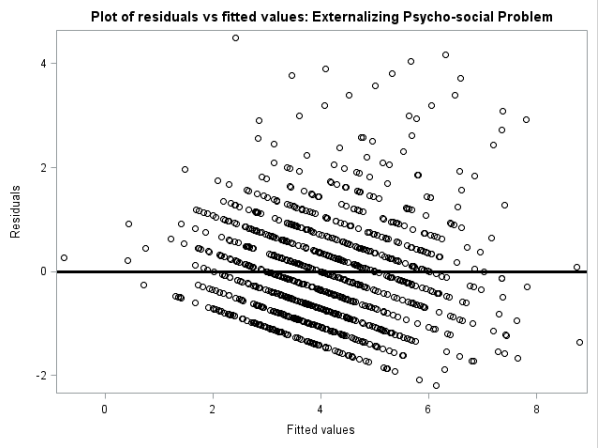
Graphic S1.1. SDQ Total Score in Germany

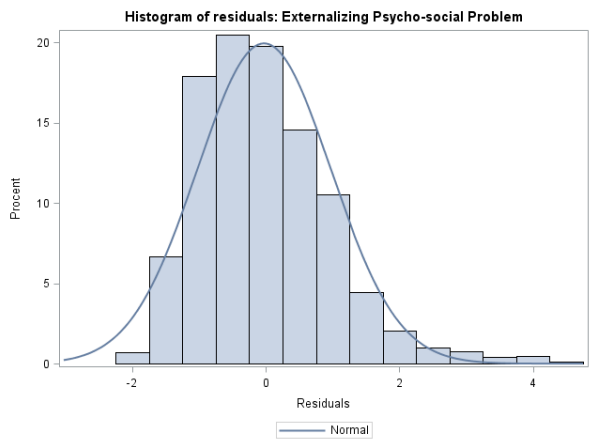


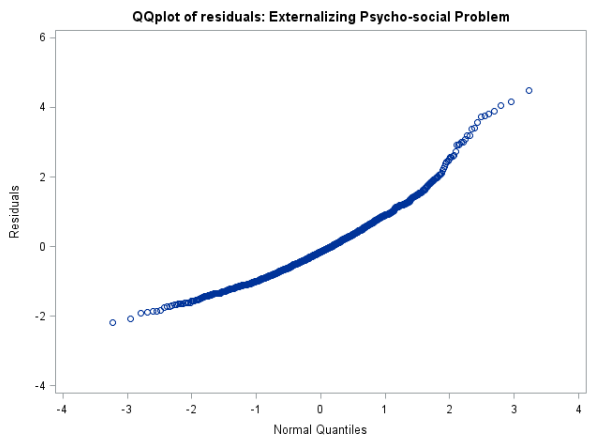




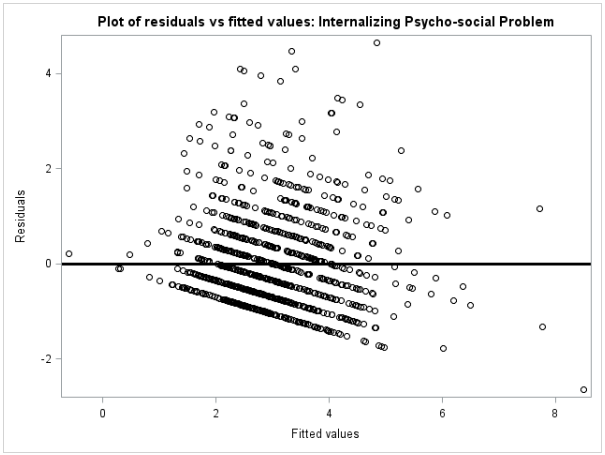
Graphic S1.2. Externalizing Psycho-social Problems in Germany

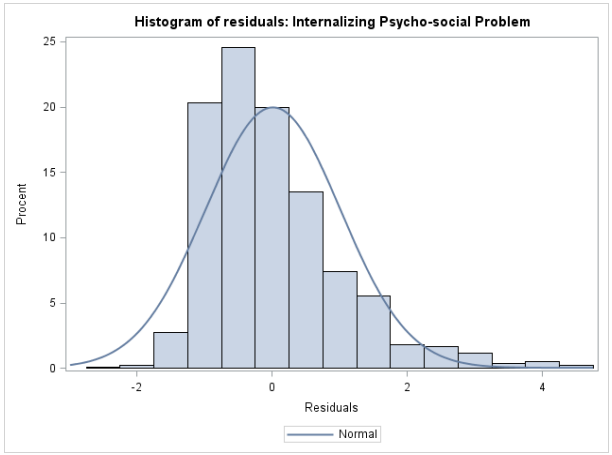


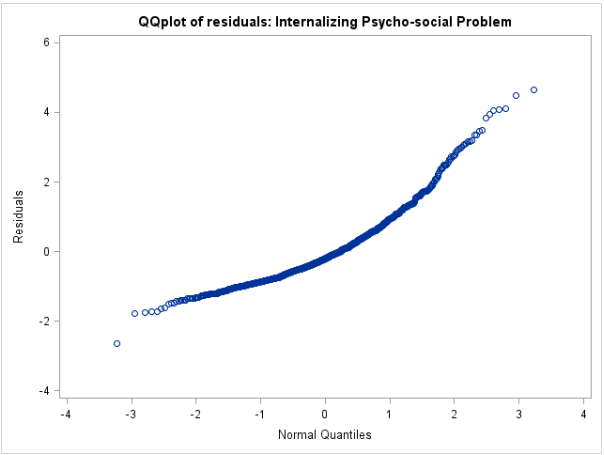




Graphic S1.3. Internalizing Psycho-social Problems in Germany







7. Distribution of SES and other Covariates by ECEC-start-age in West and East Germany

Table S4.1 Distribution of SES by ECEC-start-age in West and East Germany

	West Germany (n=621)			East Germany (n=401)		
	Low SES (%)	Middle SES (%)	High SES (%)	Low SES (%)	Middle SES (%)	High SES (%)
Below age 1	3.2	4.1	14.4	11.7	21.2	37.3
Age 1-2	1.2	4.7	12.6	47.0	47.8	36.2
Age 2-3	39.1	44.8	41.9	35.5	26.1	21.9
Age 3+ and before schooling	27.6	30.9	21.6	5.9	3.6	3.9
Only cared in Family before schooling	28.9	15.6	9.6	0	1.4	0.7
Total	47	365	203	46	243	111
Chi-Square	**P<0.0001**			P=0.151		

The weight factor for baseline data was applied in the frequency and statistical tests. The number of missing values for West Germany was 6, and for East Germany was 1.

Table S4.2 Distribution of Family Structure by ECEC-start-age in West and East Germany

	West Germany (n=621)		East Germany (n=401)	
	Natural parents in a joint household (%)	Other Family Structure (%)	Natural parents in a joint household (%)	Other Family Structure (%)
Below age 1	6.2	16.0	24.5	23.4
Age 1-2	6.1	11.7	47.3	29.7
Age 2-3	43.2	44.3	23.7	38.9
Age 3+ and before schooling	27.9	25.3	3.3	8.0
Only cared in Family before schooling	16.7	2.7	1.2	0
Total	572	45	338	59
Chi-Square	**P=0.007**		P=0.179	

"other family structure" refers to the family structures except for "Natural parents in a joint household".

