CHILDHOOD MALTREATMENT AS A SOCIAL DETERMINANT OF MIDLIFE HEALTH-RELATED QUALITY OF LIFE IN WOMEN: DO PSYCHOSOCIAL FACTORS EXPLAIN THIS ASSOCIATION?

by

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ABSTRACT

Background: Few studies have assessed the life-course impact of childhood maltreatment (CM) on the midlife health-related quality of life (HRQoL) or quality-adjusted life years (QALY) over time in women. In three papers, we evaluated 1) if CM is associated with lower midlife HRQoL at one point in time and with midlife HRQoL/QALY over a 9-year follow-up; and 2) if these associations are explained by potential adulthood psychosocial mediators. **Methods:** We used data from a community sample of 443 women enrolled in the Pittsburgh site of the longitudinal Study of Women's Health Across the Nation-Mental Health Study (SWAN-MHS) in 1996-97. The analyses included 342 women who completed Childhood Trauma Questionnaire and at least one Short Form-36 (SF-36) from 2002-12. The mental (MCS) and physical (PCS) component scores were two primary outcomes for cross-sectional and longitudinal HRQoL. QALY per year was based on SF-6D generated from SF-36. Generalized estimating equations were used to assess the association between CM and HRQoL/QALY over time. The mediation role of each psychosocial factor in the relationship between CM and HRQoL/QALY over time was investigated by a series of structural nested mean models after accounting for childhood and adulthood confounders. **Results:** Thirty-eight percent reported any CM type and 20% reported multiple CM types. CM was associated with both reduced midlife mental and physical HRQoL with moderate to clinically important effect sizes in women at baseline and over 9 years. Women

with multiple CM types had a clinically meaningful 28.3 fewer healthy days per year than those without CM. In separate mediation analyses, low levels of optimism, time-varying sleep problems, and time-varying low social support partially explained the relation between multiple CM types and HRQoL/QALY over time. **Conclusions:** CM is a life-course social determinant of midlife HRQoL and QALY over time (52-62 years old) in women. The partial mediators are potentially modifiable and could be targets of interventions that could mitigate the negative impact of CM on midlife HRQoL/QALY in women. **Public Health Significance:** It is important to increase the awareness among health professionals that in addition to medical conditions a woman's midlife well-being may be influenced by early adverse experiences.

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PREFACE

This dissertation is submitted for the degree of Doctor of Philosophy at the Department of Epidemiology at the University of Pittsburgh. I conducted this research investigation under the supervision of Dr. Joyce T. Bromberger and with the guidance from four committee members: Dr. Ashley I. Naimi, Dr. Maria M. Brooks, Dr. Gale A. Richardson, and Dr. Jessica G. Burke between 2015 and 2017. I developed the research hypotheses, performed the statistical analyses as well as wrote the entire dissertation independently. Dr. Joyce Bromberger reviewed, edited, and provided valuable feedback and comments for the entire dissertation to improve the focus and the clarity of the research investigation. Dr. Ashley I. Naimi provided knowledge for statistical analyses, particularly mediation analyses, and programming support. Dr. Maria M. Brooks provided inputs for statistical analyses and interpretation of findings. Dr. Gale A. Richardson reviewed and made helpful suggestions for the drafts in each milestone exam. Dr. Jessica G. Burke provided inputs to address the implications of our study findings in the community settings. This dissertation should be of interest to researchers, health professionals, and policymakers to advance research and increase our ability to mitigate the negative impact of early adverse exposures on later health-related quality.

This research was in part of the The Study of Women's Health Across the Nation (SWAN) which has grant support from the National Institutes of Health (NIH), DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR) and

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1.0 INTRODUCTION

1.1 OVERVIEW AND RATIONALE

Health-related quality of life (HRQoL) is a vital multidimensional measure of health that encompasses physical functioning, general health, physical symptoms, role functioning, social functioning, and well-being. The importance of HRQoL has increased in recent years because health is recognized not just as the absence of disease or disability but the totality of functioning and resilience (WHO, 1948). The impact of a specific illness on domains of HRQoL is not fixed and generally varies from person to person and over time (Fayers & Machin, 2016). This is because although HRQoL reflects aspects of life most likely to be affected by changes in health status, it is also affected by other factors, including psychological status and characteristics of the environment such as stress, socioeconomic status, and social supports (Naughton et al., 2016). Another important potential contributor to adult impaired HRQoL is early adverse childhood circumstances and toxic stressors, such as chronic maltreatment, child abuse or neglect which have been associated with long-term physical and mental health. However, little is known about the effects of early adverse childhood exposures on health-related quality of life in adulthood. Advancing knowledge of the multiple proximal and distal determinants, specifically childhood maltreatment, of adult HRQoL is important to inform effective interventions and prevent or minimize disability and impairment, particularly in an aging nation. Indeed, improvement of

HRQoL was identified as a central public health goal in *Healthy People 2000, 2010, and 2020* (CDC, 2000).

A systematic review of 19 cross-sectional studies primarily clinical found a robust relationship between childhood maltreatment and lower HRQoL with effect sizes ranging from small to moderate in children and adults. However, more community or population studies and longitudinal studies are needed to increase the generalizability of study results and assess the causal role of CM on HRQoL over time and the pathways between them. Possible risk factors or protective factors (e.g. medical conditions, marital status, childhood family SES, optimism levels) for decreased HRQoL should be taken into account. Although childhood maltreatment is prevalent in western societies, research on the overall well-being of childhood maltreated survivors is still relatively sparse (Weber, Jud, & Landolt, 2016).

This dissertation will address the limitations of our knowledge about the influence of early childhood exposures to adversity on HRQoL in adulthood using data collected in the Study of Women's Health Across the Nation (SWAN), a multi-site, community-based, longitudinal study of menopause and aging in midlife women. Additional data were obtained from a SWAN ancillary study conducted in Pittsburgh, PA, the Mental Health Study (MHS). The latter collected information on psychiatric disorders and multiple aspects of mental health including a measure of childhood maltreatment. Details of the SWAN are described in Section 3.0.

Our study can help identify: 1) if early exposure to childhood maltreatment is related to reduced subjective well-being, life functioning, and quality-adjusted survival in adulthood; 2) if a particular type of childhood maltreatment is most salient to the HRQoL among middle-aged women. The overall goal of our proposal is to increase understanding of the impact of childhood maltreatment on HRQoL in women at midlife. The effect modifiers or mediators identified in our

analyses for the relationship of childhood maltreatment with HRQoL can be targeted for future intervention studies. Early intervention for childhood maltreated female survivors may be beneficial for healthy aging. The QALY estimation results from our study can be used as one of the references for prioritizing management or interventions for maltreated female victims in the U.S.

1.2 BACKGROUND

1.2.1 Health-Related Quality of Life (HRQoL)

1.2.1.1 What is HRQoL and why is it important?

The World Health Organization (WHO) stated that health is "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity* (WHO, 1948)." As stated above, HRQoL measures aim to capture these multidimensional aspects of health perceived by individuals. HRQoL measures generally include aspects of health such as physical functioning, general health, physical symptoms, role functioning, emotional functioning, and social functioning.

