ASSOCIATION OF CHILDHOOD STRESS AND HOME ENVIRONMENT WITH LATE-LIFE DEMENTIA AND ALZHEIMER’S DISEASE:
THE KIHD STUDY

Gwendolyn Donley
Master’s thesis
Public Health
School of Medicine
Faculty of Health Sciences
University of Eastern Finland
29 May 2017
ABSTRACT

UNIVERSITY OF EASTERN FINLAND, Faculty of Health Sciences

Public Health (Epidemiology)

DONLEY, GWENDOLYN A.R.: Association of childhood stress and home environment with late-life dementia and Alzheimer’s disease: the KIHD study

Master’s thesis, 57 pages, 0 attachments.

Instructors: Dr. Jussi Kauhanen, PhD and Dr. Tomi-Pekka Tuomainen, MD, PhD.

May 2017

Key words: aging, dementia, childhood, stress, life-course

ASSOCIATION OF CHILDHOOD STRESS AND HOME ENVIRONMENT WITH LATE-LIFE DEMENTIA AND ALZHEIMER’S DISEASE: THE KIHD STUDY

In social epidemiology, there remains a dearth of life-course studies analyzing childhood environment and late-life chronic illness. In particular, no such studies have been completed that examine possible early-life predictors of dementia and Alzheimer’s disease (AD). This issue is of particular interest today, as populations worldwide are aging and facing increasing burdens from geriatric illnesses.

The present study examines the associations between childhood social factors with later-age dementia and specifically with AD. We used data from the population-based Kuopio Ischemic Heart Disease Risk Factor Study of ageing men (N= 2682), who participated in an extensive health examination between 1984 and 1989, when they were between 42 and 60 years of age. In addition to physical examination, data from childhood were collected in structured questionnaires. A composite variable representing childhood stress was created, including living in custody/in an orphanage, experience of crisis in childhood, having problems with teachers, and emigration from Karelia because of war, a specific stressor affecting some of the cohort in childhood. Additionally, childhood home environment characteristics (living in a strict or quarrelsome home) were examined. Data on incident cases of any-type dementia or AD during the follow-up until year 2014 were obtained through linkage with the national health registries. The risk of developing dementia was estimated using Cox regression models with adjustment to age, to other baseline diseases, to income and education, and to other covariates.

Childhood stress was associated with greater risk of dementia diagnosis later in life. The associations remained statistically significant after adjustment for age, education, income, and common comorbid diseases (HR = 1.95, 95 % CI: 1.09 - 3.48, p = 0.03) for all dementias, and was near significance for AD, with a similar magnitude HR.

Findings indicate the importance of childhood environment and stress with regards to late-life dementia and AD risk. There is a need for wider research on possible childhood social and environmental influences on late-life diseases, in various populations, to develop a more holistic understanding of the life-course development of disease burden.
ABBREVIATIONS

AD – Alzheimer’s disease
BMI – body mass index
CI – confidence interval
CVD – cardiovascular disease
DBP – diastolic blood pressure
FTD – frontotemporal dementia
HR – hazard ratio
ICD – international classification of diseases
IHD – ischemic heart disease
KIHD – Kuopio Ischemic Heart Disease risk factor study
LBD – dementia with Lewy bodies
LDL – low-density lipoprotein
LTPA – leisure time physical activity
MRI – magnetic resonance imaging
PAR – population-attributable risk
PD – Parkinson’s disease dementia
QoL – quality of life
SBP – systolic blood pressure
SES – socioeconomic status
SSR – Special Reimbursement Register
VaR – vascular dementia
WHO – World Health Organization
# TABLE OF CONTENTS

1 INTRODUCTION

2 THEORETICAL BACKGROUND

2.1. Dementia

2.1.1. Alzheimer’s Disease

2.1.2. Other Forms of Dementia

2.1.3. Implications of Dementia

2.2. Social Disparities as Predictors of Future Adverse Health Outcomes

2.3. International Research: Sociodemographic Data and Dementia

2.3.1. Areas in Need of Further Research

2.4. Possible confounding factors

2.4.1. Age and Socio-Economic Characteristics

2.4.2. Comorbid Conditions

2.4.3. Physical and Biological Markers

3 AIMS OF THE STUDY

4 METHODOLOGY

4.1. Kuopio Ischemic Heart Disease Risk Factor Study

4.1.1. Social Epidemiological Data from the KIHD Study

4.2. Data Collection

4.2.1. Participant Recruitment

4.2.2. Biomarker Collection and Questionnaire Administration

4.2.3. Identification of Incident Dementia and Alzheimer’s Disease

4.3. Childhood Stress Index

4.4. Statistical Analyses
LIST OF TABLES AND FIGURES

Figure

Figure 1 (page 10) – Forms of dementia and percentages of total dementia prevalence

Tables

Table 1 (page 29) – Childhood variable indices
Table 2 (page 32) – Study population characteristics
Table 3 (page 33) – Distributions and proportions of covariates by dementia and AD status
Table 4 (page 34) – Distribution of childhood variables by incident dementia/AD
Table 5 (page 35) – Multivariate models examining childhood stress, quarrelsome home, and strict upbringing with dementia and AD
Table 6 (page 38) – Relative hazards of incident dementia and AD by childhood variables, adjusting for covariates
1 INTRODUCTION

Dementia is an umbrella term for several different conditions reflecting cognitive impairment. These conditions may occur alone or be comorbid with one another (ICD-10 1992). Between 50-75% of patients who have dementia suffer from Alzheimer’s disease (AD). Strictly, AD cannot be absolutely diagnosed prior to death and without autopsy (Fearing et al. 2007). However, by clinical examination, neuroimaging and neuropsychological tests physicians are able to achieve a clinically-relevant diagnosis (American Psychiatric Association 2013). A strong risk factor for AD is genetic background. However, although having a first-degree relative with the disease doubles the risk of getting it oneself due to potential inheritance of the apolipoprotein E ε4 allele, only a minority of cases are soundly related to genetic factors (Budson & Solomon 2011). Risk also increases with age, brain injury, and presence of Down’s syndrome (ICD-10 1992).

The implications of dementia are not purely physical; they may be a significant financial, emotional, and time-consuming burden to the individual and his/her caretakers. A 2010 report by Alzheimer’s Disease International (ADI) estimated that worldwide costs of dementia care and treatment were over US$600 billion, and costs were, and continue to be, expected to sharply rise as low- and middle-income countries transition to higher incomes and life expectancies subsequently increase (Prince et al. 2016). By some estimates, this could rise to as much as one trillion USD or more by 2030 (Prince et al. 2016). ADI also reported that an estimated 27 million to 36 million people worldwide were living with AD or other forms of dementia in 2010 and predicted an increase in this number to nearly 132 million by 2050 (Wimo and Prince 2010, Prince et al. 2016).

From as early as gestation, the physical and social environment around a child can significantly impact later risk of illness, particularly chronic disease. For example, Barker and Fall (1993) described the relationship between intrauterine growth abnormalities and cardiovascular disease later in life. Other life-course epidemiological research has linked childhood experiences with later-life adverse health outcomes and behaviors, such as binge drinking (Kauhanen et al. 2011). Few studies have been able to take a life-course epidemiological approach and examine these changes over the course of the entire lifetime.
Globally, studies have examined links between various social factors and dementia outcomes, including work by Orrell et al. (2000), which showed that individuals with better support networks had improved survival, and Bennett et al. (2013), demonstrating that education and social networks can impact associations of cognition and neuropathology. Although there is a wealth of literature surrounding dementia, the social research available pertains almost entirely to late-life social characteristics and environmental conditions of patients. Still largely unexamined is the potential significance of childhood social factors on these outcomes. In particular, it is uncertain whether early-life social disparities in things like education and family income might affect brain health in older age. We examined associations of childhood stress with dementia and AD outcomes using data from the KIHD study.
2 THEORETICAL BACKGROUND

2.1. Dementia

Dementia includes a complex group of diseases that manifest in many forms. Dementia encompasses several different conditions reflecting cognitive impairment (ICD-10 1992, American Psychiatric Association 2013). These conditions may occur alone or be comorbid with one another. Figure 1 lists the different forms of dementia and the percentage of all dementia patients affected by each. All forms are marked by damage to brain matter and consequent physical, mental, and/or behavioral changes (ICD-10 1992). To be given a diagnosis of dementia, a patient must have both memory impairment as well as another form of cognitive deficiency (American Psychiatric Association 2013). Other forms of cognitive impairment could include dysfunction in normal executive actions, apraxia, aphasia, and/or agnosia (American Psychiatric Association 2013). Frequently, individuals experience changes in general behavior, social relationships, and emotions in addition to cognitive dysfunction (Alzheimer’s Association 2016). Changes to brain structure associated with dementia may be temporary, but are usually permanent and tend to worsen over time (Alzheimer’s Association 2016).

To give a diagnosis specific to one form of dementia, clinicians may utilize biomarkers in combination with the commonly used DSM-V criteria and other diagnostic criteria (Quinn 2013). Diagnosis can become more complicated and convoluted with age, as some older individuals present multiple pathologies that may overlap or obscure dementia-associated impairments (Quinn 2013). Health professionals also use medical records to make accurate dementia diagnoses, meaning that when a patient lacks such records then the clinician may have more difficulty providing a clear diagnosis (Quinn 2013).
**(Number %) indicates the percentage of all dementia cases contributed by each type; e.g., AD patients comprise 50-75% of all dementia patients. (Lange and Paul 2005, American Psychiatric Association 2013, National Institutes of Health 2015, Alzheimer’s Association 2016)**

### 2.1.1. Alzheimer’s Disease

The majority of patients who have dementia suffer from Alzheimer’s disease (AD), which affects anywhere from 50-75% of said patients. As discussed above, AD cannot be absolutely diagnosed prior to death, as autopsy of brain matter is required (American Psychiatric Association 2013). However, given the diagnostic criteria found in the International Classification of Diseases, a health professional may make a very accurate diagnosis prior to death given the presence of a certain number and severity of symptoms (ICD-10 1992). Clinical diagnoses of AD are confirmed during post-mortem autopsies in 90% of patients (Quinn 2013).
Features of early-stage AD are memory loss, learning impairment, depression, and apathy; these are followed by the possibility of psychotic changes and agitation in moderate stages, and language deficits, visuospatial impairment, difficulty walking, and seizures in late/severe cases (American Psychiatric Association 2013). A prominent risk factor for AD is genetic background, but a myriad of social, lifestyle, and environmental factors may interact to mitigate or increase risk (Budson & Solomon 2011). Risk also increases with age, brain injury, and presence of Down’s syndrome (American Psychiatric Association 2013).