The weight factor for baseline data was applied in the frequency and statistical tests. The number of missing values for West Germany was 4, and for East Germany was 4.

Table S4.3 Distribution of Migration Background by ECEC-start-age in West and East Germany

	West Germany (n=621)		East Germany (n=401)	
	Non-migrant (%)	Migrant (%)	Non-migrant (%)	Migrant (%)
Below age 1	7.7	2.1	25.9	2.1
Age 1-2	7.1	3.3	44.6	42.8
Age 2-3	42.4	47.7	24.6	48.9
Age 3+ and before schooling	27.5	29.6	4.3	0
Only cared in Family before schooling	15.3	17.3	0.7	6.1
Total	540	78	387	10
Chi-Square	P=0.080		P=0.155	

The weight factor for baseline data was applied in the frequency and statistical tests. The number of missing values for West Germany was 3, and for East Germany was 4.

Table S4.4 Distribution of Mother's Employment Status by ECEC-start-age in West and East Germany

	West Germany (n=621)			East Germany (n=401)		
	Full-time employed (%)	Part-time employed (%)	Unemployed (%)	Full-time employed (%)	Part-time employed (%)	Unemployed (%)
Below age 1	23.9	8.0	3.4	36.1	23.0	11.6
Age 1-2	9.1	9.0	4.3	47.0	51.7	33.6
Age 2-3	35.6	43.4	43.9	14.3	21.9	45.0
Age 3+ and before schooling	22.1	28.0	28.2	2.1	2.9	7.5
Only cared in Family before schooling	9.2	11.6	20.1	0.5	0.5	2.3
Total	53	253	304	141	129	128
Chi-Square	**P=0.005**			**P=0.004**		

The weight factor for baseline data was applied in the frequency and statistical tests. The number of missing values for West Germany was 11, and for East Germany was 3.

Table S4.5 Distribution of Age of Mother at Birth by ECEC-start-age in West and East Germany

	West Germany (n=621)				East Germany (n=401)			
	Till 24 years old	25-29 years old	30-34 years old	35+ years old	Till 24 years old	25-29 years old	30-34 years old	35+ years old
Below age 1	6.1	5.7	4.0	13.9	26.1	26.2	24.2	17.9
Age 1-2	4.8	8.2	5.5	7.5	43.1	45.4	46.3	40.7
Age 2-3	48.1	44.1	42.3	39.6	24.8	23.3	26.1	34.0
Age 3+ and before schooling	25.4	26.8	29.8	27.7	3.9	5.1	2.9	3.7
Only cared in Family before schooling	15.5	15.1	18.4	11.3	2.1	0	0.5	3.8
Total	68	136	247	158	66	143	127	54
Chi-square	P=0.128				P=0.311			

The weight factor for baseline data was applied in the frequency and statistical tests. The number of missing values for West Germany was 12, and for East Germany was 11.

Note: The p-values keep in the same direction even after excluding the rows with 0 cells in East Germany for these Tables (S4.1-S4.5).

8. Table to support Figures 2 and 3 in the main paper

Table S5.1. Mean values and 95% CI of psycho-social problems in adolescence by ECEC-start-age group

	ECEC-start-age groups		SDQ Total Score	Externalizing Psycho-social Problems	Internalizing Psycho-social Problems
		n	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
Germany (n=1022)	Below age 1	144	8.10 (6.93, 9.28)	4.99 (4.23, 5.74)	3.12 (2.47, 3.77)
	Age 1-2	214	7.72 (6.78, 8.67)	4.69 (4.05, 5.32)	3.04 (2.61, 3.46)
	Age 2-3	366	6.81 (6.23, 7.40)	3.96 (3.53, 4.38)	2.85 (2.52, 3.18)
	Age 3+ and before schooling	205	7.71 (7.00, 8.42)	4.21 (3.79, 4.63)	3.50 (3.08, 3.91)
	Only cared in Family before schooling	93	8.15 (6.60, 9.71)	5.08 (4.09, 6.08)	3.07 (2.29, 3.85)

Table S5.2. Mean values and 95% CI of psycho-social problems in adolescence by ECEC-start-age group and region

	ECEC-start-age groups		SDQ Total Score	Externalizing Psycho-social Problems	Internalizing Psycho-social Problems
		n	Mean (95%CI)	Mean (95%CI)	Mean (95%CI)
West Germany (n=621)	Below age 1	45	9.17 (7.34, 11.00)	5.60 (4.43, 6.77)	3.57 (2.50, 4.65)
	Age 1-2	41	8.16 (5.81, 10.51)	5.04 (3.43, 6.64)	3.12 (2.15, 4.10)
	Age 2-3	261	6.67 (6.03, 7.32)	3.94 (3.46, 4.42)	2.74 (2.39, 3.08)
	Age 3+ and before schooling	185	7.63 (6.91, 8.35)	4.18 (3.75, 4.61)	3.45 (3.03, 3.87)
	Only cared in Family before schooling	89	8.15 (6.57, 9.73)	5.09 (4.08, 6.10)	3.07 (2.27, 3.86)
East Germany (n=401)	Below age 1	99	6.70 (5.69, 7.70)	4.18 (3.55, 4.81)	2.51 (1.94, 3.09)
	Age 1-2	173	7.47 (6.75, 8.18)	4.48 (4.04, 4.93)	2.99 (2.58, 3.39)
	Age 2-3	105	7.72 (6.47, 8.98)	4.09 (3.35, 4.82)	3.64 (2.61, 4.66)
	Age 3+ and before schooling	20	9.81 (5.34, 14.27)	5.14 (2.89, 7.39)	4.67 (2.22, 7.11)
	Only cared in Family before schooling	4	8.10 (5.36, 10.85)	4.92 (-0.11, 9.95)	3.19 (0.49, 5.88)

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Zhou et al. BMC Geriatrics (2016) 16:9
DOI 10.1186/s12877-016-0184-7

BMC Geriatrics

RESEARCH ARTICLE Open Access

Years of life lost due to lower extremity injury in association with dementia, and care need: a 6-year follow-up population-based study using a multi-state approach among German elderly

Ying Zhou[1,2], Hein Putter[3] and Gabriele Doblhammer[1,2,4*]

Abstract

Background: Dementia and care need are challenging aging populations worldwide. Lower extremity injury (LEI) in the elderly makes matters worse. Using a multi-state approach, we express the effect of LEI on dementia, care need, and mortality in terms of remaining life expectancy at age 75 (rLE) and years of life lost (YLL).

Methods: A population-based random sample of beneficiaries aged 75–95 years was drawn from the largest public health insurer in Germany in 2004 and followed until 2010 (N 62,103; Mean Age ± SD 81.5 ± 4.8 years; Female 71.2 %). We defined a five-state model (*Healthy*, *Dementia*, *Care*, *Dementia & Care*, *Dead*), and calculated transition-specific hazard ratios of LEI using Cox regression. The transition probabilities as well as the YLL due to LEI were estimated.