Studying HRQoL over time is important to increase understanding of the interrelationships among physical health, mental health, and HRQoL, as well as the influence of early life adverse exposures on these health outcomes. In addition to the traditional measures of mortality and morbidity, such knowledge can inform clinical practice, social service, and health policy (CDC, 2000). Knowledge of factors that affect HRQoL can guide relevant interventions to help individuals to cope better.

1.2.1.2 Types of HRQoL instruments

This dissertation will focus on two types of HRQoL: *health profiles and quality-adjusted survival calculated by a health index* (i.e. *utility weights*). The first type is a generic measure of HRQoL that assesses individuals' subjective health profiles in specific domains of health such as physical health, mental health, and social functioning (Fayers &Machin, 2016). We will ascertain such profiles with the 36-item Medical Outcomes Study Short-Form Health Survey (SF-36). The SF-36 is comprised of eight subscales which can be used to generate two summary scores [e.g. Mental Component Score (MCS) and Physical Component Score (PCS)], both of which have good validity in predicting utilization of health care services and five-year mortality rates (Ware &Kosinski, 2001). MCS and PCS are calculated by standardizing each of the eight SF-36 scales using a z-score transformation, computing an aggregate component score from weighted z-scores, and then transforming the aggregate score to a norm-based score with a mean of 50 and standard deviation of 10 in the 1998 general U.S. population (McHorney, Ware, &Raczek, 1993). Table 1-1 shows the summary description of each SF-36 subdomain (Ware, 2002). The MCS and the PCS will be used to indicate the two dimensions of HRQoL health profiles in this dissertation.

The second type of HRQoL we will investigate is called quality-adjusted life years (QALY). QALY is determined using *health index* (*i.e. utility weights*). A validated scoring algorithm developed by Brazier et al. can derive a Short Form-6 Dimensions (SF-6D) health index from a subset of SF-36 items (Table 1-2) (Brazier, Roberts, &Deverill, 2002; Brazier, Usherwood, Harper, &Thomas, 1998). A health index reflects the proportion of the health-related functioning limitation influenced by an individual's perception of the impact of diseases or conditions. A health index is anchored at 1.0 indicating good health and at 0 that is equivalent

to death. The SF-6D allows researchers to generate QALY for estimations of lifetime losses in quality of life (Brazier et al., 1998; Corso, Edwards, Fang, &Mercy, 2008). For example, a health index of 0.6 indicates an individual will have an estimated 0.6 year of QALY (equivalent to 219 days) in good health per year of life (i.e. quality-adjusted life years). Said another way, this individual will be expected to experience 0.4 years (146 days) with health-related functioning limitations or disability per year. Investigating if the decreased quality-adjusted survival is associated with early exposure to childhood maltreatment is one of the important aims of the present study.

In summary, health profiles illustrate an individual's perception of the impact of specific domains of health (i.e. PCS and MCS), while QALY can further provide a single summary index of expected good HRQoL per year of life and can be used as one of the references for prioritizing management or interventions.

Table 1-1 Summary information of SF-36 scales.

Scales	Items*	Lowest Possible Score	Highest Possible Score
Physical Functioning (PF)	10	Very limited in performing all physical activities, including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role-Physical (RP)	4	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities
Bodily Pain (BP)	2	Very severe and extremely limiting pain	No pain or no limitations due to pain
General Health (GH)	5	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality (VT)	4	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
Social Functioning (SF)	2	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems
Role-Emotional (RE)	3	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities
Mental Health (MH)	5	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Physical Component Summary (PCS)	35	Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated “poor”	No physical limitations, disabilities, or decrements in well-being, high energy level, health rated excellent”
Mental Component Summary (MCS)	35	Frequent psychological distress, social and role disability due to emotional problems, health rated “poor”	Frequent positive affect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated “excellent”

Adapted from Ware, 2000.

*All but one of the 36 items (self-reported health transition) are used to score the eight SF-36 scales.

Table 1-2 Summary information of SF-6D scales.

Level	Physical functioning	Role limitations	Social functioning	Pain	Mental health	Vitality
	SF-36 Item 3, 4, and 12	SF-36 Item 15 and 18	SF-36 Item 32	SF-36 Item 21 and 22	SF-36 Item 24 and 28	SF-36 Item 27
1	Your health does not limit you in *vigorous activities*	You have no problems with your work or other regular daily activities as a result of your physical health or any emotional problems	Your health limits your social activities none of the time	You have no pain	You feel tense or downhearted and low none of the time	You have a lot of energy all of the time
2	Your health limits you in *vigorous activities*	You are limited in the kind of work or other activates as a result of your *physical health*	Your health limits your social activities a little of the time	You have pain but it does not interfere with your normal work (both outside the home and housework)	You feel tense or downhearted and low a little of the time	You have a lot of energy most of the time
3	Your health limits you a little in *moderate activities*	You accomplish less than you would like as a result of *emotional problems*	Your health limits your social activities some of the time	You have pain that interferes with your normal work (both outside the home and housework) a little bit	You feel tense or downhearted and low some of the time	You have a lot of energy some of the time
4	Your health limits you a lot in *moderate activities*	You are limited in the kind of work or other activities as a result of your *physical health* and accomplish less than you would like as a result of *emotional problems*	Your health limits your social activities most of the time	You have pain that interferes with your normal work (both outside the home and housework) moderately	You feel tense or downhearted and low most of the time	You have a lot of energy a little of the time
5	Your health limits you a little in *bathing and dressing*		Your health limits your social activities all of the time	You have pain that interferes with your normal work (both outside the home and housework) quite a lot	You feel tense or downhearted and low all of the time	You have a lot of energy none of the time
6	Your health limits you a lot in *bathing and dressing*			You have pain that interferes with your normal work (both outside the home and housework) extremely		

Adapted from Brazier, Roberts, &Deverill, 2002.

1.2.1.3 Characteristics associated with HRQoL in aging women

Age

The United States normative SF-36 average scores are lower for women than men (Ware, 2000; Ware, Snow, Kosinski, &Gandek, 1993). In a review of three longitudinal studies measuring HRQoL over time in healthy populations in UK and Canada, women consistently reported lower scores across SF-36 subdomains compared with men (Obidoa, Reisine, &Cherniack, 2010). In the U.K. Whitehall II study of British civil servants with a mean of 36 months (range 23-59 months) follow-up, the largest mean change (adjusted for baseline score) in SF-36 scores per year of follow-up among women aged 50 to 54 years was seen in physical role limitations (-8.8), and emotional role functioning (-5.8), while the smallest mean change was seen in general mental health (-1.6) and vitality (-2.5). Improved mean change in SF-36 scores per year was observed among women more than 55 years old for general mental health (0.6) and vitality (1.1) (Hemingway, Stafford, Stansfeld, Shipley, &Marmot, 1997).

Changes in SF-36 scores over 5 years by age groups are the largest in midlife women (35-54 years) for both physical health and mental health. Over time, the physical component scores (PCS) decrease while the mental component scores (MCS) increase in midlife women (Hemingway et al., 1997; Hopman et al., 2004, 2006; Obidoa et al., 2010). The U.S. general population norm-based SF-36 scores also show a pattern of similar changes with decreased physical health HRQoL and slightly improved mental health HRQoL among older female groups compared to younger women (Ware, 2000; Ware et al., 1993).