One study examined the percentage of AD cases worldwide that could be attributed to potentially modifiable risk factors (Norton et al. 2014). To estimate this percentage, researchers first calculated the global population-attributable risk (PAR) of AD for seven risk factors of the disease. Attributable risk refers to the difference in disease incidence between an exposed and unexposed group for a certain (or multiple) risk factor(s) (Bruzzi et al. 1985). PAR then accounts for the difference in overall incidence of disease in a theoretically unexposed versus actual exposed population (Bruzzi et al. 1985). Norton and colleagues calculated this PAR using the relative risk for AD for risk factors examined (midlife obesity and hypertension, physical inactivity, diabetes, smoking, depression, and low educational attainment); reports came from studies based in the USA, Europe, the UK, and elsewhere worldwide (Norton et al. 2014). These risk factors are all considered to be potentially modifiable, as lifestyle changes can have a significant effect on AD risk (Norton et al. 2014). Researchers found that approximately one third of global AD cases could be attributed to the risk factors, with physical inactivity contributing to the greatest proportion in the UK, USA, and Europe (Norton et al. 2014). Based on AD incidence estimates in 2010, this PAR is equivalent to approximately 9.6 million of the year’s total cases (Norton et al. 2014). Research such as this emphasizes the importance of studying modifiable social and environmental factors that may contribute to disease risk and burden.

2.1.2. Other Forms of Dementia

AD commonly occurs in conjunction with vascular dementia (VaD), which affects somewhere between 20-30% of patients in the United States (American Psychiatric Association 2013). VaD is thought to be the third most common form of dementia, preceded by AD and dementia with Lewy bodies (discussed in greater detail later) (Lange and Paul 2005). Individuals diagnosed with
VaD have a life expectancy of only approximately 3.1 years following diagnosis, a comparable rate to those diagnosed with AD (Lange and Paul 2005). Frequently, VaD occurs in the elderly after suffering a stroke; often, symptoms go unnoticed due to the lingering symptoms of stroke (Román 2005). VaD often presents itself through depression and apathy, personality changes, slowed mental capacity and cognitive ability, social inhibition, and slowed motor movements (Román 2005). This form of dementia is also difficult to diagnose because in many cases, patients perform normally on cognitive tests such as the Mini-Mental State Examination or the Cambridge cognitive capacity scale (Folstein et al. 1975, Huppert et al. 1995).

VaD may be comorbid with Dementia with Lewy Bodies (LBD), which occurs when Lewy bodies are found in the cortex, but medial temporal structures are not affected (American Psychiatric Association 2013). LBD affects approximately 10-25% of dementia patients, making it the third most common form of dementia (American Psychiatric Association 2013, National Institutes of Health 2015). Its prevalence in the United States alone is estimated at 1 million, typically in adults over age 50 (National Institutes of Health 2015). Decreased longevity among LBD patients is seen among those with later age at onset, hallucinations, and inconsistent cognitive functioning, as well as comorbidity with AD (Jellinger et al. 2007). Biologically, LBD differs from Parkinson Dementia (discussed in detail later) via presence of increased Pittsburg Compound B binding, which also expresses itself phenotypically in LBD patients (Silbert and Kaye 2010). It is also associated with abnormal deposits of the alpha-synuclein protein in the brain (National Institutes of Health 2015). Early symptoms of LBD are quite similar to and may be confused with those of AD, making early diagnosis and treatment complex (National Institutes of Health 2015). On average, LBD lasts between 5 and 7 years from patient diagnosis until death, but this span ranges widely depending on environmental, behavioral, and social factors (National Institutes of Health 2015).

Parkinson’s Disease Dementia (PD) is a form of LBD (National Institutes of Health 2015). It is preceded by Parkinson’s disease for at least one year and is marked by the beginning of cognitive decline (American Psychiatric Association 2013, National Institutes of Health 2015). Between 50 and 80% of individuals living with Parkinson’s disease will develop PD (Aarsland and Kurz 2010, Alzheimer’s Association 2016). Out of these cases, it takes an average of 10 years to develop
dementia (Aarsland and Kurz 2010, Alzheimer’s Association 2016). Individuals who display rigid or unstable posture and non-normal gait are at risk of shorter time until PD onset (Aarsland and Kurz 2010). Prior to dementia onset, neuroimaging has shown that patients exhibit low cortical volume and resting metabolic activity as well as increased diffusion of white matter in the brain (Silbert and Kaye 2010). They are also at higher risk for additional disability, psychosis, premature mortality, and reduced quality of life when compared with non-PD/dementia patients in the general population (Aarsland and Kurz 2010). PD patients may have shorter life expectancy when faced with similar symptoms as regular LBD: late-onset PD, cognitive fluctuations, and hallucinations (Jellinger et al. 2007). Typical symptoms of dementia usually arise later in disease progression for those with PD, with movement problems appearing before the onset of dementia (National Institutes of Health 2015).

Finally, 10-15% of patients suffering from dementia have frontotemporal dementia (FTD). FTD may present itself through behavioral impairments, language impairments, or both. FTD contains several variants including semantic dementia, FTD with motor neuron disease, behavioral variant FTD, and progressive nonfluent aphasia (Roberson 2011). Each variant includes overlapping and distinctive forms of neurological and motor dysfunction (Roberson 2011). Inheritance plays a strong role in risk of FTD, with the disease linked to mutations in the MAPT, GRN, VCP, and CHMP2B genes (Clark et al. 1998, Hutton et al. 1998, Skibinski et al. 2005, Gass et al. 2006, Kimonis et al. 2008). The neuropathology of FTD is significantly more complex than that of AD, as are the symptoms (Roberson 2011). FTD currently has no effective treatments, with selective serotonin reuptake inhibitors being used to alleviate symptoms (Roberson 2011).

There are other, less-common forms of dementia as well. These include Huntington’s disease, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, and Wernicke-Korsakoff syndrome (American Psychiatric Association 2013). Huntington’s disease is characterized by motor, cognitive, and psychological dysfunction and disturbance (van den Bogaard et al. 2013). It may present itself through rigidity, psychomotor function slowing, ocular disturbances, hypokinesia, weight loss, mood disturbances, and chorea (Aziz et al. 2010, van den Bogaard et al. 2013). This disease is genetically based, with patients having a trinucleotide repeat in the Htt gene (van den Bogaard et al. 2013). Onset of Huntington’s disease is earlier than that of most dementias, with
most diagnoses occurring in midlife and life expectancy ranging from 15-20 years after presentation of symptoms (Novak and Tabrizi 2010, van den Hogaard et al. 2013).

Creutzfeldt-Jakob disease features progressive dementia and is caused by the metabolism and/or accumulation of prion proteins (Johnson 1998). It is rare, affecting only about 1 in every 1 million people, with onset usually occurring between age 50 and 70 (Glatzel et al. 2005, Gençer et al. 2011). Diagnosis is usually made using electroencephalography, cerebrospinal fluid analysis, cranial magnetic resonance imaging (MRI), or, in the case of death, autopsy (Gençer et al. 2011). Normal pressure hydrocephalus displays similar symptoms as other forms of dementia, with the addition of urinary incontinence (Rosseau 2011). The combination of these symptoms with ventriculomegaly, or dilation of the lateral ventricles, and without the presence of increased intracranial pressure leads to a diagnosis of normal pressure hydrocephalus (Rosseau 2011). Finally, Wernicke-Korsakoff syndrome is caused by thiamine deficiency and manifests through ocular dysfunction, confusion, and ataxia, often accompanied by memory impairment and other cognitive problems like insomnia and anxiety (Brockington 2006). Amnesia and delirium are also common symptoms, caused by lesions to the third ventricle of the brain (Brockington 2006). Wernicke-Korsakoff syndrome is often induced by alcoholism or excessive vomiting during pregnancy (Brockington 2006).

2.1.6. Implications of Dementia

From this introduction to the various forms of dementia, it is clear that the manifestations of the disease are complex and intricate. The implications of dementia are not purely physical, often including significant emotional and financial burdens for affected individuals and their caretakers. For example, the 2015 World Alzheimer Report (supported by Alzheimer’s Disease International) estimated that in Switzerland alone, the cost of an AD health pathway for one person seeing a specialist was approximately USD$2558 (Prince et al. 2016). The estimated global cost of dementia in 2018 is one trillion U.S. dollars, which is expected to double to $2 trillion by 2030 (Prince et al. 2016). It has also been found that people living with dementia have also have decreased probability of admission or referral for treatments that could potentially improve quality of life. These include interventional procedures such as cancer care and cataract surgery (Prince et al. 2016). This potentially leads to greater decreases quality of life for individuals already suffering
from chronic illness. Additionally, when people living with dementia are admitted to hospitals, they have higher rates of in-hospital mortality, acquired infections, and long length of stay than others (Prince et al. 2016). However, this may be in part due to the later age of those with dementia who are admitted to the hospital, particularly in terms of in-hospital mortality (Prince et al. 2016).