Results: LEI significantly increased the risk for each transition, with a maximum risk for the transition from *Healthy* to *Care* (HR: 1.70, 95 % CI: 1.63-1.77) and a minimum risk for the transition from *Care* to *Dead* (HR: 1.16, 95 % CI: 1.10-1.22). If the elderly had LEI-history, their age-specific mortality was generally higher and their probabilities of transient states peaked at younger ages. At age 75, initially dementia-free and care-independent elderly experiencing LEI lost about 2 years of life, of which more than 90 % were life years free of dementia or care need. Dementia patients lost about one and a half year, more than 60 % were free of long-term care need.

Conclusions: LEI not only casts a large health burden on care need, but is also associated with cognitive decline and shortened rLE. LEI plus dementia extend the relative life time in need of care, despite generally shortening rLE. Using the composite measure YLL may help to better convey these results to the elderly, families, and health professionals. This may strengthen preventive measures as well as improve timely and rehabilitative treatment of LEI, not only in cognitive and physically intact elderly.

Keywords: Long-term care, Mortality, Cohort analysis, Dementia, Multi-state analysis

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Background

As the world's population ages, age-dependent disorders are of great concern. Dementia, a key age-dependent disorder, dramatically contributes to disability and dependency, thereby challenging the health care system substantially [1].

Geriatric trauma, another age-related disorder, is also drawing more attention in public health [2]. With age, physiological reserve capability declines, physiologic reaction to injury degenerates, and age-related multimorbidity and polypharmacy worsen disability and mortality after injuries [3, 4]. Traumatic injuries also pose a challenge to health care [2], and rank as the fifth leading causes of death in elderly [3].

The lower extremities, covering the hip, thigh, knee, lower leg, ankle and foot, are one of the most likely region of the body for traumatic injuries in old adults [5, 6]. We focus on lower extremity injury (LEI), which includes not only hip fractures but also other types of fractures and fall-induced LEI, all of which increase the risk of mortality and deleterious disability and long-term care [7, 8]. LEI is also related with limitation of mobility and social participation [9, 10].

Numerous studies demonstrate an association between geriatric LEI and care need [7, 10–13]. LEI dramatically contributes to functional decline and increased dependency for basic and instrumental activities of daily living (ADL) [7, 10, 11]. In particular, dementia patients suffering the LEI are more likely to get poor functional outcomes and long-term care need [10, 14]. In turn, those living in long-term care institutions have also substantially increased rates of falls and fractures [12].

Previous research suggests an association between geriatric LEI and dementia [15–17]. Dementia increases the risk of falling and LEI disproportionately [18, 19]. In turn, LEI might lead to depression and delirium, as well as the restricted physical and social activity, which contributes to a cognitive decline and dementia onset [16, 20–24].

A bunch of studies reveal that geriatric LEI increases mortality considerably [8, 10, 25–29]. The mortality following LEI is even higher in people with dementia than people without dementia [25, 30, 31]. Moreover, the impairment in basic ADL (BADL) prior to LEI is also significantly associated with increased risk of mortality following LEI [32].

But most of the previous studies analyzed the associations separately. It lacks research to evaluate the effects of LEI on functional and survival outcomes during the aging process holistically. The aging process covers two major functional declines, namely physical decline and cognitive decline [33]. Dementia can be regarded as a later state of cognitive impairment [33], whereas the impairment in the BADL and the consequent care need can be regarded as a later state of physical impairment.

A holistic analysis of LEI effects in the aging is valuable because all forms of dementia, care need and premature mortality add a health burden on a society with an aging population, and also because LEI and dementia as well as mobility and cognitive dysfunction may interact and in particular aggravate one another, leading to a profound combined effect on care need and mortality [33, 34]. Moreover, the investigation of both survival and functioning outcomes simultaneously has also been recommended in the geriatric research such as LEI and successful aging [35, 36].

Hence, we used a multi-state model to simultaneously evaluate the effect of LEI on the endpoints dementia, care need, and death with the focus on the transitions from one state to another over age [37–39]. As successfully applied in previous studies, multi-state models help quantify how risk factors at the individual level alter life expectancy at the population level [40]. The compound measures derived from multi-state models, such as remaining life expectancy (rLE) and years of life lost (YLL), are highly intuitive to the public and to health professionals and help quantify the health burden and make intervention choices [40].

Additional methodological shortcomings in prior research include sample size and short-term follow up in longitudinal studies [26, 27]. Previous studies have commonly been based only in hospital settings, or used cohorts consisting only of voluntary participants, both of which excluded nursing home residents.

Therefore, we aimed to use a large nationally representative sample of Germans living in private households and in nursing homes with a 6-year follow-up to: (1) simultaneously investigate the association between LEI and dementia, care need, as well as death; (2) explore the transition probabilities of getting dementia, care need, and dying from various initial states, stratified by LEI; (3) estimate to what extent LEI influences rLE, as well as rLE with dementia and care need; and (4) quantify the consequences of LEI in terms of YLL.

Methods

Sample and study design

We used claims data from the largest public health insurer in Germany (AOK), which covered about one-third of the German population. A national 2.2 % random sample of AOK beneficiaries aged 50 years and older, regardless of whether they went to the doctor, was drawn in the first quarter of 2004. We used the data in 2004 to classify the initial states, and followed the 62,103 individuals in our sample who were between 75 and 95 years of age from 2005 to 2010. In this age range, usually various transitions to dementia, care need and

death occur. Medical and care need data were available from both the inpatient and the outpatient sectors for each person for each quarter, except that the data of care need from 2004 to 2006 were documented only once a year. The dataset supporting the conclusions of this article is not publicly available. Data access was legally approved by the "Wissenschaftliches Institut der Ortskrankenkassen" (WIdO). The study is based on anonymised administrative claims data that never involved patients directly. Individual patients cannot be identified and the analyses presented do not affect patients whose anonymized records were used.

Variables of interest

We used ICD-10 to identify dementia (Dementia: G30, G31.0, G31.82, G23.1, F00, F01, F02, F03, and F05.1). To account for false positive diagnoses we developed a validation procedure. First, only diagnoses indicated as "verified" by a medical doctor were included from outpatient services, while from inpatient services only the discharge and secondary diagnoses were considered. Second, only those diagnoses with a second occurrence in the same quarter by different types of physicians or over time were considered. The only exception was when a patient died immediately after a dementia diagnosis in the same quarter; all of these cases were considered valid dementia cases [41].

We defined care need as receiving benefits from the statutory long-term care insurance in Germany. Such insurance includes cover for long-term care at home or in an institution, and is statutory and compulsory for all citizens in Germany [42]. The long-term care benefits are available for all insured persons, irrespective of age or wealth. The Medical Advisory Service of the Statutory Health Insurance Funds assesses whether there is need of care. Based on the German law regarding long-term care insurance in the study period (2004-2010), care need in our study refers to a minimum of assistance for at least 90 min per day, with more than 45 min per day attributable to basic care in the BADLs such as washing, eating or dressing. This implies that dementia patients with intact ADLs do not receive benefits and, thus, in our study are not coded as being in need of care.