Race/Ethnicity

African-American and Hispanic women reported greater limitations in bodily pain and social functioning than Whites. In contrast, African-American women reported better HRQoL in vitality and role emotional compared to Whites (Ylitalo et al., 2013). A Women's Health Initiative (WHI) cohort of women aged 80 and older also found that African-American women self-rated better general health compared to non-Hispanic White women (Naughton et al., 2016). However, the differences in HRQoL by racial/ethnic groups could be explained by important covariates such as sociodemographics, socioeconomic status, health, lifestyle, and social circumstances (Avis & Colvin, 2007).

Health-related quality of life and social-psychological factors

Naughton et al. (2016) suggested that social-psychological and current health variables were more strongly associated with a global HRQoL score than medical conditions in a Women's Health Initiative (WHI) cohort of women aged 80 and older (Naughton et al., 2016). Midlife women who were physically active had higher average scores of HRQoL (Dugan et al., 2009). Women who had higher BMI or were current smokers had greater limitations in physical functioning than those who had normal BMI or were not a current smoker (Ylitalo et al., 2013). Menopausal status had little impact on HRQoL among midlife women after adjusting for vasomotor symptoms and other psychosocial covariates (Avis et al., 2003, 2009; Avis, Assmann, Kravitz, Ganz, &Ory, 2004). Women who were married, had a college degree or higher, low financial strain, higher social support, lower perceived stress, fewer upsetting events, and lower depressive symptom scores had higher average scores of HRQoL than their counterparts (Avis et al., 2009; Naughton et al., 2016; Ylitalo et al., 2013). A higher level of optimism was significantly associated with better HRQoL in a study of 1529 patients (men and women)

hospitalized for chronic diseases after 6 months (Kepka et al., 2013). In a meta-analysis of 11 studies (DuBois et al., 2015), positive psychological constructs (e.g. optimism, positive affect, hope, etc.) were significantly associated with lower rates of rehospitalization or mortality in a pooled adjusted analysis with an odds ratio (95% CI) of 0.89 (0.84, 091). Higher depressive symptoms are negatively correlated with the mental component scores but not the physical component scores in women with a first myocardial infarction (White &Groh, 2007). Lower cognitive function scores are significantly associated with lower physical functioning scores over a 4-year follow-up period in SWAN midlife women (n=2,405) (Ford et al., 2010). Sleep disturbances are also found to be significantly associated with lower quality of life in midlife women in a community sample (n=112) (Greenblum, Rowe, Neff, &Greenblum, 2013).

Early life experiences

There has been a growing interest in examining if early life exposure to adversities in psychosocial and physical environments influence the biological and psychosocial developmental processes from childhood to adult life (Blane, Higgs, Hyde, &Wiggins, 2004; Braveman &Barclay, 2009; Geoffroy, Hertzman, Li, &Power, 2013; Greenfield, 2010; Trotta, Murray, &Fisher, 2015). The accumulation of disadvantages over the life course in girls may lead to physical diseases, mental disorders, damaging health behaviors, and poor overall well-being as they age. It is biologically plausible to hypothesize that childhood adverse environmental exposures leave enduring biological imprints on the body and shape individual behaviors during the sensitive developmental stages (Kuh &Hardy, 2002).

Longitudinal studies can help us better understand the natural history of HRQoL in adult women and identify life course risk factors that are associated with reduced HRQoL. The

identified modifiable factors can be targeted for interventions starting in midlife women as well as early in life to support the process of healthy aging.

1.2.2 Childhood Maltreatment (CM)

1.2.2.1 Epidemiology of CM

Child maltreatment (CM) is a serious public health and social welfare problem in the United States and worldwide. U.S. Child Protective Services reported approximately 686,000 children (9.2 per 1000) were identified as victims of maltreatment in 2012 and over 1,640 children died from maltreatment in the U.S.(2.2 per 100,000 children) (U.S. Administration for Children and Families, 2013), with 155,000 child deaths worldwide each year (Pinheiro, 2006). Due to underreporting and lack of uniform definitions of CM across states, health agency data often underestimate the actual prevalence of CM. Based on a self-reported national survey in 2011, 1 in 10 U.S. children experienced at least one type of CM in the past year (Finkelhor, Turner, Shattuck, &Hamby, 2013).

Child maltreatment includes *"any act or serial acts of commission (child abuse) or omission (child neglect) by caregivers that lead to harm, potential harm, or threats of harm to a child"* (U.S. Administration for Children and Families, 2013). Child abuse includes physical abuse, sexual abuse, and emotional abuse. Child neglect involves failure to provide a child's basic physical or emotional needs including food, housing, clothing, education, and access to medical care (U.S. Administration for Children and Families, 2013).

Among maltreated children less than 18 years old, primary types of maltreatment were child neglect (60%), physical abuse (10%), emotional abuse (11%), sexual abuse (7%), and multiple types (12%) based on the U.S. Administration for Child and Family report in 2012

(Leeb, Paulozzi, Melanson, Simon, &Arias, 2008; U.S. Administration for Children and Families, 2013). In the U.S., 80.3% of substantiated cases of CM were perpetrated by parents, followed by relatives (6.1%), and unmarried partners (4.2%). Fifty-four percent of perpetrators were women (Leeb et al., 2008).

In the U.S., physical abuse and sexual abuse have been decreasing in the past 10 years (22% and 40% decrease in victim numbers, respectively), while the estimated number of neglected children more than doubled from 1993 to 2006 (Sedlak et al., 2010). A similar trend was observed in England (Department for Children Schools and Family, 2008). Studies have shown that child neglect has the same long-term consequences as physical or sexual abuse; however, it has received less public and scientific attention (Gilbert et al., 2009).

1.2.2.2 Socioeconomic burden of CM

The estimated lifetime cost is $210,012 for one nonfatal victim in 2010 dollars. The costs include childhood health care, child welfare, adult medical care, productivity losses, special education, and criminal justice (Fang, Brown, Florence, &Mercy, 2012). Overall, CM is estimated to cost $124 billion in the US each year (Fang et al., 2012). The estimated socioeconomic burden of CM is comparable to or larger than many other substantial public health problems. For example, obesity beginning at age 20 has estimated lifetime costs between $5,580 and $30,770, depending on sex and race (Finkelstein et al., 2008). Because the aging population in the United States also presents challenges to policy makers and health care programs (Ortman, Velkoff, &Hogan, 2014), more comprehensive studies investigating childhood maltreatment and related adulthood health outcomes are needed. Such knowledge can help reach at-risk midlife populations and better assist in allocating clinical and community resources (i.e., behavioral and mental health care services, or social support).

1.2.2.3 Characteristics of CM victims

Age

Based on a 2014 Childhood Maltreatment report published by the Children's Bureau of the U.S. Department of Health and Human Services, the rates of victimization and fatality are the highest among children less than one year and decrease after and through teenagers (U.S. Administration for Children and Families, 2016). The lifetime prevalence of any maltreatment by caregivers is approximately 41% among youth aged 14-17 years old based on US national survey in 2011 (Finkelhor et al., 2013). In a 2010 U.S. health survey, 37.6% of a midlife population age 50+ reported any adverse childhood experiences (Brown, Thacker, &Cohen, 2013).