The prevalence of dementia in 2010 was approximately 35.7 million and rose to 46 million in 2015 (Quinn 2013; Prince et al. 2016). Global prevalence is estimated to reach 74.7 million by 2030 and 131.5 million by 2050 (Prince et al. 2016). At the current rate, the worldwide prevalence of dementia will approximately double every 20 years (Prince et al. 2016). An increasing number of incident cases occur in middle- and low-income countries, where approximately 94% of patients are cared for in their homes, rather than by health professionals (Prince et al. 2016). Currently, about 58% of people living with dementia are located in these countries. Of all global dementia patients in 2015, 9.4 million lived in North and South America, 10.5 million in Europe, 4 million in Africa, and 22.9 million in Asia, with the numbers in poorer countries increasing each year (Prince et al. 2016).

Most incident cases of dementia, in all forms, occur among adults aged 65 and over (Quinn 2013). This segment of the global population is now over 900 million (Prince et al. 2016). Additionally, life expectancies worldwide are increasing and mortality rates are falling (Prince et al. 2016). As the global population ages, both incidence and prevalence of chronic diseases, including dementia, increase; this is known as the epidemiologic transition (Prince et al 2016).

The theory of epidemiologic transition was first proposed in 1971 as part of an effort to incorporate more varied fields and methodologies into studies of demography and population dynamics (Omran 1971). A multidisciplinary approach, it fuses demographic, sociological, biological, economic, and psychological sciences to understand changes in health and disease in populations (Omran 1971). It involves a few key elements; mortality is closely related to demography, the most notable changes in health during transitions are seen among children and women, long-term shifts occur in both mortality and patterns of disease based on chronic versus infectious diseases, and these shifts may occur at rapid or gradual rates depending on a large number of cultural, economic, social, and environmental factors (Omran 1971). In the context of dementia, this means that as
low- and middle-income countries economically transition to higher income status, the epidemiology of disease within them transitions as well. Infectious diseases become less prevalent and chronic diseases increase in incidence as life expectancy lengthens. Dementia, a disease most commonly seen among the elderly, is expected to increase in incidence and prevalence throughout these countries as the transitions continue (Prince et al. 2016). This is the primary reason for the enormous projections of prevalence and cost of dementia over the next few decades (Prince et al. 2016).

2.2. Social Disparities as Predictors of Future Adverse Health Outcomes

The Kuopio Ischemic Heart Disease risk factor (KIHD) study will be described in detail later in the methodology of this study. KIHD publications linked certain social and behavioral indicators with negative health outcomes. For example, a 1997 study used survey questions regarding feelings of hopelessness to predict carotid atherosclerosis progression (Everson et al. 1997). In this study, a sample of eastern Finnish men were assessed for intima-media thickening, which can determine carotid atherosclerosis progression. They were also asked questions about their overall feelings of hopefulness; these questionnaires, as well as biomarker collection, were administered at baseline and again four years later to track longitudinal progress. Researchers found that high levels of hopelessness were significantly positively associated with faster progression of carotid atherosclerosis (Everson et al. 1997).

Another study focused on the potential influence of social functioning on overall mortality. The social questions included in the relevant questionnaire consisted of participation in community programs, shyness, number of friends, marriage, and quality of social relationships. Researchers were interested in whether indications of poor social functioning and interactions had an effect on current death risk (Kaplan et al. 1994). Using the national death registry, they collected data for all-cause mortality among the cohort; from study entry through the end of 1992, 167 individuals died. To account for covariate interactions, researchers controlled for smoking status, alcohol consumption, health status, coffee intake, body mass index (BMI), and income. They found that fewer number of friends, being unmarried, and not participating in social organizations all were associated with greater risk of premature mortality (Kaplan et al. 1994).
Focusing on early-life social disparities, Laura Kauhanen and colleagues examined associations between these disparities and mortality from various chronic diseases later in life using KIHD data (2006). They examined all-cause mortality and mortality specific to cardiovascular disease, coronary heart disease, and acute coronary events using the male portion of KIHD participants (Kauhanen et al. 2006). For these purposes, they constructed an index for defining a socially disadvantaged childhood, which included poor hygiene, poor social conditions at home, attending a special summer camp, and participating in the school meal program (Kauhanen et al. 2006). Calculating the age- and examination-year-adjusted risk for mortality events, the authors determined that a socially disadvantaged childhood was associated with greater risk of acute coronary events later in life (Kauhanen et al. 2006).

2.3. International Research: Sociodemographic Data and Dementia

Some studies from around the world have examined links between various socio-environmental factors and dementia outcomes. This research often examines social and psychiatric assessments in comparison to dementia status and risk, determining any potential interactions. In the UK, one such study collected data from patients in the Life Events and Senile Dementia Study in London (Orrell et al. 2000). Researchers examined associations of dementia with age, sex, duration of illness, degree of cognitive impairment, and social interactions. Their findings suggested that lack of social support, particularly social isolation, was related to decreased longevity (Orrell et al. 2000).

In the United States, scientists from AD and dementia research centers joined to conduct a meta-analysis of articles examining some of the myriad predictors and severity of dementia outcomes (Bennett et al. 2013). They investigated and found associations of many social variants with dementia (specifically AD): education, loneliness, linguistic ability, late- and early-life cognitive activities, a sense of purpose in life, presence of social networks, emotional neglect, conscientiousness, and harm avoidance (Bennett et al. 2013). Associations such as these highlight the importance of conducting social research in the context of chronic illness, specifically dementia.
In Hungary, researchers examined associations of social interactions with cognitive ability in patients with high-functioning autism, frontotemporal dementia, and AD (Kéri 2014). Participant data was collected through the National Institute of Psychiatry and Addictions in Budapest and the University of Szeged in southern Hungary. To assess cognitive functioning, researchers administered the Mini-Mental State Examination, the Wechsler Abbreviated Scale of Intelligence, Addenbrooke’s Cognitive Evaluation, the Autism Quotient, and the Neuropsychiatric Inventory to participants (Kéri 2014). Participants then performed memory and cognition tests, some of which included social context (real-life memory tests using researchers) and others that were only computer-based. They found that individuals with AD performed much better when they had interaction with real people and not just the computer (Kéri 2014). However, they did not see these same associations among individuals with high-functioning autism or frontotemporal dementia. According to researchers, this means that social context and interactions can boost associative learning and performance among individuals living with AD and may or may not be beneficial for those in other groups, depending on degree of cognitive impairment and related social context (Kéri 2014).

2.3.1. Areas in Need of Further Research

Despite a large amount of dementia research available today, few studies aside from those already discussed concentrate specifically on associations of social and cultural factors with dementia outcomes. The social research available, including that which is discussed above, typically focuses on social settings and factors for those already in their middle ages or older. This means that associations of childhood social characteristics and dementia outcomes remain unexamined. Life-course epidemiological studies can be quite difficult due to costs, time constraints, and high attrition rates, resulting in a dearth of available literature on the subject. The KIHD study contains extensive childhood data from participants, as it includes information from retrospective questionnaires. The methodology of the KIHD study will be discussed in greater detail later.

2.4. Possible Confounding Factors

As outlined in the discussion of the various forms of dementia, many conditions frequently occur comorbidly with dementia and AD. One meta-analysis included a total of 74 studies from the UK, USA, non-UK Europe, Canada, Australia, and Japan, as well as international reviews, and
examined pooled results for associations of dementia and comorbid conditions (Bunn et al. 2014). Researchers found that diabetes, stroke, and visual impairment all commonly occurred alongside dementia in patients worldwide (Bunn et al. 2014). They also discussed the importance and quality of patient care, specialist services, and relationships between patients, health professionals, and care-givers (Bunn et al. 2014).

This evidence suggests that other factors may associate with, or mitigate associations between, dementia/AD outcomes and the exposure variables analyzed in the present study. Covariates included in this study are age, education, and income, as well as prior or existing stroke, ischemic heart disease (IHD), and diabetes diagnosis. Additional covariates used in final analyses included systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, leisure time physical activity (LTPA), BMI, waist-to-hip ratio, low-density lipoprotein (LDL) cholesterol, hypercholesterolemia, and total cholesterol. Income was based on the previous year’s tax returns, and responses were measured from one to five on questionnaires, with one being the lowest. All covariates used were obtained at baseline.

2.4.1. Age and Socio-Economic Characteristics

Old age is one of the most prominent risk factors for all forms of dementia and therefore must be included in analyses in order to eliminate the possibility of confounding (American Psychiatric Association 2013). Education and income may also be indicative of dementia risk. Greater education and higher income have previously been shown to associate with decreased risk of dementia development over the same timespan as those with less education and lower income (Bennett et al. 2013).

A meta-analysis conducted in 2006 compiled multiple studies examining the associations between education level and dementia, including specific AD diagnosis (Caamaño-Isorna et al. 2006). Examining studies published from 1966 to 2005 and excluding those that did not fit criteria (for example, studies needed to include odds ratio or relative risk and use clear diagnostic criteria), nineteen were included in final analyses. These included both cohort and case-control studies. Results of the meta-analysis suggested that lower education level was a risk factor for dementia,
specifically AD (Caamaño-Isorna et al. 2006). The authors even determined a certain degree of causality due to the strong associations shown, the correct dose-response relationship, temporality, consistency, analogy, and biological plausibility (Caamaño-Isorna et al. 2006). Thus, they reported that there is likely a causal relationship between lower education level and increased risk of dementia (Caamaño-Isorna et al. 2006). However, they were not able to determine whether education level determined actual risk of the disease, or rather the manifestation of clinical features (Caamaño-Isorna et al. 2006). Additionally, a Norwegian study with over 45,000 participants examined associations between education, midlife income, and dementia (Strand et al. 2015). Using male participants in The Norwegian Counties Study and The Cohort of Norway, researchers assessed income, education, and dementia status. Similar to the meta-analysis, results indicated once again that lower educational level was associated with greater risk of dementia in late life (Strand et al. 2015).