Our exposure of interest was LEI, namely injuries to the hip and thigh, the knee and lower leg as well as the ankle and foot [6]. We used ICD to identify LEI (S70 - S99 and its related T section of the ICD codes, see details in Additional file 1: Table S1).

Model

We applied a multi-state model to assess the risk of LEI for the eight possible transitions between the four transient states *Healthy*, *Dementia*, *Care*, *Dementia & Care*, and the only absorbing state *Dead* (Fig. 1). The state *Healthy* contains all individuals without a dementia diagnosis and without care need. Those with an incident or prevalent dementia diagnosis but without care need are contained in the state *Dementia*; those with incident or prevalent care need but without a dementia diagnosis are in the state *Care*. Insurants who have both a dementia diagnosis and are in need of care are included in the state *Dementia & Care*. The model does not consider recovery from dementia and from care need, which is reflected in Fig. 1 by the absence of the respective transitions. At present dementia cannot be treated and mild cognitive impairment, which can revert, has a separate ICD-10 number and is not part of our study. Recovery from care need is excluded because of the very small number of cases with a transition from care need to no care need. Individual persons may experience multiple transitions across different states during the follow-up period; as recovery is not possible, there are no multiple transitions of the same type.

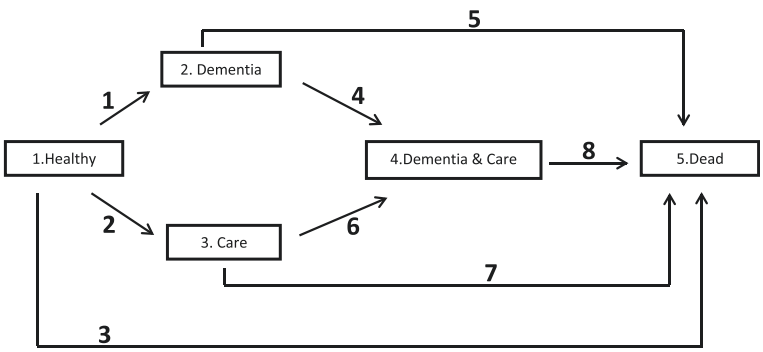

Fig. 1 Multi-state model of the stages of healthy, dementia, care and dead. The boxes represent five states: (1) *Healthy* refers to no dementia, no care need. (2) *Dementia* includes incident and prevalent dementia, but without care need. (3) *Care* includes incident and prevalent care need, but without dementia (4) *Dementia & Care* refers to both dementia and care need. (5) *Dead* refers to a dead state, the only absorbing stage in our model. The other four states are transient states. The arrows represent the eight transitions from the ORIGIN STATE to the DESTINATION STATE

We estimated stratified Cox proportional hazard models, with LEI as a time-dependent and transition-specific explanatory variable, sex as a stratification factor, and age as process time, under consideration of right censoring and left truncation [43]. Right censoring was identified as changing to another health insurer, reaching age 95 during the follow-up, and staying in one of the transient states on December 31, 2010. For each individual the date of birth was given; the date of death was recorded if he/she died during the study time; the date of the dementia and LEI diagnoses were also given by the quarter of the year which also applied to the variable care need between 2007 and 2010. Age on January 1, 2005 was used for the left truncation. In addition, when estimating transition hazards, for each transition, age of entry into the origin state of that transition was used as left truncation. We treated dementia, care need, and LEI as "ever"-variables, which have the value one the first time they are recorded in the data and thereafter; otherwise they have the value zero. Since care need before 2007 was only recorded annually, it was assumed to occur in the middle of the year if the individual survived to the end of that year; for individuals who died in that year it was placed in the middle of the survival period. In addition, given our quarter-based data, we assumed that all the transitions and LEI occurred in the midpoint of each quarter with the following exceptions: if an individual experienced multiple transitions and/or LEI in the same quarter of the year, then dementia, care need and LEI occurred before death; dementia occurred before care need; LEI occurred before care need and dementia. We conducted sensitivity analyses under different assumptions of the ordering which did not affect our results. We also checked the proportional hazard assumptions in the Cox models which were generally fulfilled.

We obtained the hazard ratio and 95 % confidence interval of LEI for each transition hazard in our multi-state model. The transition probability was defined as $P_{hj}(s,t) = P(X(t) = j|X(s) = h)$, which denoted the transition probability from state h to state j in the time (age) interval (s,t] [44], namely the probability that the subject is in state j at age t, given that he/she is in state h at age s. Estimates of the transition probabilities were obtained from the estimated transition hazards using the Aalen-Johansen formula [43, 45]. We estimated and plotted the age-specific transition probabilities of men and women by LEI in the age range between 75 and 95, starting at an individual's 75^{th} birthday with various initial states. Furthermore, we estimated the state-specific rLE for a 75-year-old individual by calculating the state-specific expected duration of stay for a 75-year-old individual with various initial states. Moreover, we compared the state-specific rLE under LEI exposure and under no-LEI exposure by using the composite measure YLL due to LEI. We restricted the state-specific rLE from age 75 to 95 according to the age range of our study population. We bootstrapped 95 % confidence intervals for the state-specific rLEI and YLL by performing a thousand replications to resample the sample data with replacement. We used the "mstate" package in R 3.0 to perform the multi-state analysis [44].

Results

In the first quarter of 2005 our sample comprised 62,103 insured persons (mean age ± standard deviation: 81.5 ± 4.8 years; 71.2 % female); of these 74 % ($N = 45,758$) were in the state *Healthy*, 5 % ($N = 2,888$) in the state *Dementia*, 13 % ($N = 7,835$) in the state *Care*, and 9 % ($N = 5,622$) in the state *Dementia & Care*. During the follow up, 25,730 persons died, 1,538 persons changed to other health insurance companies, and 6,651 persons reached ages over 95.

The first part of Table 1 (Col I-VI) shows the number of persons at risk of transitioning in each ORIGIN STATE (Col I) as well as the number of transitions from ORIGIN STATES to DESTINITION STATES during follow up (Col II to VI). Between 2005 and 2010, 45,758 individuals were at risk of transitioning from the state *Healthy* (Col I). Of these, 7,699 (17 %) experienced a transition to the state *Dementia*, 12,302 (27 %) to *Care*, 5,446 (12 %) to *Dead*, and 20,311 (44 %) remained in state *Healthy* through the end of the study or the time point of right censoring (Col II ~ VI). Of the 10,587 individuals in the risk population of the state *Dementia* between 2005 and 2010 (Col I), 6,977 individuals changed to the state *Dementia & Care* (Col IV), 1,349 to the state *Dead* (Col V), and 2,261 had no change (Col VI). The second part of Table 1 shows the number of persons with LEI and the proportion of LEI in each ORIGIN STATE (Col VII ~ VIII). 10,690 individuals had LEI-history in the state *Healthy* (Table 1, Col VII). In the states *Dementia* and *Care* about 30 % individuals had LEI-history (30.5 % and 31.9 % respectively), in the state *Dementia & Care* it was 41.7 % (Col VIII). Additional file 2: Table S2 details this information by 5-year age groups.