Sex

The rates of victimization were higher in girls (9.8 per 1000) than boys (9.0 per 1000) in the U.S. in 2014 (U.S. Administration for Children and Families, 2016). In high-income countries, girls have a greater risk of being sexually abused, while the rates for other types of CM are similar in both sexes. In low-income countries, girls are more likely to be the victims of sexual abuse, neglect, and infanticide, while boys have a greater risk of harsh physical punishment (Pinheiro, 2006). In the U.S., females are also more likely to experience sexual abuse than males: lifetime prevalence 17.4% versus 4.2% (Finkelhor et al., 2013).

Race/ethnicity

In the context of race/ethnicity, the incidence of victimization per 1,000 children in 2013 was 14.6 for African Americans, followed by 12.5 for American Indian/Alaska Natives, 10.6 for multiracial individuals, 8.5 for Hispanics, 8.1 for non-Hispanic Whites, and 1.7 for Asians (U.S. Administration for Children and Families, 2013). The decrease in incidence rates of CM from

1993 to the 2005–2006 study year was not the same for all races and ethnicities (NIS-3). The incidence of physical abuse decreased among white children but increased among Black and Hispanic children. Moreover, the incidence of emotional neglect increased less among White children than it did among Black and Hispanic children (Sedlak et al., 2010).

Disability

Some studies have shown that children with disabilities have a higher risk of being maltreated, especially with physical abuse and sexual abuse (Jones et al., 2012). A study by Sullivan and Knutson (2000) showed the cumulative prevalence of any maltreatment was 31% among disabled children as compared to 9% among non-disabled children, and a quarter of maltreated children in this study had a disability. However, there is insufficient evidence to conclude if the disability is a cause or consequence of maltreatment, which leaves gaps in knowledge that need to be addressed (Jones et al., 2012).

Family and community environment

According to the NIH-4 report, the incidence of CM differs by several characteristics of the children's family. Children with no parent in the labor force, and those living in low socioeconomic status households, in a single parent household and a live-in partner, in large families with 4 or more children, or in rural counties had higher rates of CM compared to their counterparts (Sedlak et al., 2010). Mackenzie et al. (2011) suggested several family characteristics that are associated with higher rates of CM in a sample of 842 mother-infant dyads with 16 years of follow-up: low maternal education, maternal abuse history, social services, low household income, and etc. (Kotch et al., 1995; Kotch, Browne, Dufort, &Winsor, 1999). It is challenging to determine if the aforementioned risk factors are causally related to the

incidence of CM since the majority of these risk factors are inextricably clustered (Gilbert et al., 2009).

1.2.2.4 CM as a life-course social determinant of adult health

A growing body of evidence has suggested that child abuse and neglect experiences can affect an individual's health and function well beyond childhood and into adulthood (Braveman &Barclay, 2009; Gilbert et al., 2009; Greenfield, 2010; Shonkoff &Garner, 2012). Childhood maltreatment has been conceptualized as a life course social determinant of adult health in both public health and clinical settings. The life-course perspective of social health disparities beginning in childhood has drawn a large amount of attention for research questions that cannot be answered by simply focusing on exposures occurring proximal to the health outcomes (Braveman &Barclay, 2009).

CM and education, employment, and delinquency

CM is significantly associated with low educational achievement, low skilled employment, and criminal behaviors in adolescents. Adults with CM are at a high risk of having neurodevelopmental and cognitive difficulties as well as social development problems resulting in learning difficulties and barriers to higher education. Lower educational attainment translates into fewer career opportunities and a lower income potential in adulthood (Anda et al., 2006; Bremner &Vaccarino, 2015; Gilbert et al., 2009; Perry &Pollard, 1998; Weiss, Longhurst, &Mazure, 1999).

CM and behavioral and mental health problems

A systematic review (Gilbert et al., 2009) of more than 40 studies from cohort and cross-sectional studies, as well as review papers, has shown strong relationships of CM with several health risk behaviors and mental health disturbances at different life stages, including substance abuse, smoking, alcoholism, multiple sexual partners, depressed affect, and suicide attempts. Post-traumatic stress disorder, eating disorders, and depression among adolescents, adults, and middle-aged populations have also been associated with childhood maltreatment (Gilbert et al., 2009; Greenfield, 2010).

CM and physical health outcomes

The link between CM and physical health outcomes is still not clear. Based on the current literature, childhood maltreatment is related to the following physical health problems. 1) Type 2 diabetes—one systematic review indicated that child neglect had a stronger association with Type 2 diabetes (pooled odds ratio=1.92; 95%CI= 1.43-2.57) than other CM types (Huang et al., 2015). 2) Sleep disorders—a review suggested adults with CM history compared to those without had higher odds (OR range: 1.7-3.7) of sleep disorders (Kajeepeta, Gelaye, Jackson, &Williams, 2015). 3) Neurological and musculoskeletal problems: A meta-analytic review of 24 studies reported the largest effect sizes for the relationship of childhood maltreatment with adulthood physical health outcomes were for neurological (i.e. migraines) and musculoskeletal (i.e. arthritis, broken bones) problems, followed by respiratory problems, cardiovascular disease, and metabolic disorders. However, 22 of 24 studies in this meta-analytic review were about effects for child sexual abuse. The health impact of the most prevalent form of CM, child neglect, was not investigated in most studies. The literature also tends to ignore the sequelae of cumulative abuse types (Wegman &Stetler, 2009). CM was also found to be associated with

vasomotor symptoms (Thurston et al., 2008), obesity and central adiposity (Midei, Matthews, &Bromberger, 2010), incident metabolic syndrome (Midei, Matthews, Chang, &Bromberger, 2013), subclinical cardiovascular disease (Thurston et al., 2016), and elevated levels of C-reactive protein (Matthews, Chang, Thurston, &Bromberger, 2014).

1.2.2.5 Plausible biological explanation of the impact of CM on health

CM experience is a form of toxic stress, which leads to strong, frequent, and prolonged activation of the body's stress response system and brain functions. There has been a surge of scientific evidence of altered brain structure, activity, and functioning among victims of child abuse and neglect that may link it to later physical and emotional health. There is evidence of the following (Center on the Developing Child at Harvard University, 2011; Child Welfare Information Gateway, 2015; McCrory, DeBrito, &Viding, 2010; Shonkoff &Garner, 2012; Wilson, Hansen, &Li, 2011):

1) Reduced volume in the hippocampus, which is responsible for learning and memory, and reduced capacity of the hippocampus to recover the cortisol levels back to normal

2) Decreased volume of the corpus callosum, which is the center for interhemispheric communication and the processes for cognitive function, emotion, and arousal

3) Reduced volume in the cerebellum, which coordinates motor behavior and executive functioning

4) Smaller prefrontal cortex, which is crucial for cognition, emotion, and behavior regulation, particularly observed in children with severe neglect. Physically abused children also had reduced volume in the orbitofrontal cortex, which is responsible for emotional and social regulation.

5) Over-activity in the amygdala, which helps determine if a stimulus is threatening and triggers emotional responses

6) Cortisol levels may be low or high depending on maltreatment types. Lower morning cortisol levels were observed in children with severe physical neglect, which may lead to decreased energy resources affecting learning and socialization, externalizing disorders, and increased vulnerability to autoimmune diseases. In contrast, children with more severe emotional maltreatment had higher morning cortisol levels, which could lead to adverse effects on cognitive processes and subdue immune and inflammatory reactions. Specific forms of maltreatment seem to have differential effects on the hypothalamic-pituitary-adrenocortical (HPA) system (Center on the Developing Child at Harvard University, 2011; McCrory et al., 2010; Shonkoff &Garner, 2012; Wilson et al., 2011).