Other studies have examined the associations between income levels and dementia. One study based in the eastern United States showed that predictors of socioeconomic status, including total annual household income, were negatively associated with AD (Evans et al. 1997). Those in lower income categories had higher reports of AD than those in higher categories (Evans et al. 1997). Similar results were reported in a prospective U.S. study of elderly biracial adults (Yaffe et al. 2013). A third study conducted in Finland reported that midlife income was not a predictor of dementia (including AD), but late-life low income was (Anttila et al. 2002). The authors reported that this may be because low income is a consequence of living with dementia, rather than the other way around (Anttila et al. 2002). Thus, although there may be associations between income level and dementia, the direction and strength of these associations has varied widely in the current literature.

2.4.2. Comorbid Conditions

It is important to include commonly comorbid conditions when analyzing associations between dementia and different exposure variables. As discussed above, dementia and AD frequently occur in conjunction with chronic conditions such as diabetes and heart disease (ICD-10 1992). The biological foundation of diabetes can be tied to dementia via pathways necessary for cognitive and emotional functioning. These pathways can be damaged by insulin resistance or hyperglycemia
and additionally affected by changes in insulin level in the central nervous system (Rosenblat et al. 2014). People with diabetes thus often have cognitive impairment resulting from damage to neural circuits (Rosenblat et al. 2014).

Stroke is quite important in the context of dementia predictors and comorbid conditions, as it is a leading cause of dementia worldwide (Leys et al. 2005). There are numerous neuropsychological changes in the brain that frequently occur following a stroke, including neurofibrillary pathology and problems with memory and orientation (Pinkston et al. 2009). Although most of those who have suffered a stroke recover without permanent neurological damage, a significant percentage develop dementia, frequently AD or VaD (Pinkston et al. 2009).

IHD is associated with both dementia and the presence of certain apolipoprotein E polymorphisms (Rassmussen 2016). Biological variations associated with greater risk of atherosclerosis and IHD are also related to dementia (including AD) outcomes (Rassmussen 2016). This association of underlying factors common to both IHD and dementia makes IHD a good candidate for inclusion in covariate analyses. Another similarly-structured cohort study in Israel found that individuals who survived midlife without development of cardiovascular disease or diabetes, among other conditions, were significantly less likely to develop dementia in late life (Beeri et al. 2014). With approximately 40% of centenarians developing incident dementia, predictors in early- and mid-life may be highly important in the overall context of dementia risk and association studies (Beeri et al. 2014).

Based on the availability of KIHD data, stroke, IHD, and diabetes status are included in this study’s analyses. Stroke, diabetes, and IHD were existing conditions and/or diagnosed prior to baseline; diagnoses given during or after follow-ups were not included in the analyses presented here.

2.4.3. Physical and Biological Markers
Covariates included in the final model were SBP, DBP, smoking status, LTPA, BMI, waist-to-hip ratio, LDL cholesterol, hypercholesterolemia, and total cholesterol. Elevated blood pressure earlier in life has been linked to greater risk of later cognitive impairment and/or dementia diagnosis
Hypertension specifically is associated with both AD and VaD, as is the case with stroke (Birkenhäger and Staessen 2004). Although blood pressure tends to fall soon before onset of dementia (especially AD), this fall is only seen after earlier occurrence of elevated blood pressure levels (Birkenhäger and Staessen 2004).

Included in the many adverse health effects of smoking is increased risk of dementia (Ott et al. 1998). A recent study showed that usage of nicotine patches in lieu of smoking could potentially improve cognitive functioning; in a randomized controlled trial, those who used nicotine patches had greater Clinician Rated Global Improvement than those who used placebos (Grayson and Thomas 2012). However, smoking still remains a widely accepted predictor of dementia (Grayson and Thomas 2012).

Regular physical activity has been shown to associate with improved overall cognitive functioning and has a protective effect on the brain against dementia (Hunt and Hellwig 2016). It also helps prevent development of the previously mentioned comorbid diseases often occurring alongside dementia: diabetes, stroke, and heart disease (Haskell et al. 2007). Certain types of exercise appear to be especially effective for protecting the body against dementia, specifically types of aerobic exercise like walking and gardening (Haskell et al. 2007). Aerobic exercise has been shown to associate with improved frontal and parietal brain region activity; these regions are also involved with attention, task orientation, and focus, which are commonly negatively impacted by dementia (Colcombe et al. 2004). Greater fitness levels are also associated with larger hippocampal volume, which is related to storage and processing of memories (Haskell et al. 2007). Exercises such as these can be considered leisure time physical activity and thus are arguably an important covariate for analyses of associations of environmental and social factors with dementia.

Recent studies have shown that increased BMI and weight gain may raise risk of dementia later in life (Beydoun et al. 2008, Fitzpatrick et al. 2009). BMI may relate to cognitive health due to its interaction with the hypothalamic-pituitary-adipose axis and the fat-brain axis (Elmquist et al. 2004, Schaffler et al. 2005). Both very low and high BMI may lead to increased risk of dementia, specifically AD and VaD, as demonstrated by multiple studies (Whitmer et al. 2007, Fitzpatrick et al. 2009, Chen et al. 2010). BMI change over time may also lead to increased or decreased risk
of dementia, with presence and degree of these associations influenced by sex and geographic location of subjects (Chen et al. 2010).

Similar to BMI is waist-to-hip ratio, which is representative of abdominal fat. One study found that women with lower waist-to-hip ratios, but higher BMI, had poorer cognitive functioning than others (Kerwin et al. 2010). Another research group found that (in men) those with the highest waist-to-hip ratio had significant cortical thinning when compared to those in lower ratio brackets (Kim et al. 2014). Cortical thinning is also related to frontal lobe thickness and performance, and is observed in areas of the brain including the left medial frontal lobe and the posterior cingulate gyrus (Kim et al. 2014). Because waist-to-hip ratio is an indicator of abdominal fat, it can be used as a proxy for obesity; in these studies, higher body fat percentage has a protective or beneficial effect on cognitive functioning, while abdominal fat shows the opposite relationship (Kerwin et al. 2010, Kim et al. 2014).

Elevated LDL cholesterol is associated with greater risk of dementia development in the elderly, particularly for those in the highest quartile of serum LDL levels (Moroney et al. 1999). Total cholesterol level is also an indicator of dementia risk, along with many other cerebrovascular conditions and forms of cognitive impairment (Panza et al. 2009). Studies have indicated associations of high total cholesterol with greater risk of AD and other forms of cognitive dysfunction (Evans et al. 2000, Yaffe et al. 2002). However, some recent additions to the current literature indicate that higher cholesterol in late life may actually be protective against dementia, as opposed to high midlife cholesterol being associated with greater risk of dementia (Evans et al. 2000, Yaffe et al. 2002, Panza et al. 2009). Hypercholesterolemia, or the presence of elevated cholesterol levels in the bloodstream and also a type of hyperlipoproteinemia, is associated with both greater risk of cardiovascular conditions as well as cognitive decline and dementia (Jancin 2004). The presence of hypercholesterolemia was associated with a greater risk of dementia development of approximately 36% in one study (Jancin 2004). However, studies have also shown that the mechanisms by which hypercholesterolemia and dementia function are not necessarily the same, although they are poorly understood (Etcheto et al. 2015). Problems with cholesterol metabolism, which are implicated in hypercholesterolemia, are also linked to dementia and AD.
specifically (Ettcheto et al. 2015). Overall, hypercholesterolemia is associated with cognitive decline and dysfunction (Ettcheto et al. 2015).

Due to the established relationships between these factors and dementia, they have been included as covariates in the following analyses. They are not necessarily confounders; rather, most of them are effect modifiers and may play a role in the strength of the association between dementia and the examined exposures (childhood stress, quarrelsome home, and strict upbringing).
AIMS OF THE STUDY

Few studies exist addressing key issues in the discussion of dementia and AD risk and childhood factors. Additionally, life-course research examining childhood factors and dementia and AD outcomes has not yet been conducted within the KIHDD study. The present study addresses whether childhood stress, living in a quarrelsome home in childhood, and having a strict upbringing play a role in dementia and AD risk in late life. It also examines whether these associations remain after adjustment for covariates and possible confounding factors.
4 METHODOLOGY

4.1. Kuopio Ischemic Heart Disease Risk Factor Study

To fully understand the aims, methodology, and implications of the present study, the KIHD study must first be described. The KIHD study is a longitudinal cohort study that began in 1984. In the latter half of the twentieth century, Finland had some of the highest rates of cardiovascular disease (CVD) in the world (Keys 1970). Within Finland, the rates in the eastern area of the country were considerably higher than elsewhere (Tuomilehto et al. 1986). With high rates of morbidity and mortality from CVD within eastern Finland, particularly North Karelia, the local population petitioned the government for provincial control of CVD (Puska et al. 1981). In 1972, the North Karelia Project was initiated as a community-level intervention program. The primary goal of the project was to decrease the high levels of morbidity and mortality from CVD occurring in the region (Puska et al. 1981). Derived from this goal were other objectives; namely, to reduce smoking prevalence, elevated blood pressure, and high serum total cholesterol within the population (Puska et al. 1981).

From early studies using project data, researchers found that middle-aged men in North Karelia had high rates of smoking, diets high in saturated fat, elevated serum total cholesterol and blood pressure, and high risk and rates of hypercholesterolemia (Salonen et al. 1981). These results were produced by comparing the baseline survey data in 1972 with data at follow-ups and via links to medical registries. The KIHD study has produced a large number of research papers using a variety of biological, psychological, behavioral, social, and economic data obtained from participants.