LEI accelerated health deterioration and significantly increased the risk of each transition (Table 2). LEI increased the risk of almost all transitions from the states *Healthy* or *Dementia* by about 50 % or more, whereas LEI increased the risk of all other transitions to a smaller extent (by 16–28 %). Among all eight transitions the effect of LEI was largest for the risk of a transition from *Healthy* to *Care*: it was 70 % higher for those with LEI than for those without LEI (HR: 1.70, 95%CI: 1.63-1.77). The two sexes did not differ significantly in their effect sizes (results not shown).

Table 1 Numbers and percentages of transitions and exposure of interest (LEI)

	I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
Origin State	Risk set (persons)[a]	Destination state				No change[b]	N of	% of LEI[c]
		2. Dementia	3. Care	4. Dementia & care	5. Dead		LEI	
1. Healthy	45,758	7699	12,302		5446	20,311	10,690	23.4
	100 %	17 %	27 %		12 %	44 %		
2. Dementia	10,587			6977	1349	2261	3228	30.5
	100 %			66 %	13 %	21 %		
3. Care	20,137			5734	7705	6698	6422	31.9
	100 %			28 %	38 %	33 %		
4. Dementia & Care	18,333				11,230	7103	7637	41.7
	100 %				61 %	39 %		

[a]numbers of individuals who were under the risk of the transitions from "ORIGIN STATE" to "DESTINATION STATE" on January 01,2005 or during the follow up. [b] numbers and percentage of individuals who entered or began with the particular ORIGIN STATE and stayed in that state until the end of the study or until the time point of right censoring. [c] proportion with LEI in the ORIGIN STATE

Figure 2 shows the age-specific estimated probabilities of the transitions from the four initial states *Healthy* (1st row), *Dementia* (2nd row), *Care* (3rd row) and *Dementia & Care* (4th row), stratified by the presence of LEI and sex. For example, Fig. 2, 1st row illustrates the transition probabilities for a synthetic cohort initiating in the state *Healthy* on the 75th birthday. At exact age 85, the probability of a woman without LEI to be in state *Dementia* was 5.7 %, in state *Care* 9.5 %, in state *Dementia & Care* 10.6 %, in state *Dead* 32.7 %, and to remain in the state *Healthy* 41.4 %. For most transitions, the age-specific probability for both sexes of entering a deteriorating state was larger for those with LEI than for those without LEI. Regarding the transitions to transient states, for both sexes the transition probabilities peaked at younger ages for those with LEI than for those without LEI. In the transitions with care need as the DESTINATION STATE (from *Healthy* to *Care*, or from *Dementia* to *Dementia & Care*), women had a markedly larger age-specific probability to experience these transitions than men. Regarding the transitions to the absorbing state death, men with LEI had the largest age-specific probability to die. In both sexes individuals with LEI always had a larger age-specific probability of dying than individuals without LEI.

For both sexes, the elderly with LEI spent generally shorter periods in each transient state than those without LEI (Table 3). At age 75, women who started healthy (initial state *Healthy*) but experienced LEI lost 2.10 years of rLE, males lost 1.97 years. More than 90 % of the years lost were years free of dementia and independent of long-term care (women 2.00 years, males 1.79 years), while the years with dementia and care need were reduced only marginally. Women who started with dementia (initial state *Dementia*) lost 1.72 years of rLE, men lost 1.35 years. Again, the majority of YLL were years with dementia but free of care need (women: 1.05 years = 61 %; men: 0.93 years = 69 %). The same was true for those who started with care need but were free of dementia. The YLL (women: 0.56 years = 68 %; men 0.33 years = 69 %) were mainly years with physical limitations but intact cognitive functioning. For most transitions the YLL due to LEI were significantly different from zero at conventional significance levels. Furthermore, the elderly with LEI experienced more years with dementia and care as compared to years with dementia

Table 2 Hazard ratio of LEI for each transition

Transition		Hazard ratio	95 % CI of HR	*P*
1	1 Healthy - > 2 Dementia	1.54	1.46–1.62	<0.001
2	1 Healthy - > 3 Care	1.70	1.63–1.77	<0.001
3	1 Healthy - > 5 Dead	1.24	1.16–1.33	<0.001
4	2 Dementia - > 4 Dementia & Care	1.46	1.39–1.54	<0.001
5	2 Dementia - > 5 Dead	1.50	1.33–1.69	<0.001
6	3 Care - > 4 Dementia & Care	1.26	1.19–1.33	<0.001
7	3 Care - > 5 Dead	1.16	1.10–1.22	<0.001
8	4 Dementia & Care - > 5 Dead	1.28	1.23–1.33	<0.001