1.2.2.6 CM and HRQoL

A handful of research studies found that maltreated adolescents had impaired physical and emotional HRQoL (Agorastos et al., 2014; Jud, Landolt, Tatalias, Lach, &Lips, 2013; Lanier, Kohl, Raghavan, &Auslander, 2015; Seiler et al., 2015). The extent to which CM influences midlife health-related quality of life (HRQoL) is not clear as only two studies in the Netherlands (Afifi et al., 2007; Cuijpers et al., 2011) and one study in the USA (Rikhye et al., 2008) have evaluated this association in community or population samples (Weber et al., 2016). The majority of the previous studies were based on clinical or health insured samples, results of which are less generalizable than are those of community or population samples (Bonomi, Cannon, Anderson, Rivara, &Thompson, 2008; Corso et al., 2008; Dickinson, DeGruy, Dickinson, &Candib, 1999; Draper et al., 2008; Evren et al., 2011; Walker et al., 1999).

Furthermore, the question of how childhood maltreatment may be linked to midlife HRQoL still remains unclear.

As noted above, a systematic review of 19 cross-sectional studies of primarily clinical samples found a relationship between childhood maltreatment and lower HRQoL with effect sizes ranging from small to moderate in children and adults. Six out of the 19 studies investigated specific types of CM. For the mental HRQoL scores, the effect sizes were moderate for neglect (Cohen's d= -0.5, number of studies n=1), moderate for emotional abuse (d= -0.46, n=1), small to moderate for physical abuse (d= -0.1 to 0.47, n=3), and small to moderate for sexual abuse (d=-0.2 to -0.36, n=5). For the physical HRQoL scores, the effect size was small for neglect (d= -0.14, n=1), moderate for emotional abuse (d= -0.25, n=1), small for physical abuse (d= -0.2, n=3), and small to moderate for sexual abuse (d= -0.14 to -0.37, n=4). The meta-analysis also found a dose-response relationship between the total number of CM types and HRQoL in adult populations. Weber et al. highlighted limitations and suggestions for future work in this research field. Of particular relevance for the current dissertation are the following: 1) the results for specific types are limited because only 5 studies examined each type; 2) more community or population studies are needed to increase the generalizability of study results; 3) longitudinal studies are needed to assess the causal role of CM on HRQoL over time; 4) total numbers of CM types and severity of CM should be assessed thoroughly; 5) the relation between child neglect and HRQoL needs to be further examined; 6) possible risk factors or protective factors (e.g. medical conditions, marital status, childhood family SES, optimism) for decreased HRQoL should be taken into account; and 7) mental disorders should be considered as mediators, not confounders, and should be evaluated with appropriate analytic approaches.

Although childhood maltreatment is prevalent in western societies, research on the overall well-being of childhood maltreated survivors is still relatively sparse (Weber et al., 2016).

1.2.2.7 Why focus on maltreated female survivors?

Women are more susceptible to the adverse effects of child abuse and neglect than men. Not only are the rates of victimization higher in girls (9.8 per 1000) than boys (9.0 per 1000) (U.S. Administration for Children and Families, 2016), but physical abuse or sexual abuse are robust predictors of female but not male violent offenses (Hubbard &Pratt, 2002). The association between childhood abuse and adulthood substance use problems is also greater among maltreated females (Simpson &Miller, 2002). Female adult survivors are more vulnerable to the substantial burden of long-lasting mental health problems resulting from abuse or neglect than males due to several potential processes: 1) females are more likely to have intense feeling of self-blame for being the victims of violence; 2) women tend to respond to negative emotion through rumination; 3) females are at higher risk of being sexually abused which has been posited as a risk factor for adult health; and 4) women may have higher susceptibility to neuroendocrinological adverse effects resulting from traumatic experiences (Cutler &Nolen-Hoeksema, 1991; Greenfield, 2010; Weiss et al., 1999). Furthermore, mothers with adverse childhood experiences are less likely to provide stable and supportive relationships and environments for their children compared to mothers who grew up without adverse experiences, which results in an intergenerational cycle of adversity (Braveman &Barclay, 2009).

1.3 SPECIFIC AIMS FOR THREE PAPERS

SWAN is a community-based study with comprehensive demographic, life behavioral, physical, and mental health measures, and HRQoL assessment. The Mental Health ancillary study also included a measure of childhood maltreatment, which provided a unique opportunity for investigators to examine if CM is related to several health outcomes in midlife women. A research gap still exists in knowledge about the effect of CM on certain health outcomes across the lifespan among female survivors, including HRQoL and QALY. Identifying potential risk or protective effect modifiers and mediators of the relationship of child abuse and neglect with HRQoL or QALY can inform future intervention studies for maltreated female victims. We will examine if early exposure to childhood maltreatment is an important risk factor contributing to disparities in HRQoL and to identify effect modifiers and mediators of this relationship, within the SWAN-MHS cohort. Our three papers aim to:

Paper 1: Examine if early-life exposure to childhood maltreatment is associated with lower midlife physical and mental health-related quality of life (HRQoL) at visit 6 or visit 8 (for women who did not complete SF-36 at visit 6) in SWAN-MHS. In addition, we investigate if this association differs by race. Next, we evaluate hypothesized psychosocial mediators (e.g., lifetime psychiatric history, depressive symptoms, sleep problems, very upsetting life events, or low social support) at visit 6 or visit 8 in the relation between childhood maltreatment and HRQoL.

Paper 2: Investigate the relationship between childhood maltreatment and midlife physical and mental HRQoL over 9 years in SWAN-MHS. In addition, we investigate if this association differs by race. Furthermore, we determine if potential time-fixed psychosocial factors (e.g. lifetime psychiatric history, lifetime post-traumatic stress disorder, low levels of optimism) or time-varying psychosocial factors (e.g. depressive symptoms, sleep problems, very upsetting life

events, low social support) explain the relationship between childhood maltreatment and reduced midlife HRQoL over a 9-year period.

Paper 3: Evaluate whether early-life exposure to childhood maltreatment is associated with the lower quality-adjusted life years (QALY) over a 9-year period in SWAN-MHS. In addition, we investigate if this association differs by race. Furthermore, we determine if potential time-fixed psychosocial factors (e.g. lifetime psychiatric history, lifetime post-traumatic stress disorder, low levels of optimism) or time-varying psychosocial factors (e.g. depressive symptoms, sleep problems, very upsetting life events, low social support) explain the relationship between childhood maltreatment and lower QALY over a 9-year period.

1.4 STUDY POPULATION

In the current study, we seek to address the limitations in the previous literature using data collected from the 443 Black and White women who were recruited into the Pittsburgh site of SWAN study in 1996-97 and also participated in the Mental Health ancillary study (SWAN-MHS). SWAN is a multi-site, community-based, cohort study that aimed to investigate middle-aged women's mental and physical health during the transition to menopause and aging. Women recruited at the screening stage in 7 cities in the United States were eligible to participate in the longitudinal study starting in 1996 if they met the inclusion criteria: 42 to 52 years old, with at least one menstrual period in the previous three months, not currently using exogenous hormone preparations affecting ovarian function, no surgical removal of the uterus and/or both ovaries, not pregnant, and not breastfeeding.