4.1.2. Social Epidemiological Data from the KIHD Study

In order to examine the underlying social and behavioral influences affecting high CVD risk, researchers administered questionnaires covering a wide range of social data. Three different questionnaires were compiled that contained questions regarding family history, education, income, religion, psychological state, and work history. Depending on the study, these questionnaires were sometimes supplemented with additional questions based on relevant literature. For example, a 1997 study examining associations of workplace conditions, economic and social status, and risks of mortality and cardiovascular events included supplemental questions.
further detailing physical exertion, unemployment, and other factors relevant to the researchers (Lynch et al. 1997). In most KIHD-based studies, these questionnaires (if used) were then tied to biomarker and anthropometric data to better determine the impact and associations of these social and behavioral variants on and with various health outcomes. Additionally, many studies included use of outside questionnaires with well-established validity to determine exclusion of cases, psychological events, and other items not established by KIHD study questionnaires (Lynch et al. 1997).

At the most general level, this research aims to determine associations of dementia, including AD independently, with childhood stress and childhood home environment (quarrelsome home and strict upbringing). It does so by determining not just these associations, but also associations as modified by the inclusion of study covariates, discussed previously and later on in further detail. Findings provide a life-course epidemiological perspective of the associations between childhood social and environmental factors with late-life dementia and AD risk and outcomes. Based on this newly acquired information, additional study implications could be formulated based on the potential of findings to influence policy changes, interactions of healthcare professionals and caregivers with dementia patients, and future research of similar focus that could be conducted in other populations to develop a greater understanding of these associations in a global context. Such aims are not directly addressed by this study, but rather could be formulated based on interpretation of study results in the context of other current literature.

4.2. Data Collection

4.2.1. Participant Recruitment

The KIHD Study began in 1984 with enrollment of 2682 participants, recruited from 1984 to 1989 in the city of Kuopio and surrounding areas. Men were aged 42, 48, 54, or 60 years at baseline. With 1926 as the earliest birth year in the cohort, many are now considered elderly. KIHD study guidelines involving human subject research were approved by the Research Ethics Committee of the University of Kuopio. Participants voluntarily took part in the study, with no monetary or other incentives and provided signed informed consent. Additional details regarding study population can be found in other KIHD publications (Salonen 1988; Salonen et al. 1991; Ylilauri et al. 2017).
4.2.2. Biomarker Collection and Questionnaire Administration

Biomarkers, as well as anthropometric data, were collected at baseline and at follow-ups for all participants. These included height, weight, blood pressure, and blood samples. The KIHD study also includes questionnaires consisting of items related to social environment, childhood characteristics, and health habits. These childhood data represent social disparities in education, income, and housing. Questionnaires were administered at baseline and follow-ups. The present study uses information from the childhood section, which includes years of education, family situation and home environment, neighborhood characteristics, and health status.

4.2.3. Identification of Incident Dementia and Alzheimer’s Disease

At follow-up at the end of 2014, data were collected pertaining to dementia including AD, as well as death status. Incident cases of dementia and AD were also documented via computer linkages to the Hospital Discharge Registry (Care Register), the Special Reimbursement Register, as well as the National Death Registry (Statistics Finland). The Special Reimbursement Register (SRR) functions through the Social Insurance Institution of Finland. The SRR recorded cases of AD or, less frequently, other dementias, on the condition that the following prerequisites were met: the patient had symptoms consistent with diagnosis of dementia; over a period of at least 3 months, the patient experienced decreased social functioning; they had received an MRI or computer tomography scan; other possible diagnoses were ruled out; and a geriatrician or neurologist had confirmed the diagnosis (Ylilauri et al. 2017). Further details regarding the SRR are detailed in other publications (Kajantie et al. 2006; Ylilauri et al. 2017). Diagnostic criteria for dementia and AD followed International Classification of Diseases (ICD) guidelines (Ylilauri et al. 2017). To identify cases of dementia, ICD-8 code 290, ICD-9 codes 290 and 4378A, and ICD-10 codes F00, F01, F02, F03, G30, and G31 were used (Ylilauri et al. 2017). For incident AD, ICD-8 codes 29000 and 29010 were used, as well as ICD-9 codes 290 and 3310A and ICD-10 codes F00 and G30 (Ylilauri et al. 2017).

4.3 Childhood Stress Index

To examine the joint influence of multiple childhood variables, this study used a childhood stress index, comprised of the following variables: living in custody or an orphanage, experience of
trauma in childhood, problems with teachers, and emigration from Karelia. In 1944, over 400,000 people living in Karelia had to move from ceded areas to other parts of Finland, and some of the men in the KIHD cohort were among those as a child. Individuals with answering “yes” to one or more variables in the childhood stress index received a score of 1 in the childhood stress construct (versus 0 = no childhood stress). This combined variable was used in all subsequent analyses. Table 1 gives components of the childhood stress index and number of participants with a response of “yes” to each variable. Family injury/death and childhood trauma composite measures were also created and analyzed for associations with dementia or AD. However, these indices did not yield statistically significant results and therefore were not included in the later analyses.

Table 1. Childhood Variable Indices

<table>
<thead>
<tr>
<th>Childhood Stress</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>In custody/orphanage</td>
<td>7</td>
</tr>
<tr>
<td>Crisis in childhood</td>
<td>8</td>
</tr>
<tr>
<td>Problems with teacher</td>
<td>21</td>
</tr>
<tr>
<td>Immigrated from Karelia</td>
<td>33</td>
</tr>
</tbody>
</table>

4.4 Statistical Analyses

4.4.1. Univariate Analyses and Cox Proportional Hazard Models

Cross-tabulations were completed to determine frequencies of dementia and AD by childhood stress status and quarrelsome/strict home environment. Descriptive statistics of covariates (income, education, stroke, ischemic heart disease, diabetes, SBP, DBP, smoking status, LTPA, BMI, waist-to-hip ratio, LDL cholesterol, hypercholesterolemia, and total cholesterol) were also determined. Cox proportional hazard models were constructed using dementia or AD diagnosis and years to diagnosis (for each separately). Covariates included childhood stress, quarrelsome home, and strict upbringing for all analyses; separate analyses were carried out for each model with dementia or AD. In total, 24 Cox regressions are included in results. Hazard ratios, 95% confidence intervals, and p-values are included in text and/or tables.
4.4.2. Covariate Models

Four models were created to demonstrate relative hazards of incident dementia and AD adjusting for covariates. Model 1 included age; model 2 augmented model 1 with adulthood socioeconomic status (income and education); model 3 included components of model 2 plus stroke, diabetes, and IDH diagnoses; and model 4 augments model 3 with SBP, DBP, smoking status, LTPA, BMI, waist-to-hip ratio, LDL cholesterol, hypercholesterolemia, and total cholesterol. Income was based on the previous year’s tax returns. Income and education were measured from one to five on questionnaires, with one being the lowest. For the present analyses, each were divided into two categories (1-2 = low [0]; 3-5 = medium/high [1]). All analyses were completed using SPSS version 23 (IBM Corp.).
5 RESULTS

5.1. Baseline Characteristics

At baseline, study participants (N = 2682) had a mean age of 53.1, ranging from 42 to 61.3. Data on study population characteristics, including means, standard deviations, and range, are described in Table 2. Table 3 shows distributions and proportions of covariates by dementia and AD status. Finally, Table 4 described distribution of dementia/AD status by the childhood stress index, quarrelsome home, and strict upbringing. This table also includes total numbers of participants in each category and sub-category, regardless of whether they were diagnosed with dementia/AD or responses to the childhood stress index, quarrelsome home, or strict upbringing.

Average follow-up time for all participants was 22.2 years, ranging from 0.02 to 30.8 years. Figure 2 details the timeline for KIHD participants, including follow-ups, age groups, and attrition rates (Ylilauri et al. 2017). To clarify, only data from the end of 2014 is included in the present study. Distinctions are not made for diagnoses occurring at different points during KIHD study follow-ups.

By the end of 2014, there were 360 cases of dementia (13.4% of participants) and 282 cases of AD (10.5%). 13 out of the 360 dementia cases (4% of cases) and 10 of the 282 AD cases (4%) reported childhood stress. 76 and 77 of the dementia cases reported living in a quarrelsome home or having a strict upbringing, respectively (approximately 21% each). 54 reported a quarrelsome home and AD diagnosis (15%) and 57 reported strict upbringing and AD diagnosis (16%). Overall, 51 reported childhood stress with no diagnosis of dementia/AD (80% of all childhood stress cases), 634 reported a quarrelsome home without diagnosis (89%), and 595 reported strict upbringing without a diagnosis (86%).
### Table 2. Study Population Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income</td>
<td>2.39 (0.76)</td>
<td>1-4</td>
</tr>
<tr>
<td>Education</td>
<td>3.01 (1.41)</td>
<td>1-5</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.10 (0.30)</td>
<td>0-1</td>
</tr>
<tr>
<td>IHD(^a)</td>
<td>0.25 (0.43)</td>
<td>0-1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.06 (0.24)</td>
<td>0-1</td>
</tr>
<tr>
<td>SBP (mm Hg)(^a)</td>
<td>134.20 (17.10)</td>
<td>87.67-221.17</td>
</tr>
<tr>
<td>DBP (mm Hg)(^a)</td>
<td>88.73 (10.53)</td>
<td>56.67-136.67</td>
</tr>
<tr>
<td>Cigarette pack years(^b)</td>
<td>8.66 (17.10)</td>
<td>0-174.25</td>
</tr>
<tr>
<td>LTPA(^a, c)</td>
<td>1701.77 (1583.36)</td>
<td>0-24581.07</td>
</tr>
<tr>
<td>BMI(^a)</td>
<td>26.88 (3.59)</td>
<td>31.45-17.10</td>
</tr>
<tr>
<td>Waist-to-Hip Ratio</td>
<td>0.95 (0.06)</td>
<td>0.71-1.73</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.01 (0.11)</td>
<td>0-1</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/l)</td>
<td>5.91 (1.08)</td>
<td>0.68-8.46</td>
</tr>
<tr>
<td>LDL Cholesterol (mmol/l)(^a)</td>
<td>4.04 (1.02)</td>
<td>0.68-8.46</td>
</tr>
<tr>
<td>Childhood Stress(^d)</td>
<td>0.02 (0.15)</td>
<td>0-1</td>
</tr>
<tr>
<td>Quarrelsome Home(^d)</td>
<td>3.17 (1.15)</td>
<td>0-5</td>
</tr>
<tr>
<td>Strict Upbringing(^d)</td>
<td>2.08 (0.72)</td>
<td>0-4</td>
</tr>
</tbody>
</table>