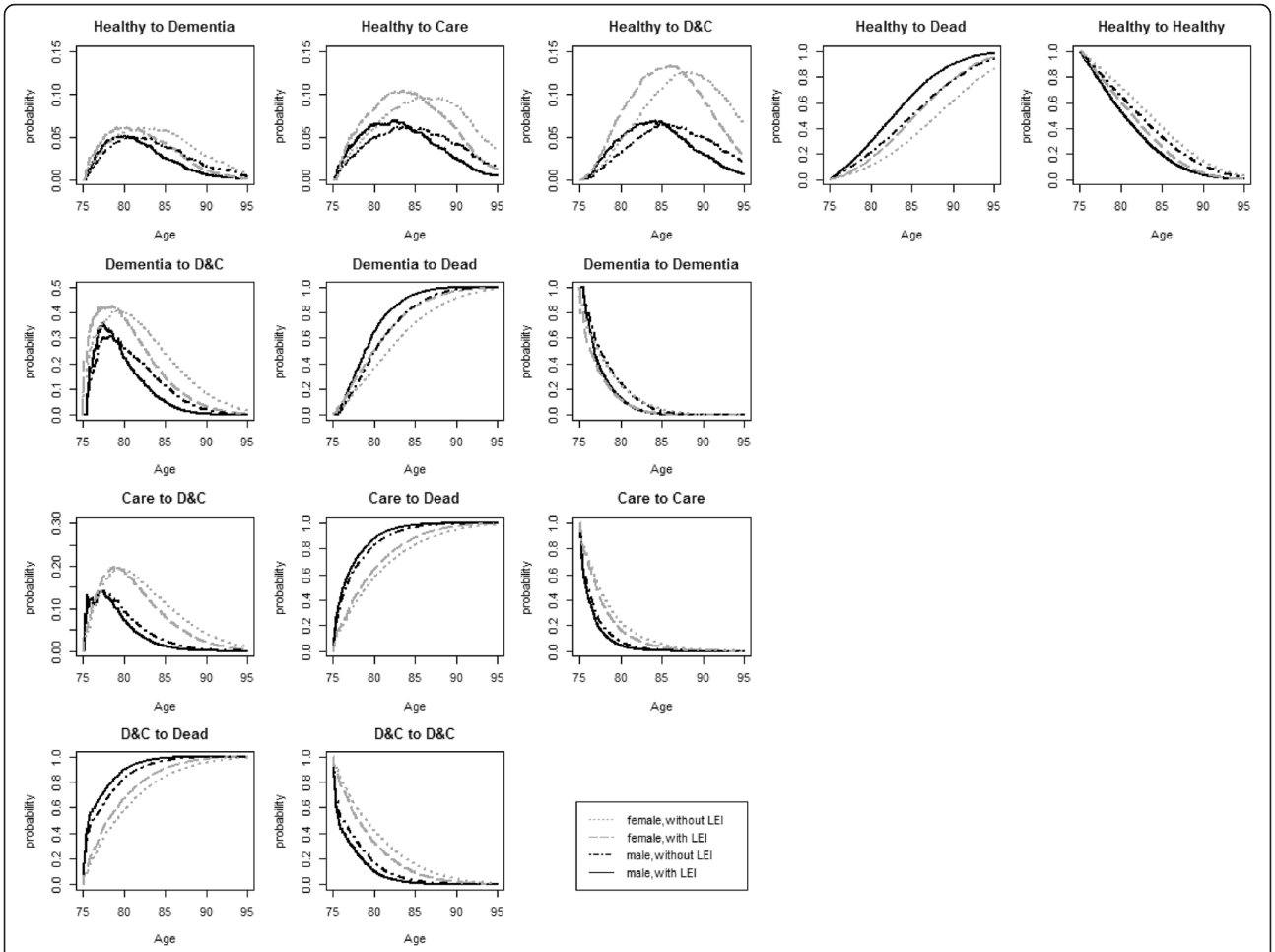

Fig. 2 Estimated transition probabilities in the age interval 75–95, stratified by sex and LEI. For the populations with different initial states on the 75th birthday. (1st row: from *Healthy* as the initial state; 2nd row: from *Dementia* as the initial state; 3rd row: from *Care* as the initial state; 4th row: from *Dementia & Care* as the initial state). "Without LEI" refers to individuals who do not experience LEI during the whole period. "With LEI" refers to individuals who start out with LEI in their initial state. Abbreviation: D&C: *Dementia & Care*

alone. Taking a 75-year-old *healthy* woman as an example, under the exposure of no-LEI her rLE in the state *Dementia & Care* was 1.56 years, and 0.77 in the state *Dementia* which is a ratio of 2.03. For her counterpart with LEI, in contrast, the ratio is 2.53 (rLE 1.62 years *Dementia & Care*: rLE 0.64 years *Dementia*). A similar ratio existed for men, and for *Dementia* as the initial state.

Discussion

Exploring individual transitions in a large population-based data set, we found that LEI in the elderly significantly increased the risk of the entire adverse chain from health over dementia and care need to death and resulted in a large loss of years of life. Similarly important, we found that these lost years were mainly years with better health and fewer limitations, independently of whether the individual was initially healthy or suffered from dementia or was in need of care. LEI increased all age-specific death probabilities (particularly in men), and shifted the age-peak of the probabilities of the transient transitions forward (particularly the transitions to care need in women). LEI was generally associated with shortened life expectancy, but with relatively expanded life time with dementia and care need.

To our knowledge, this is the first study to explore the effect of LEI on the risk of dementia, care need, and death simultaneously in a multi-state model. Earlier studies primarily looked at separate endpoints at the individual level and did not derive compound measures at the population level, such as life expectancy and years of life lost. Our findings provide insight into the effects of LEI on both the functional outcomes (dementia, care need) and the survival outcomes holistically, which is highly recommended in the research fields of successful aging [35].

Furthermore, we studied LEI instead of only hip fractures or fall-induced fractures, because they are not as

Table 3 Remaining life expectancy at age 75 (rLE) and 95 % confidence intervals by initial state, stratified by sex and LEI

Initial state	Destination state	rLE without LEI[a]	rLE with LEI[a]	YLL due to LEI[b]
Females				
1. Healthy	1. Healthy	8.95	6.95	2.00
		(8.83 9.06)	(6.79 7.13)	(1.84 2.13)
	2. Dementia	0.77	0.64	0.13
		(0.74 0.81)	(0.59 0.68)	(0.09 0.18)
	3. Care	1.33	1.30	0.03
		(1.29 1.38)	(1.24 1.37)	(-0.03 0.09)
	4. Dementia & Care	1.56	1.62	−0.06
		(1.52 1.61)	(1.56 1.70)	(-0.13 0.01)
	Total	12.61	10.51	2.10
2. Dementia	2. Dementia	3.19	2.14	1.05
		(1.95 4.01)	(0.82 2.98)	(0.90 1.23)
	4. Dementia & Care	4.31	3.64	0.67
		(3.97 4.59)	(3.20 3.94)	(0.49 0.90)
	Total	7.50	5.78	1.72
3. Care	3. Care	3.40	2.84	0.56
		(2.86 3.89)	(2.31 3.33)	(0.43 0.69)
	4. Dementia & Care	1.96	1.70	0.26
		(1.63 2.38)	(1.38 2.12)	(0.16 0.37)
	Total	5.36	4.54	0.82
4. Dementia & Care	4. Dementia & Care	5.24	4.21	1.03
		(4.23 5.99)	(3.15 4.99)	(0.86 1.20)
Males				
1. Healthy	1. Healthy	7.96	6.17	1.79
		(7.81 8.12)	(5.96 6.38)	(1.63 1.94)
	2. Dementia	0.57	0.46	0.11
		(0.53 0.60)	(0.42 0.51)	(0.07 0.14)
	3. Care	0.82	0.79	0.03
		(0.79 0.87)	(0.74 0.85)	(-0.01 0.08)
	4. Dementia & Care	0.79	0.75	0.04
		(0.75 0.83)	(0.70 0.81)	(-0.01 0.07)
	Total	10.14	8.17	1.97
2. Dementia	2. Dementia	3.44	2.51	0.93
		(3.01 3.92)	(2.08 2.95)	(0.79 1.07)
	4. Dementia & Care	2.42	2.00	0.42
		(2.20 2.65)	(1.77 2.24)	(0.31 0.52)
	Total	5.86	4.51	1.35
3. Care	3. Care	1.74	1.41	0.33
		(1.30 2.18)	(0.99 1.82)	(0.24 0.42)
	4. Dementia & Care	0.91	0.76	0.15
		(0.61 1.25)	(0.48 1.07)	(0.09 0.24)
	Total	2.65	2.17	0.48
4. Dementia & Care	4. Dementia & Care	2.52	1.86	0.66
		(1.72 3.34)	(1.13 2.62)	(0.86 1.20)

rLE remaining life expectancy at age 75, *CI* 95 % Confidence intervals bootstrapped by 1000 replications,*YLL* years of life lost, [a]"Without LEI" refers to individuals who do not experience LEI during the entire period. "With LEI" refers to individuals who start out with LEI at age 75 in their initial state. [b]YLL due to LEI, calculated by the difference between the columns "rLE Without LEI" and "rLE With LEI"

fatal but are still associated with worse disability outcomes and long-term care need [7, 28] and result in enormous societal costs [1]. In addition, given the large number of underreported falls [46], LEI is easier to notice for a doctor, a caregiver or a family member.

Our results not only confirm findings in previous studies, but also deepen the knowledge about the association between LEI and dementia, care need and death. We shall now discuss them briefly.

LEI and care need

We show that LEI increases the risk of care need, both among *healthy* elderly and among *dementia* patients. It is well known that fracture or fall-induced injuries in elderly are associated with poor functional outcomes and high burden of care, including longer stay in hospital and higher likelihood of long-term care facility [7, 13]. The presence of dementia aggravates these negative effects [47]. The underlying mechanisms might be that LEI speeds up the course of dementia [48], or that dementia slows down functional recovery after LEI, thus increasing care need in patients with dementia [34, 49].