Each site of SWAN was required to recruit approximately 450 women with white women and a prespecified minority group of women (African American, Hispanic, Japanese, or Chinese). Details of the study design of SWAN have been described in a previous paper (Sowers et al., 2000). In Pittsburgh 463 Black and White women were recruited into SWAN, and 443 women also participated in the Mental Health ancillary study (SWAN-MHS). Women were followed annually to provide biological specimens and to complete extensive questionnaires about physical, psychosocial, lifestyle, and psychological factors. As part of the SWAN-MHS, women also completed the Structural Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders (SCID) (Spitzer, Williams, Gibbon, &First, 1992) at baseline and within three months of each follow-up visit. The study protocol and all the instruments of SWAN core and MHS were approved by the University of Pittsburgh Institutional Review Board, and all participants provided written informed consent at each follow-up visit. We refer to the SWAN baseline visit as "the study entry" and visit 6 as "the analysis baseline" hereafter. Table 1-3 lists the main predictors, outcomes, effect modifiers, mediators, and confounders. Figure 1-1 shows the analytic diagram of the present investigation and the following Figure 1-2 shows the study flow chart with available SF-36 outcomes at visit 6, 8, 10, 12, and 13.

Table 1-3 List of variables included in the research investigation.

Variables	Study Entry 1996-1997 42-52 years	Other Visits	Visit 6 2002-2003 48-58 years	Visit 8 2004-2005 50-60 years	Visit 10 2006-2007 52-62 years	Visit 12 2010-2011 55-65 years	Visit 13 2011-2012 57-67 years
X: Independent variables Childhood maltreatment (CM)				X			
Y: Dependent variables-HRQoL							
SF-36 Mental Component Score			X	X	X	X	X
SF-36 Physical Component Score			X	X	X	X	X
SF-6D Health Index			X	X	X	X	X
M: Psychosocial mediators							
Lifetime psychiatric history			X				
Lifetime Post-Traumatic Stress Disorder						X	
Optimism		V1					
Depressive symptoms			X	X	X	X	X
Sleep problems			X	X	X	X	X
Very upsetting life events			X	X	X	X	X
Social support			X	X	X	X	X
C_{XY}: Confounders for CM and HRQoL							
Race/Ethnicity	X						
Age			X	X	X	X	X
Father's Education		V7					
Mother's Education		V7					
Childhood family owned a car		V7					
Childhood family owned a home		V7					
Childhood family ever received public assistance		V7					
Childhood family ever had difficulty paying for food or rent		V7					
L_{MY}: Confounders for psychosocial mediators and HRQoL							
Educational attainment	X						
Marital Status			X				
Adulthood financial strain			X	X	X	X	X
Smoking			X	X	X	X	X
Alcohol use			X	X	X	X	X
Physical activities			X	X	X	X	X
Body Mass Index			X	X	X	X	X
# Medical conditions			X	X	X	X	X
Menopausal status			X	X	X	X	X
Hormone therapy use			X	X	X	X	X
Vasomotor symptoms			X	X	X	X	X
Lifetime medication for emotional problems			X				
Trait anxiety		V7					
Trait anger		V7					

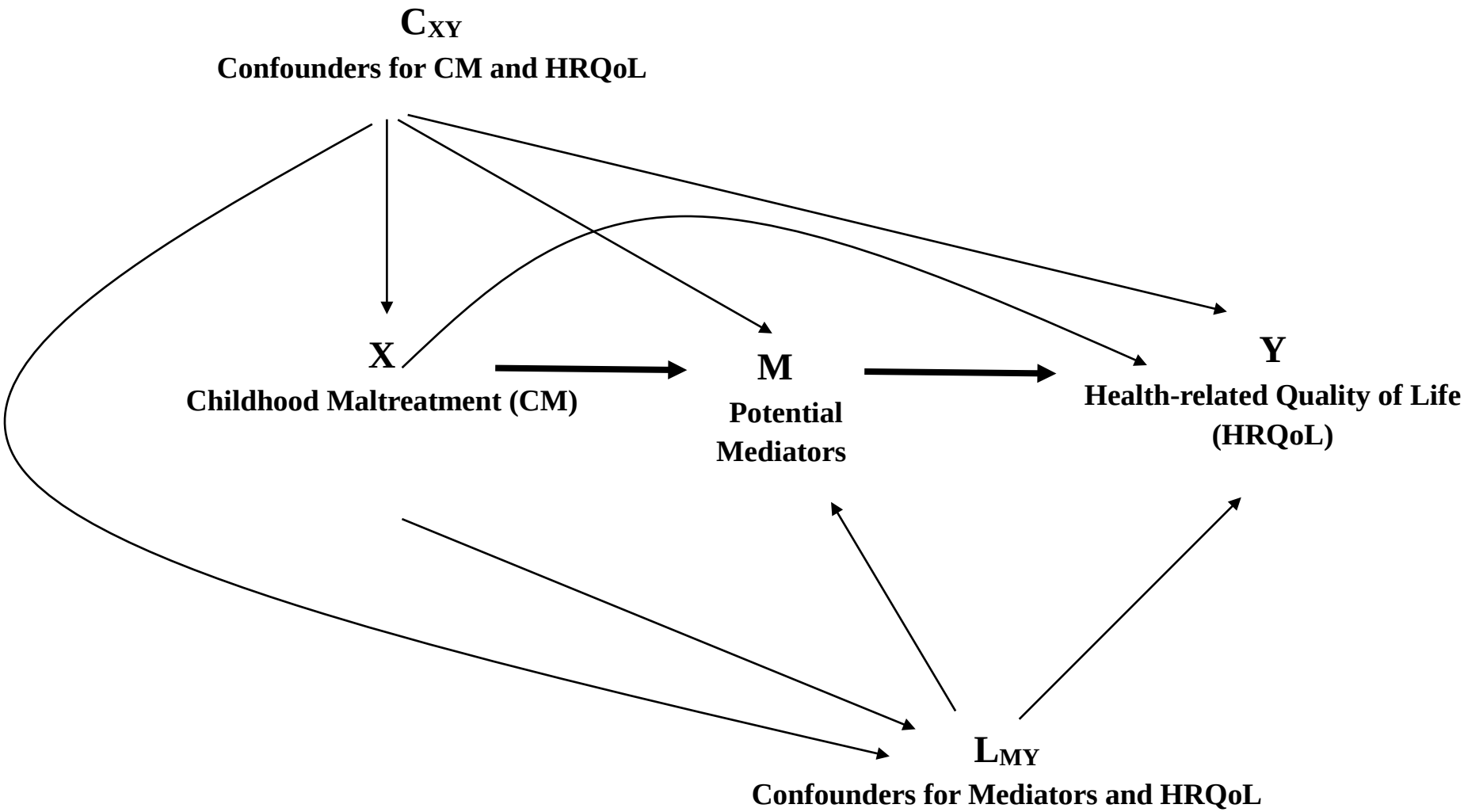

Figure 1-1 Analytic diagram of the research investigation.

The relationship between childhood maltreatment (X), potential psychosocial mediators (M), and HRQoL outcomes (Y). Mediator-outcome confounders (L_{MY}) are associated with the early-life exposure X.