---

\(^a\) Abbreviations: SES = socioeconomic status; SBP = systolic blood pressure; DBP = diastolic blood pressure; LTPA = leisure time physical activity; BMI = body mass index; LDL = low-density lipoprotein

\(^b\) Cigarette pack years = cigarette packs/day * years of smoking

\(^c\) LTPA = MET hours/year

\(^d\) Childhood stress: 0 = no stress, 1 = stress

Quarrelsome home: 0 = not quarrelsome at all, 5 = very quarrelsome

Strict upbringing: 0 = very liberal, 4 = very strict
Table 3. Distributions and Proportions of Covariates by Dementia and AD Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dementia (N=360)</th>
<th>AD (N=282)</th>
<th>Neither (N=2322)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income&lt;sup&gt;a&lt;/sup&gt;</td>
<td>152 (42.2)</td>
<td>113 (40.1)</td>
<td>685 (29.5)</td>
</tr>
<tr>
<td>Education&lt;sup&gt;a&lt;/sup&gt;</td>
<td>43 (11.9)</td>
<td>30 (10.6)</td>
<td>225 (9.7)</td>
</tr>
<tr>
<td>Stroke&lt;sup&gt;b&lt;/sup&gt;</td>
<td>58 (16.1)</td>
<td>33 (11.7)</td>
<td>270 (11.6)</td>
</tr>
<tr>
<td>IHD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>92 (25.6)</td>
<td>65 (23.0)</td>
<td>585 (25.2)</td>
</tr>
<tr>
<td>Diabetes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14 (3.9)</td>
<td>6 (2.1)</td>
<td>148 (6.4)</td>
</tr>
<tr>
<td>SBP (mm Hg)&lt;sup&gt;c, d&lt;/sup&gt;</td>
<td>25 (6.9)</td>
<td>19 (6.7)</td>
<td>172 (7.4)</td>
</tr>
<tr>
<td>DBP (mm Hg)&lt;sup&gt;c, d&lt;/sup&gt;</td>
<td>199 (55.2)</td>
<td>158 (56.0)</td>
<td>1290 (55.6)</td>
</tr>
<tr>
<td>Smoker&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90 (25.0)</td>
<td>68 (24.1)</td>
<td>776 (33.4)</td>
</tr>
<tr>
<td>LTPA&lt;sup&gt;d, e&lt;/sup&gt;</td>
<td>16 (4.4)</td>
<td>15 (5.3)</td>
<td>82 (3.5)</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;c, d&lt;/sup&gt;</td>
<td>260 (72.2)</td>
<td>204 (72.3)</td>
<td>1567 (67.5)</td>
</tr>
<tr>
<td>Waist-Hip Ratio&lt;sup&gt;c&lt;/sup&gt;</td>
<td>285 (79.2)</td>
<td>223 (79.1)</td>
<td>1851 (79.7)</td>
</tr>
<tr>
<td>Hypercholesterolemia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7 (1.9)</td>
<td>6 (2.1)</td>
<td>25 (1.1)</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/l)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>158 (43.9)</td>
<td>123 (43.6)</td>
<td>778 (33.5)</td>
</tr>
<tr>
<td>LDL Cholesterol (mmol/l)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>179 (49.7)</td>
<td>141 (50.0)</td>
<td>979 (42.2)</td>
</tr>
<tr>
<td>Childhood Stress&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13 (3.6)</td>
<td>10 (3.5)</td>
<td>51 (2.2)</td>
</tr>
<tr>
<td>Quarrelsome Home&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76 (24.3)</td>
<td>54 (22.0)</td>
<td>634 (30.2)</td>
</tr>
<tr>
<td>Strict Upbringing&lt;sup&gt;b&lt;/sup&gt;</td>
<td>77 (21.5)</td>
<td>57 (20.4)</td>
<td>595 (25.7)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Low level (income/education; does not include medium/high)

<sup>b</sup> Response/status/diagnosis (e.g., diagnosis of diabetes and dementia)

<sup>c</sup> Based on World Health Organization cut-points (WHO 2004):
SBP ≥ 160 mm Hg; DBP ≤ 90 mm Hg; BMI ≥ 25; Waist-Hip Ratio ≥ 0.77;
Total Cholesterol ≥ 6.2 mmol/l; LDL Cholesterol ≥ 4.1 mmol/l

<sup>d</sup> Abbreviations: SES = socioeconomic status; SBP = systolic blood pressure; DBP = diastolic blood pressure; LTPA = leisure time physical activity; BMI = body mass index; LDL = low-density lipoprotein

<sup>e</sup> LTPA cut-point: < 118.415 (low LTPA), ≥ 118.415 (medium/high LTPA); based on one standard deviation from total mean LTPA (n = 2656)
Table 4. Distribution of childhood variables by incident dementia/AD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood stress</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>51</td>
<td>64</td>
<td>10</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>No</td>
<td>347</td>
<td>2271</td>
<td>2618</td>
<td>272</td>
<td>94</td>
<td>366</td>
</tr>
<tr>
<td>Total</td>
<td>360</td>
<td>2322</td>
<td>2682</td>
<td>282</td>
<td>12</td>
<td>300</td>
</tr>
<tr>
<td>Quarrelsome home</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>76</td>
<td>634</td>
<td>710</td>
<td>54</td>
<td>192</td>
<td>246</td>
</tr>
<tr>
<td>No</td>
<td>237</td>
<td>1468</td>
<td>1705</td>
<td>192</td>
<td>1513</td>
<td>1705</td>
</tr>
<tr>
<td>Total</td>
<td>313</td>
<td>2102</td>
<td>2415</td>
<td>246</td>
<td>1716</td>
<td>2415</td>
</tr>
<tr>
<td>Strict upbringing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>77</td>
<td>595</td>
<td>672</td>
<td>57</td>
<td>1775</td>
<td>632</td>
</tr>
<tr>
<td>No</td>
<td>281</td>
<td>1717</td>
<td>1998</td>
<td>223</td>
<td>1775</td>
<td>1998</td>
</tr>
<tr>
<td>Total</td>
<td>358</td>
<td>2312</td>
<td>2670</td>
<td>280</td>
<td>3770</td>
<td>2670</td>
</tr>
</tbody>
</table>

*Percentage is proportion of total independent variable within dementia/AD status.

5.2. Multivariate models of the association between childhood stress and dementia

To examine the influences and possible attenuations of multiple covariates or confounders on associations of childhood stress, quarrelsome home, and strict upbringing with dementia/AD, four models were created. The first is age-adjusted, the second includes socioeconomic-defining characteristics, the third includes commonly comorbid conditions, and the fourth includes physical and biological markers associated independently with the outcomes. Components of all models are listed in Table 5.
Table 5. Multivariate models examining childhood stress, quarrelsome home, and strict upbringing with dementia and AD

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-adjusted</td>
<td>SES-adjusted$^1$</td>
<td>Disease-adjusted</td>
<td>Biomarker and body habitus-adjusted</td>
</tr>
<tr>
<td>Age</td>
<td>Model 1 component</td>
<td>Model 2 components</td>
<td>Model 3 components</td>
</tr>
<tr>
<td></td>
<td>Income</td>
<td>Stroke</td>
<td>SBP$^1$</td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td>Diabetes</td>
<td>DBP$^1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD$^1$</td>
<td>Smoking status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LTPA$^1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BMI$^1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Waist-to-hip ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LDL cholesterol$^1$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total cholesterol</td>
</tr>
</tbody>
</table>

$^1$Abbreviations: SES = socioeconomic status; SBP = systolic blood pressure; DBP = diastolic blood pressure; LTPA = leisure time physical activity; BMI = body mass index; LDL = low-density lipoprotein

Model 1 adjusts for age (in years). Analysis of Model 1 showed statistically significant associations of childhood stress with incident dementia (HR = 1.87, 95% CI = [1.07, 3.26], p = 0.03) (Table 6). Analysis of associations with AD showed a similar hazard ratio and was near significance (HR = 1.87, 95% CI = [0.99, 3.52], p = 0.05). Both results indicate increased hazard risk (diagnosis of dementia or AD) and decreased time before diagnosis (in years; Table 5). Using AD as the outcome of interest, a quarrelsome childhood home (HR = 0.72, 95% CI = [0.53, 0.98], p = 0.03) and strict upbringing (HR = 0.74, 95% CI = [0.56, 0.99], p = 0.05) (Table 6) also displayed significant associations. These two independent variables indicated decreased hazard risk (diagnosis of dementia or AD) and increased survival time (years until diagnosis; Table 5). Associations of strict upbringing with dementia approached significance (HR = 0.80, 95% CI = [0.62, 1.02], p = 0.07). Detailed hazard ratios, confidence intervals, and p-values for all variables and models can be found in Table 6.

Model 2 includes age with education and income as additional covariates. Examining incident dementia, childhood stress again displayed a significant positive relationship (HR = 1.99, 95% CI = [1.11, 3.55], p = 0.02). Additionally, strict upbringing approached significance (HR = 0.79, 95%
CI = [0.62, 1.02], p = 0.07). With AD, the association with childhood stress approached significance and HR did not markedly change (HR = 1.91, 95% CI = [0.98, 3.72], p = 0.06) (Table 6). Quarrelsome home was not significantly related to dementia. Strict upbringing and quarrelsome home once again demonstrated significant associations with AD (HR = 0.74 and 0.80, 95% CI = [0.55, 0.99] and [0.52, 0.96], p = 0.04 and 0.03, respectively) and hazard ratios in the opposite direction (Table 6).