In our study, women generally have a higher probability of experiencing the transition to long-term care than men, despite their higher rLE, thus, supporting the outcome of earlier studies [50, 51]; LEI shifts their age at the transition even further forward.

LEI and dementia

We show that LEI is a risk factor or a predictor of dementia for both healthy individuals and for those with care need. Various mechanisms may explain the association between LEI and dementia. First, LEI in the elderly increases the risk of cognitive impairment, including delirium and depression [16, 20], which raises the risk of dementia onset [21, 52–54], and makes dementia worse and more progressive [55, 56]. Second, LEI restricts physical activity, mobility and social participation, at least during some periods of time [9, 10], thus restricting these potential preventive factors of dementia [22, 23]. The decreased mobility in long-term care residents, in particular, is associated with various psychosocial impairments such as depression and feeling of isolation [57]. Also, falls and the consequent fear of falling might lead to activity restriction in the long run [58, 59]. Third, there exist shared risk factors for LEI and dementia such as age, ApoE4, diabetes and vascular dysfunction, executive dysfunction and gait disturbances [15, 33].

Yet the observed association must be interpreted with caution because of the possibility of reversed causality. Although we have already taken temporality into account by only using LEI which occurred prior to or simultaneous with transitions as the exposure of interest, LEI can be regarded as a pre-symptom or an early symptom of undiagnosed dementia. Patients experiencing LEI may have already suffered from mild cognitive impairment or undiagnosed moderate dementia. Particularly, gait and balance disorders are common in Non-Alzheimer's Dementia [60]. Moreover, delirium and depression may be two of the key intermediate factors between dementia and LEI, but the causal association between these and dementia is still controversial [54].

We find that women have a higher probability of developing dementia once they are in need of care, while both sexes have similar probabilities when they are healthy. This might explain why community dwelling cohort studies have not usually found significant sex-differences in the age-specific incidence of dementia [61], while studies including the institutionalized population do find higher female dementia incidence [41].

LEI and mortality

We find that LEI generally increased the risk of death, and particularly did so among dementia patients. Higher mortality has been observed in several previous studies on fractures or falls [8, 10, 25–28]. Yet the underlying mechanism is still unclear. Some studies suggested that merely the event of the fracture and post fracture conditions related to trauma, instead of pre-existing comorbidities, is mainly responsible for the excess mortality [8, 62], whereas others claimed that the underlying health or comorbidities are linked to a large part of fracture-mortality association [63]. In line with our results, several previous studies have also pointed out that dementia is an independent risk factor or a predictor for mortality after fractures [10, 25, 26, 30].

Regardless of the initial state, men always had larger death probabilities, and LEI made this even worse by further increasing age-specific death probabilities and moving the age of death forward. Consistently, many studies on fractures or falls in elderly have reported that males are at an increased risk for death after LEI [8, 26–28].

Strengths and limitations of our study

In addition to the abovementioned strengths about the composite measure (YLL) and the holistic analysis (multistate model), our study has several further strengths. First, we use a large population-based sample of community dwelling and institutionalized elderly, avoiding bias due to sample selection and granting high statistical power. Second, we include a 6-year follow-up period, which permits us to analyze multiple transitions between different states and to explore the long-term effect of LEI with high statistical power. Finally, in comparison to self-reported or interview data, claims data is relatively objective, and free of recall bias or interview bias.

Our study also has several limitations. First, the dementia in our cases was defined by a doctor's ICD diagnosis, which is prone to imperfect sensitivity and specificity. While we used an internal validation procedure to minimize the probability of false positive dementia diagnoses, we cannot account for underreporting. Second, in our data dementia may have already existed ahead of LEI, and LEI simply brought the dementia to clinical attention. Therefore, we interpreted the association observed between LEI and dementia with caution, particularly taking reverse causality into account. More research is needed to understand the interactions between cognitive and mobility decline [33], and other underlying mechanisms of the observed association between LEI and dementia.

Third, to evaluate the long-term effect, we defined LEI as an ever-variable, although some LEI may be apparently or actually cured. However, LEI can influence a patient in the long-term, even after recovery. A relationship has been found linking fall and subsequently fear-related avoidance of activity [58]. Fourth, we discussed our results in comparison with quite a few previous literature on hip fractures or falls, which might be not directly comparable. However, the hip fracture (S72) in our data is the most frequent among the first 3-digits subgroups of the ICDs chosen. Fall-induced injuries in older adults account for the majority of geriatric injuries and their related hospital admissions [3, 64]. Fifth, we have no information about other potential confounders such as education, family status, or life style factors such as smoking, obesity, or alcohol consumption. Our multistate model also does not control for polypharmacy or multimorbidity. However, in sensitivity analyses of our hazard models we further controlled for the Charlson-morbidity-index, brain injuries, osteoporosis, depression, Parkinson and Down-Syndrom at baseline, which did not alter our findings (not shown).

Moreover, given the crude nature of the quarterly-based data, we had to make assumption on the order in which LEI, dementia, care need and death occurred, in case more than one event happened within one quarter. Sensitivity analysis changing these orders still found a significantly increased risk of LEI for most transitions, albeit of smaller effect sizes (not shown).

Conclusion

Our study suggests that prevention and timely treatment of LEI as well as rehabilitative care after LEI may be of utmost importance in delaying or reducing the onset of care need and death, not only among cognitive intact elderly but also among dementia patients. These measures will not only help to save years of life, but also to increase the quality of life of the elderly and reduce the burden for families, public health, and the care system. Expressing the detrimental effect of LEI in terms of the composite measure YLL should prove helpful for the elderly, their families, and health professionals to holistically appreciate the scale of the problem and the substantial benefits of preventive and rehabilitative measures.

Additional files

Additional file 1: Table S1. ICDs used to identify dementia and lower extremity injury (ICD- 2010-GM). To list the concrete ICDs, which we used to identify dementia and lower extremity injury in our study. (DOCX 15 kb)

Additional file 2: Table S2. Numbers and percentages of transitions and exposure of interest (LEI) by age. Differentiates Table 1 which is included in the main document by 5-year age groups. (DOCX 19 kb)

Abbreviations

ADL: activities of daily living; BADL: basic activities of daily living; CI: confidence interval; Col: column; HR: hazard ratio; ICD: International Statistical Classification of Diseases and Related Health Problems; LEI: lower extremity injury; rLE: remaining life expectancy; SD: standard deviation; WIdO: Wissenschaftliches Institut der Ortskrankenkassen; YLL: years of life lost.

Competing interests

None of the authors declared a conflict of interest.

Authors' contributions

YZ performed the statistical analysis and wrote the first version of the paper. GD planned the study, supervised the data analysis, and contributed to writing the paper. HP contributed to statistical analysis. All authors revised the manuscript, and read and approved the final version.

Acknowledgements

We thank Anne Fink, Alexander Barth, and Anja Vatterrott who helped in handling the data, and provided advice in the statistical analysis. We are grateful to the scientific research institute of the AOK, WIdO, for providing the data. We thank the two anonymous referees for their comments which have led to substantial improvements of the article and Renee Flibotte-Lüskow for her English editing service.