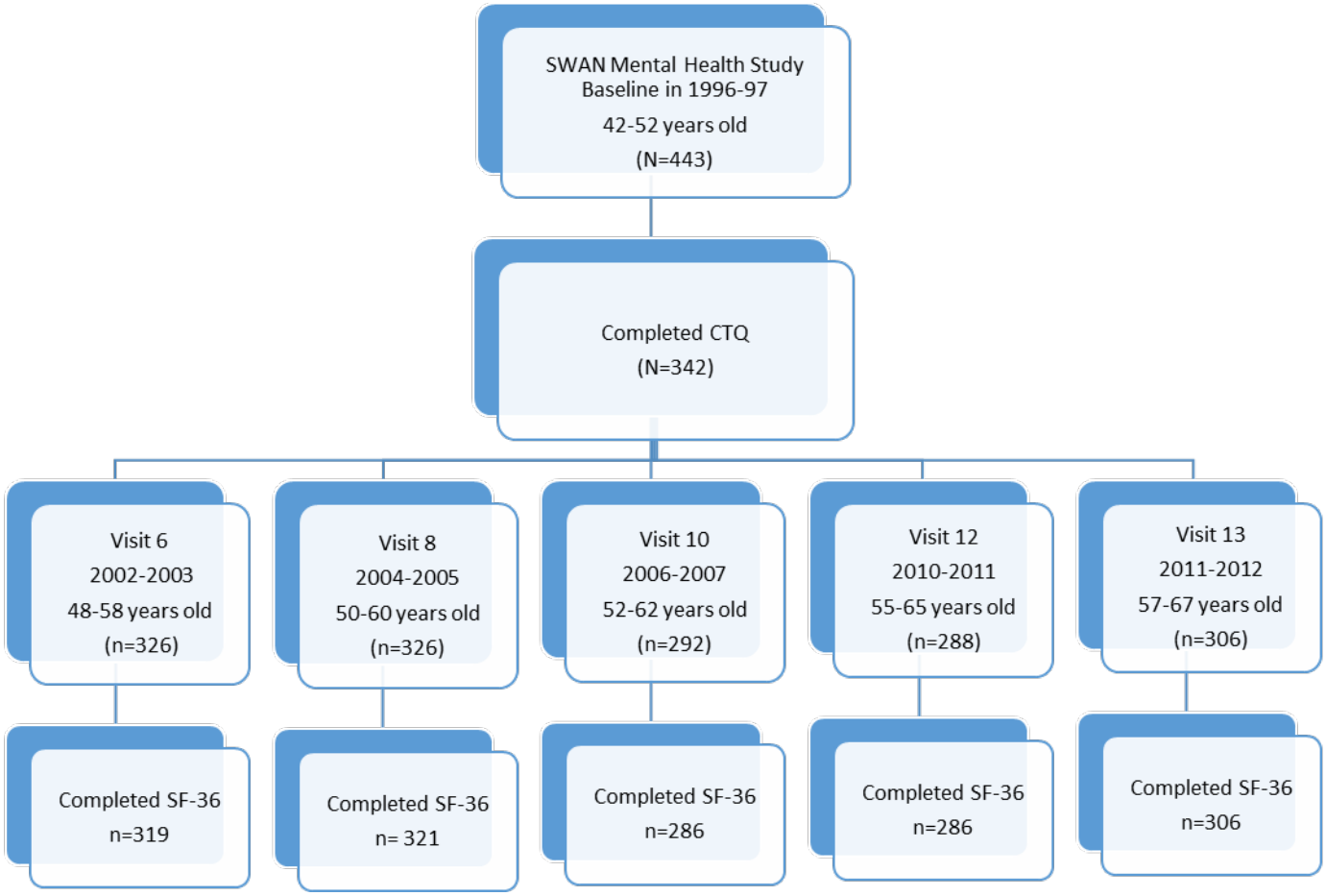

Figure 1-2 Study flow chart of the research investigation.

CTQ: Childhood Trauma Questionnaire, SF-36: Short Form-36 was completed at visit 6, 8, 10, 12, and 13.

2.0 PAPER 1: CM AND MIDLIFE HRQOL (BASELINE ANALYSIS)

Childhood maltreatment as a social determinant of midlife health-related quality of life in women: Do psychosocial factors explain this association?

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Keywords: childhood maltreatment, abuse and neglect, health-related quality of life, SF-36, mediation analysis, g-estimation, structural nested mean model

Abbreviations

CM: Childhood Maltreatment

HRQoL: Health-Related Quality of Life

SWAN-MHS: The Study of Women's Health Across Nation-Mental Health Study

SNMM: Structural nested mean model

2.1 ABSTRACT

We examined if childhood maltreatment (CM) is associated with worse health-related quality of life (HRQoL) in midlife women and if the association is mediated by psychosocial factors. A total of 443 women were enrolled in the Pittsburgh site of the longitudinal Study of Women's Health Across the Nation-Mental Health Study. Generalized linear regression was used to assess the association between CM and two HRQoL component scores. Structural nested mean models were used to evaluate the extent to which each psychosocial factor (lifetime psychiatric history, depressive symptoms, sleep problems, very upsetting life events, low social support) explained the association. Thirty-eight percent of women reported CM. The mean mental (MCS) and physical (PCS) component scores were 2.3 points (95%CI: -4.3, -0.3) and 2.5 points (95%CI: -4.5, -0.6) lower in women with CM than those without, respectively. In separate mediation analyses, depressive symptoms, very upsetting life events, or low social support, reduced these differences in MCS, but not PCS. CM is a life-course social determinant of midlife HRQoL in women. The relationship between CM and MCS was partially explained by psychosocial mediators. It is important to increase the awareness among health professionals that a woman’s midlife well-being may be influenced by early life adversity.

2.2 INTRODUCTION

Health-related quality of life (HRQoL) is a multidimensional evaluation of physical, emotional, and social/role functioning (Fayers & Machin, 2016), and it is an important outcome in the evaluation of disability and disease progression. Although HRQoL typically reflects aspects of life most likely to be affected by changes in health status, it is also related to psychosocial status and characteristics of the environment such as stress, financial strain, and social supports, and may be influenced by distal factors like childhood maltreatment (CM), which includes abuse or neglect experienced before 18 years old. CM has been viewed as a life-course social determinant of adult health with substantial socioeconomic cost (Greenfield, 2010). Importantly, previous studies showed female adult survivors are more vulnerable to the long-lasting burden of mental health problems from abuse or neglect than males (Cutler & Nolen-Hoeksema, 1991; Weiss, Longhurst, & Mazure, 1999).

It is not clear whether CM is associated with midlife HRQoL in general populations. Two studies from the Netherlands (Afifi et al., 2007; Cuijpers et al., 2011) and the USA (Rikhye et al., 2008) identified negative associations between CM and HRQoL in community or population samples (Weber, Jud, & Landolt, 2016). Most research to date is based on clinical or health insured samples (Bonomi, Cannon, Anderson, Rivara, & Thompson, 2008; Corso, Edwards, Fang, & Mercy, 2008; Dickinson, deGruy, Dickinson, & Candib, 1999; Draper et al., 2008; Evren et al., 2011; Walker et al., 1999), which may limit generalizability. Furthermore, studies assessing the impact of CM on HRQoL often used standard regression methods to adjust for the potential confounding of adult psychosocial factors (Afifi et al., 2007; Agorastos et al., 2014;

Aversa, Lemmer, Nunnink, McLay, & Baker, 2014; Dickinson et al., 1999; Draper et al., 2008; Rikhye et al., 2008). However, when measured in adulthood such factors may instead be mediators of the relation between CM and HRQoL. Appropriate analytic approaches are required to quantify the controlled direct association between CM and midlife HRQoL after accounting for mediator-outcome confounders that are affected by CM exposure (Vanderweele, Vansteelandt, & Robins, 2014).