Model 3 includes components of Model 2 with three potential comorbid conditions: incident stroke, ischemic heart disease, and diabetes. In order to be included in the dataset, the condition must have been diagnosed prior to or at baseline. Those receiving a diagnosis of diabetes, ischemic heart disease, or stroke during or after follow-ups were not included in the following analyses.

Childhood stress remained significantly associated with dementia (HR = 1.95, 95% CI = [1.09, 3.48], p = 0.03), and strict upbringing approached significance (HR = 0.78, 95% CI = [0.61, 1.01], p = 0.06) (Table 6). Associations of AD diagnosis with childhood stress were near significance with similar HR as for associations with dementia (HR = 1.91, 95% CI = [0.98, 3.73], p = 0.06). Strict upbringing and quarrelsome home were significantly associated with AD (HR = 0.74 and 0.71, 95% CI = [0.55, 0.99], p = 0.04 and 0.03, respectively) (Table 6). The relationship between strict upbringing and dementia was near significance (HR = 0.78, 95% CI = [0.61, 1.01], p = 0.06), and quarrelsome home did not significantly associate with dementia. As with the previous analyses, associations of childhood stress with dementia and AD had positive hazard ratios, thus indicating increased dementia/AD risk with time. Also consistent with earlier results, strict upbringing and quarrelsome home indicated the opposite (Table 6).

Finally, model 4 included all prior social, demographic, and disease-related covariates with the addition of systolic blood pressure, diastolic blood pressure, smoking status, leisure time physical activity (LTPA), BMI, waist-to-hip ratio, LDL cholesterol, hypercholesterolemia, and total cholesterol. Associations of childhood stress with both dementia and AD diagnosis were nearly significant (HR = 1.89 and 2.04, 95% CI = [0.96, 3.72] and [0.95, 4.39], p = 0.06 and 0.07, respectively) (Table 6). A quarrelsome home was not associated with dementia or AD (HR = 0.90 and 0.78, 95% CI = [0.68, 1.19] and [0.57, 1.08], p = 0.46 and 0.14, respectively). Strict upbringing
was significantly associated with both dementia and AD (HR = 0.72 and 0.70, 95% CI = [0.54, 0.98] and [0.50, 0.99], p = 0.03 and 0.04, respectively) (Table 6).
Table 6. Relative hazards of incident dementia and AD by childhood variables, adjusting for covariates

<table>
<thead>
<tr>
<th></th>
<th>All dementia</th>
<th>AD</th>
<th>All dementia</th>
<th>AD</th>
<th>All dementia</th>
<th>AD</th>
<th>All dementia</th>
<th>AD</th>
<th>All dementia</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Childhood Stress</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.871</td>
<td>1.872</td>
<td>1.987</td>
<td>1.906</td>
<td>1.947</td>
<td>1.910</td>
<td>1.892</td>
<td>2.041</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[1.074, 3.258]</td>
<td>[0.995, 3.522]</td>
<td>[1.113, 3.550]</td>
<td>[0.977, 3.722]</td>
<td>[1.089, 3.479]</td>
<td>[0.978, 3.731]</td>
<td>[0.962, 3.720]</td>
<td>[0.949, 4.388]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.027</td>
<td>0.052</td>
<td>0.020</td>
<td>0.059</td>
<td>0.025</td>
<td>0.058</td>
<td>0.064</td>
<td>0.068</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Quarrelsome Home</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.824</td>
<td>0.721</td>
<td>0.817</td>
<td>0.707</td>
<td>0.812</td>
<td>0.709</td>
<td>0.901</td>
<td>0.784</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[0.636, 1.068]</td>
<td>[0.533, 0.975]</td>
<td>[0.629, 1.060]</td>
<td>[0.521, 0.959]</td>
<td>[0.626, 1.055]</td>
<td>[0.522, 0.962]</td>
<td>[0.682, 1.189]</td>
<td>[0.566, 1.084]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.144</td>
<td>0.034</td>
<td>0.128</td>
<td>0.026</td>
<td>0.188</td>
<td>0.027</td>
<td>0.459</td>
<td>0.141</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Strict Upbringing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.795</td>
<td>0.744</td>
<td>0.793</td>
<td>0.735</td>
<td>0.784</td>
<td>0.737</td>
<td>0.724</td>
<td>0.699</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>[0.618, 1.023]</td>
<td>[0.556, 0.995]</td>
<td>[0.615, 1.023]</td>
<td>[0.548, 0.987]</td>
<td>[0.608, 1.012]</td>
<td>[0.549, 0.989]</td>
<td>[0.537, 0.977]</td>
<td>[0.495, 0.986]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P Value</td>
<td>0.074</td>
<td>0.047</td>
<td>0.074</td>
<td>0.040</td>
<td>0.062</td>
<td>0.042</td>
<td>0.034</td>
<td>0.042</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Model 1: Adjusted for age

#Model 2: Adjusted for components of model 1 plus education and income

+Model 3: Adjusted for components of model 2 plus stroke, diabetes, and ischemic heart disease status

^Model 4: Adjusted for components of model 3 plus systolic blood pressure, diastolic blood pressure, smoking status, leisure time physical activity, body mass index (BMI), waist-to-hip ratio, LDL cholesterol, hypercholesterolemia, and total cholesterol
6 DISCUSSION

We found childhood stress to be positively associated with the later age risk of dementia, and specifically with the risk of AD. The association remained statistically significant after adjustment for age, education level, income bracket, commonly comorbid diseases (IHD, stroke, and diabetes), and multiple physical and biological markers of overall health. A strict upbringing was always associated with AD and was either significantly or nearly significantly related to dementia, depending on the covariate model. Quarrelsome home displayed less constant associations, but nearly always was significantly associated with AD (with the exception of Model 4) and generally did not show any significant associations with dementia.

6.1. Interpretation of results

Results presented here must be interpreted in the context of current and recent literature on the subject and in related fields. Additionally, certain strengths and limitations of the KIHD study and this specific research must also be taken into account. In conclusion, areas in need of further research in order to more fully understand the extent of the association between childhood factors and late-life illness are discussed.

6.1.2. Results in Context of Prior Research

Childhood stress logically leads to adverse health outcomes in many situations, including (as shown by this study) dementia and AD risk. The individual components of the childhood stress composite measure (living in custody or an orphanage, having problems with the teacher, crisis in childhood, or immigration from Karelia) separately have been associated with negative health outcomes, both physical and mental, in previous studies. For example, Miller et al. (2009) examined associations of children in orphanages and other adoptees and mental health problems (among others). In this study, 28% of the individuals exhibited mental health disorders, 46% attention deficit hyperactivity disorder, and 50% behavioral symptoms (Miller et al. 2009). Another study found that students that believed their teachers cared for them had fewer symptoms of anxiety and physical health problems that were stress-related than others, suggesting that strong relationships between students and teachers are beneficial for health (Conner et al. 2014). In terms of childhood crises and trauma, Baker et al. (2009) found that, in a sample of urban Mexican men
and women, those who had experienced trauma or stressful events in childhood had increased adulthood symptoms of depression, muscular-skeletal symptoms, and cardio-pulmonary symptoms. Men exposed to trauma in childhood had significantly higher rates of depression than their counterparts, and experiencing sexual violence in childhood were significantly related to all health outcomes. Finally, the associations of immigration with health problems have also been examined in recent years, yielding similar results to those presented by our study. Berthold et al. (2014) cross-sectionally analyzed the health outcomes of Cambodian immigrants and refugees living in the United States, discovering that 61% had diagnoses of three or more physical conditions, with an additional 73% reporting posttraumatic stress disorder, depression, or both. This particular study may reflect additional physical stress related to refugee status; however, other studies have suggested relationships between immigration status and physical/mental health outcomes. For example, Breslau et al. (2011) examined mental and physical health status in Mexican migrants to the U.S., finding that they had more mental disorders than their U.S. counterparts.

A study from the University of Helsinki analyzed associations of childhood temperament and maternal parenting style (strict versus less disciplinary) and found associations that differ somewhat those produced by this study in terms of mental health effects (Katainen et al. 1997). In this study, for both boys and girls, strict disciplinary style was associated with negative emotionality and decreased sociability. However, these results do not necessarily contradict those from our study; low sociability with improved overall general or mental health are not mutually exclusive. Park and Walton-Moss looked at the relationships between parenting style, home environment, and childhood health and health behaviors (2012). In this study, an authoritative parenting style was associated with improved health-related behaviors in children. However, parental stress, which could result in a more argumentative home, was associated with worse child health behaviors (Park & Walton-Moss 2012).

There are potential explanations for the associations of strict upbringing and a quarrelsome home with decreased hazard risk in this study. Strict upbringing could imply greater focus on education and schoolwork at a young age, thus enforcing mental training and skills beginning in childhood. Alternatively, as suggested in the study by Park and Walton-Moss, stricter parenting might enforce
positive health behaviors in children, leading to improved adulthood health (Park & Walton-Moss 2012). Similarly, living in a more quarrelsome home could mean more argumentative capacity, potentially leading to improved mental functioning. However, as discussed in the same Park and Walton-Moss study, an argumentative home could lead to worse health behaviors by children, suggesting that some other aspect of a quarrelsome childhood home influences the association with decreased dementia/AD risk (2012). There is generally a dearth of research pertaining to the influences of a strict upbringing or quarrelsome home on health, including life-course health trajectories. The associations are complex, and despite the relationship between decreased dementia and AD risk with these childhood social factors, the negative health/social consequences suggested by other studies imply that this is not a black-and-white association.