Funding

This work was supported by the German Federal Ministry of Education and Research (16SV6373).

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Received: 26 February 2015 Accepted: 4 January 2016
Published online: 12 January 2016

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SUPPLEMENTARY TO STUDY 3

Table 1S. ICDs used to identify dementia and lower extremity injury (ICD- 2010-GM)

Dementia	
G30	Alzheimer disease
G31.0	Circumscribed brain atrophy
G31.82	Lewy body dementia
G23.1	Progressive supranuclear ophthalmoplegia [Steele-Richardson-Olszewski]
F00	Dementia in Alzheimer disease
F01	Vascular dementia
F02	Dementia in other diseases classified elsewhere
F03	Unspecified dementia
F05.1	Delirium superimposed on dementia
Lower Extremity Injury	
S70-S79	Injuries to the hip and thigh
S80-S89	Injuries to the knee and lower leg
S90-S99	Injuries to the ankle and foot
T00.3	Superficial injuries involving multiple regions of lower limb(s)
T00.6	Superficial injuries involving multiple regions of upper limb(s) with lower limb(s)
T01.3	Open wounds involving multiple regions of lower limb(s)
T01.6	Open wounds involving multiple regions of upper limb(s) with lower limb(s)
T02.3	Fractures involving multiple regions of one lower limb
T02.5	Fractures involving multiple regions of both lower limbs
T02.6	Fractures involving multiple regions of upper limb(s) with lower limb(s)
T03.3	Dislocations, sprains and strains involving multiple regions of lower limb(s)
T03.4	Dislocations, sprains and strains involving multiple regions of upper limb(s) with lower limb(s)

T04.3	Crushing injuries involving multiple regions of lower limb(s)
T04.4	Crushing injuries involving multiple regions of upper limb(s) with lower limb(s)
T05.3	Traumatic amputation of both feet
T05.4	Traumatic amputation of one foot and other leg [any level, except foot]
T05.5	Traumatic amputation of both legs [any level]
T05.6	Traumatic amputation of upper and lower limbs, any combination [any level]
T12	Fracture of lower limb, level unspecified
T13	Other injuries of lower limb, level unspecified
T24	Burn and corrosion of hip and lower limb, except ankle and foot
T25	Burn and corrosion of ankle and foot
T33.6	Superficial frostbite of hip and thigh
T33.7	Superficial frostbite of knee and lower leg
T33.8	Superficial frostbite of ankle and foot
T34.6	Frostbite with tissue necrosis of hip and thigh
T34.7	Frostbite with tissue necrosis of knee and lower leg
T34.8	Frostbite with tissue necrosis of ankle and foot
T35.5	Unspecified frostbite of lower limb
T87.1	Complications of reattached (part of) lower extremity

SUPPLEMENTARY

Table 2S. Numbers and percentages of transitions and exposure of interest (LEI) by age

		I	*II*	*III*	*IV*	*V*	*VI*	*VII*	*VIII*
ORIGIN STATE	**AGE [a]**	**Risk set (person)[b] (100%)**	**DESTINATION STATE**				**No change[c]**	**N of LEI**	**% of LEI[d]**
			2.Dementia	**3.Care**	**4.Dementia& Care**	**5.Dead**			
1.Healthy	**75 - <80**	24383	3250 (13%)	4916 (20%)		2614 (11%)	13603 (56%)	5711	23.4
	80 - <85	15055	3019 (20%)	4800 (32%)		1943 (13%)	5293 (35%)	3552	23.6
	85 - <90	4379	1009 (23%)	1909 (44%)		657 (15%)	804 (18%)	1034	23.6
	90 - <95	1941	421 (22%)	677 (35%)		232 (12%)	611 (31%)	393	20.2
2.Dementia	**75 - <80**	4211			2500 (59%)	432 (10%)	1279 (30%)	1264	30.0
	80 - <85	4121			2907 (71%)	504 (12%)	710 (17%)	1270	30.8
	85 - <90	1518			1137 (75%)	264 (17%)	117 (8%)	475	31.3
	90 - <95	737			433 (59%)	149 (20%)	155 (21%)	219	29.7
3.Care	**75 - <80**	6754			1505 (22%)	2637 (39%)	2612 (39%)	2159	32.0
	80 - <85	7534			2202 (29%)	2868 (38%)	2464 (33%)	2452	32.5
	85 - <90	3596			1299 (36%)	1470 (41%)	827 (23%)	1173	32.6
	90 - <95	2253			728 (32%)	730 (32%)	795 (35%)	638	28.3
4.Dementia & Care	**75 - <80**	5087				2714 (53%)	2373 (47%)	2118	41.6
	80 - <85	6941				4317 (62%)	2624 (38%)	2949	42.5
	85 - <90	3754				2762 (74%)	992 (26%)	1645	43.8
	90 - <95	2551				1437 (56%)	1114 (44%)	925	36.3

[a] age group according to the age on January 01,2005. [b]numbers of individuals who were under the risk of the transitions from "ORIGIN STATE" to "DESTINATION STATE" on January 01,2005 or during the follow up. [c] numbers and percentage of individuals who entered or began with the particular ORIGIN STATE and stayed in that state until the end of the study or until the time point of right censoring. [d] proportion with LEI in the ORIGIN STATE.

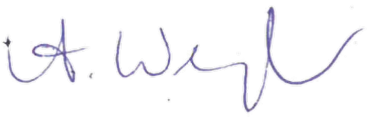
Indication of own contribution for collaborative work with multiple authors

Study II:

Zhou, Y., Wengler, A., Doblhammer, G. “Association between the starting age of non-parental Early Childhood Education and Care (ECEC), and psycho-social problems in adolescence in West and East Germany – a natural experiment using data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)”. BMC Psychol 11, 403 (2023).

Ying Zhou’s own contribution: formulating the research question: 80%, designing the study: 60%, conducting and analyzing the study: 90%, writing the texts: 90%.

With my signature I confirm the above assessment of my co-author Ying Zhou’s contribution to our collaborative work.

Name: Annelene Wengler Signature: 

Name: Gabriele Doblhammer Signature:

Indication of own contribution for collaborative work with multiple authors

Study II:

Zhou, Y., Wengler, A., Doblhammer, G. “Association between the starting age of non-parental Early Childhood Education and Care (ECEC), and psycho-social problems in adolescence in West and East Germany – a natural experiment using data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS)”. BMC Psychol 11, 403 (2023).

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With my signature I confirm the above assessment of my co-author Ying Zhou’s contribution to our collaborative work.

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Study III:

Zhou, Y., Putter, H., & Doblhammer, G. “Years of life lost due to lower extremity injury in association with dementia, and care need: a 6-year follow-up population-based study using a multi-state approach among German elderly”. *BMC Geriatrics*, 16(1), 1 (2016)

Ying Zhou’s own contribution: formulating the research question: 50%, designing the study: 60%, conducting and analyzing the study: 90%, writing the texts: 90%.

With my signature I confirm the above assessment of my co-author Ying Zhou’s contribution to our collaborative work.

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