6.2. Study Limitations
Finland has changed greatly since the early 1980s, when the KIHD study began, and even more so since the earliest birth year of participants (1926). These changes have been political, social, and cultural. Therefore, considerations for mitigation of social factors may no longer apply to this region of Finland. However, the condition of the country in 1980 may be socially representative of other regions in the world today. In this case, it is possible that results from this study could have implications on how governments and healthcare organizations respond to these social disparities.

This study was conducted using a very specific population (men from Eastern Finland). Additional research should analyze the associations of these childhood social characteristics with dementia/AD in other populations, specifically women and other ethnic populations. Eastern Finland, especially with the cohort in this study, is fairly genetically homogenous. This makes the results from KIHD studies easier to interpret with regards to genetic influence on health outcomes, but does not give a broad picture of genetic influences on these outcomes.

Retrospective studies always involve the possibility of recall bias in data collection. Participants were asked about certain childhood characteristics when they were already middle-aged or older. However, the nature of many questionnaire items used here (for example, whether or not they moved from Karelia due to the war) do not predispose towards biased answers and are more
factually based. Additionally, there exists no gap in the data or large skew that would imply any sort of selective bias.

6.3. Study Strengths
Research produced through the KIHD study is statistically strong, as it includes a large, population-based cohort that was not clinically selected. Additionally, the analyses presented here control for many covariates and include multiple measures of association between independent variables and dementia/AD outcomes.

Of importance is that the KIHD study is overrepresented in terms of patients who were diagnosed with AD after death. This helps to improve validity of the study. However, the total number of patients with AD is still objectively low in comparison to the total KIHD study population. Anthropometric and physiological data were obtained from health professionals and health registries, thus decreasing the likelihood of low validity, but the same cannot necessarily be said for retrospectively reporting various childhood characteristics. However, there is no evidence of selective memory loss in any one group of participants and gaps in memory are evenly dispersed. There is no reason to believe that there exists selective distortion of childhood data in this study.

6.4. Suggested Focus of Future Research
Additional research should analyze the associations of these childhood social characteristics with dementia/AD in other populations, specifically women and other ethnic populations. Women were not included in the present analyses because their follow-up times were short in comparison to those of male participants. Analyses of similar associations should be carried out to help determine whether sex mitigates the relationships between childhood social and environmental factors and dementia/AD later in life.

Eastern Finland, especially with the cohort in this study, is genetically homogenous. This makes the results from KIHD studies easier to interpret with regards to genetic influence on health outcomes, but does not give a broad picture of genetic influences on these outcomes. Therefore, future studies should examine other genetically heterogeneous populations. Studying these other
populations may enable greater understanding of the role genetics play in the complex interactions between genes, society, and environment and disease risk.

Finally, as will be discussed further in the following section, more research should examine childhood exposures to risk factors for multiple diseases, not just dementia and AD. Not only should more research be conducted in this area to more fully evaluate and scrutinize the associations examined here, but assessing potential early-life risk factors for other diseases is crucial for developing a greater understanding of life-course epidemiology.

6.5. Potential Policy Implications
Certain childhood social factors play significant roles in future dementia status. Here, we examine associations of childhood stress (including being in custody/orphanage, relocating from Karelia because of World War II, having problems with the teacher, and trauma during childhood) and home environment (living in a strict or quarrelsome home) with late-life dementia, including AD. Based on our findings, discussed in greater detail below, policymakers might speculate as to whether particular school, social, or governmental policies pose a risk to children in their future years. Consequently, it may be recommended that certain areas of policy are adjusted or changed to better meet the long-term health needs of the population.

That being said, this study does not seek to directly change policy, as that would be outside the scope of the proposed project. However, findings from this research may have relevant information and suggestions for alterations to current health and social policy in schools and neighborhoods with potential implications of future dementia avoidance. The degree to which study findings are relevant for such policy advisements and change is at the discretion of policymakers themselves, as well as relevant communities.

6.6. Quality of Life
Dementia, in all forms, has negative impacts on quality of life for both the patients and their caretakers. It also has significant costs for the healthcare industry in any country, which often translates to high governmental and taxpayer costs. As generations continue to grow geriatric and
the proportion of the population considered to be elderly increases, these costs swiftly rise for collective society. Therefore, it is in the best financial, emotional, and physical interest of all parties to avoid dementia when possible.

One study examined predictors of poor quality of life, including depression, apathy, disinhibition, and agitation/aggression, among dementia care-givers and care-receivers (Hoe et al. 2007). Quality of life (QoL) amongst care-receivers was higher when they had fewer poor-QoL predictive symptoms and care-giver QoL rating improved alongside improvements in care-receiver QoL (Hoe et al. 2007). Thus, QoL for care-givers and care-receivers is closely related and improvements to one, particularly that of dementia patients, can potentially improve QoL for their care-givers (Hoe et al. 2007).

In the case of this study, associations of early-life social factors and late-life dementia outcomes are under scrutiny. Findings show that certain “negative” social characteristics, such as the components of our childhood stress index, are associated with dementia. In this situation, addressing these social factors early in life could potentially improve QoL in the future for these individuals, as well as on-going quality. Again, encouraging or overseeing these sorts of changes would be beyond the scope of the current project; this falls under the judgement of families and policymakers.

6.7. Generalization to Other Populations
Finland has changed greatly since the early 1980s, when the KIHD study began, and even more so since the earliest cohort was born (1926). These changes have been political, social, and cultural. Therefore, the considerations for mitigation of social factors may no longer apply to this region of Finland. However, the condition of the country in 1980 may be socially representative of other regions in the world today. In this case, it is possible that results from this study could have implications on how governments and healthcare organizations respond to these social disparities. Analyses would be necessary to determine similarities in economic, social, cultural, political, and environmental circumstances between countries or regions.
Continued analyses should be conducted comparing social characteristics of Finland using KIHD data and characteristics of other developing/developed countries today. If results indicated similarities, then increased generalizations between populations could be made. Following this, recommendations for policy change or interventions in these countries to help reduce future dementia risk in their populations could be beneficial. The latter would be made at the discretion of relevant policymakers.

6.8. Implications of Results in Context of Life-course Epidemiology

With old age as the strongest identified risk factor for all forms of dementia, there may be an implication of senescence-related biological processes in disease risk (Qiu, Kivipelto, & von Strauss 2009). This may reflect an accumulated burden of risk factors across lifespan, supporting a life-course epidemiological approach to dementia and AD etiology as used here (Qiu, Kivipelto, & von Strauss 2009). The likely interaction of social, environmental, and genetic factors on dementia/AD risk underlies the importance of more research in the area of early-life exposure to risk factors, given the larger amount of literature already available pertaining to genetic and mid/late-life risk.
7 CONCLUSIONS

With the ever-growing global burden of dementia and AD, research analyzing associations of these outcomes with social, environmental, behavioral, and other factors is essential for developing a greater understanding of the myriad influences on geriatric illnesses. Here, we were able to determine that childhood stress associates with increased risk of developing dementia, including AD, later in life, while associations with a quarrelsome or strict home indicate the opposite. Biological mechanisms may play a role in the severity of dementia and AD risk as assessed by the childhood stress index. It is possible that similar mechanisms interact to produce the reduced risk associated with a quarrelsome home or strict upbringing. Previous literature supports the association of childhood stress and increased risk of dementia/AD through establishment of associations with individual components of the childhood stress model. While associations of dementia/AD with a quarrelsome home or strict upbringing were not predicted to occur as they did, they do not necessarily contradict previous literature. No studies have examined the specific associations of a quarrelsome home or strict upbringing with long-term, chronic illnesses, including dementia/AD. Those that have examined similar features of upbringing and parenting have often found mixed results. Wording of questions, recall bias, and other factors influencing participant responses could all potentially affect interpretation of these results. In general, the lack of research examining associations of quarrelsome home environment and strict upbringing with health outcomes, specifically with dementia and AD, indicates the need for greater focus on this area in order to draw confident conclusions.

More research is needed to determine the extent of these childhood variable associations with dementia/AD in other samples and using different study designs. Specifically, this research should examine such associations in other global populations, particularly among women and different ethnic and genetic groups. This will allow for a more holistic understanding of the many interactions between early-life social and environmental factors, genetics, and other social and biological factors, and dementia/AD risk. Future studies can also analyze these exposure variables and covariates in the context of other chronic and/or late-life diseases. These life-course epidemiological approaches can help determine the complex ways in which childhood social factors affect dementia and AD risk.
8 ACKNOWLEDGEMENTS

We thank Kimmo Ronkainen, M.Sc., for data management and assistance with statistical analyses, as well as the participants in the KIHD study. Additional thanks go to Dr. Jussi Kauhanen and Dr. Tomi-Pekka Tuomainen for their advisory roles with the study and to Dr. Eija Lönnroos, who, in cooperation with Dr. Kauhanen, served as the examiner for this thesis.
9 REFERENCES


Chen YC, Chen TF, Yip PK, Hu CY, Chu YM, Chen JH. Body mass index (BMI) at an early age and the risk of dementia. Archives of Gerontology and Geriatrics 2010: Supplement 1, 50.


Jancin B. Midlife CV risk factors boost risk of dementia: hypertension, hypercholesterolemia, and diabetes each increased the risk of getting dementia 27 years later. Internal Medicine News 2004; 21.


National Institute on Aging; National Institute of Neurological Disorders and Stroke (U.S.); National Institutes of Health (U.S.). Lewy body dementia: information for patients, families, and professional. Bethesda, Maryland: National Institutes of Health 2015.


Ylilauri MPT, Voutilainen S, Lönnroos E, Mursu J, Virtanen HEK, Koskinen TT, Salonen JT, Tuomainen TP, Virtanen JK. Association of dietary cholesterol and egg intakes with the risk of incident dementia or Alzheimer disease: the Kuopio Ischemic Heart Disease Risk Factor Study.