We sought to address the limitations in the previous literature using extensive demographic, behavioral, and HRQoL data collected from a community-based cohort of 443 women recruited into the Pittsburgh site of the Study of Women's Health Across Nation. First, we assessed if women with CM have worse midlife HRQoL than women without CM and if this is the case both for black and for white women. Next, we evaluated whether psychosocial factors previously shown to be associated with CM (lifetime psychiatric history, depressive symptoms, sleep problems, very upsetting life events, or low social support) individually explained the relationship between CM and two dimensions of HRQoL: mental component score (MCS) and physical component score (PCS).

2.3 METHODS

Study population

We used data from the Study of Women's Health Across the Nation (SWAN), a multi-site, community-based, cohort study that aimed to investigate middle-aged women's mental and physical health during the transition through menopause. A detailed explanation of the SWAN study design is available elsewhere (Sowers et al., 2000). Eligible women recruited in the U.S. between 1996-97 were: 42 to 52 years, with at least one menstrual period in the previous three months, not currently using exogenous hormones, no surgical removal of the uterus and/or both ovaries, not pregnant, and not breastfeeding. Our investigation is based on 443 women who also participated in the Mental Health ancillary study (MHS) at the Pittsburgh site. In addition to extensive questionnaires on physical, psychosocial, lifestyle, and psychological characteristics, women in SWAN-MHS also completed the Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders (SCID) (Spitzer, Williams, Gibbon, & First, 1992) at baseline and each annual follow-up visit. The study was approved by the University of Pittsburgh Institutional Review Board. For inclusion in the current analysis, completion of the full Medical Outcomes Survey Short Form 36 (SF-36) at Visit 6 (six years after the study entry, 2002-2003) or Visit 8 (2004-2005) and completion of the Childhood Trauma Questionnaire (CTQ) at Visit 8 were required.

Measures

Exposure (X): *Childhood maltreatment* before 18 years old was retrospectively ascertained by the Childhood Trauma Questionnaire (CTQ) at Visit 8 (Bernstein et al., 2003). Items were summed to derive scores on five types of CM. The summed scores were classified as scoring positive for each type of childhood maltreatment using previously validated clinical cut-offs as follows: emotional abuse (≥10), physical abuse (≥8), sexual abuse (≥8), physical neglect (≥8), and emotional neglect (≥15) (Bernstein et al., 2003; Walker et al., 1999). The CTQ has high test-retest reliability and strong convergent validity with therapists' ratings and clinical interviews (Bernstein et al., 1994). CM types above these clinical cutoffs were counted to indicate the total number of CM types ranging from 1 to 5. Women with CTQ scores below all clinical cutpoints were classified as non-maltreated. Exposure to different types of CM was also combined into 5 mutually exclusive CM subgroups: 1) emotional abuse and/ or physical abuse, 2) emotional neglect and/ or physical neglect, 3) sexual abuse only, 4) abuse and neglect, and 5) sexual abuse along with other CM types.

Outcome (Y): *Midlife HRQoL* was assessed by the SF-36, a generic measure of health profiles in physical health, mental health, and social functioning (Ware, Snow, Kosinski, & Gandek, 1993) at the visit 6 (or 8 if not completed at visit 6). The SF-36 includes eight subdomains and two component T-scores: mental component score (MCS) and physical component score (PCS). MCS and PCS were calculated by standardizing each of the eight SF-36 scales using a z-score transformation, computing an aggregate component score from weighted z-scores, and then transforming the aggregate score to a norm-based score with a mean of 50 and standard deviation of 10 in the 1998 general U.S. population (Ware et al., 1993). Higher scores indicate better

mental or physical health status. MCS or PCS below 50 is considered below the average in the general U.S. population.

Mediators (M): Data for all psychosocial mediators were from Visit 6 or 8. *Lifetime and current psychiatric history* were initially diagnosed at study entry and past year and current at each follow-up by trained mental health clinicians using the SCID (Spitzer et al., 1992), with very good reliability for lifetime depressive and anxiety disorders (kappa=0.81-0.82) (Bromberger et al., 2011). In the current study, lifetime psychiatric disorders were defined as occurring up to Visit 6 or 8 for any of the following disorders: major depression; minor depression; any anxiety disorder; alcohol use disorder, abuse or dependence; and non-alcohol use disorder, abuse or dependence. *Depressive symptoms* were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D) at baseline and each follow-up visit. The CES-D is a widely used measure of depressive symptom levels with well-established reliability, and a cut-off score ≥ 16 is used as an indicator of potential clinical depression (Radloff, 1977). *Sleep problem was self-reported by w*omen and was defined as having at least three nights of at least one of three sleep problems in each of the past two weeks. *Very upsetting life events* were assessed by the Psychiatric Epidemiology Research Interview scale (Dohrenwend, Askenasy, Krasnoff, & Dohrenwend, 1978), modified to include events relevant to midlife women or those living in low socioeconomic environments. “Very upsetting” or “very upsetting and still upsetting” life events since the last study visit were totaled and categorized as 1 or more versus none. *Instrumental and emotional social support* were assessed by the Medical Outcomes Study Social Support Survey (Sherbourne & Stewart, 1991). Participants were asked how often each of four kinds of support (two emotional and two instrumental) is available when they need it. The total score ranged from

0 to 16. A score below the 25th percentile (<12) was defined as low social support since a standard cut-point is not available and the distribution of scores is highly skewed.

Exposure-outcome confounders (C_{XY}) include age, race/ethnicity, and childhood SES. Childhood SES before 19 years old was self-reported at Visit 7, including maternal and paternal education, and childhood financial circumstances such as family owned a car, a house, or ever received public assistance. Previous work in SWAN has reported that childhood SES measured at two separated visits were highly concordant (Montez, Bromberger, Harlow, Kravitz, & Matthews, 2016).

Mediator-outcome confounders (L_{MY}): L_{MY} confounders were collected at SWAN baseline or the Visit 6/8. Adulthood sociodemographic factors included educational attainment, marital status, and adulthood financial strain (i.e., difficulty paying for basics as somewhat hard or very hard). Lifestyle behavioral variables (current smoking, weekly alcohol consumption, physical activity) and body mass index (BMI) (kg/m^2) were included as confounders. The number of lifetime medical conditions were summed from the questionnaire inquiring about 12 pre-specified medical conditions and was categorized as 0, 1 and 2 or more. Menopausal status at the time of the midlife HRQoL assessment was categorized based on menstrual bleeding patterns in the previous 12 months (WHO, 1996). The presence of vasomotor symptoms (hot flashes, night sweats) in the past two weeks, was ascertained as part of a symptom checklist. Ever use of hormone therapy since the SWAN baseline and lifetime treatment for emotional problems were self-reported. Trait anger and anxiety were assessed by the Spielberger Trait Anger and Anxiety Scales (Spielberger & Reheiser, 2009).

Statistical analysis

Variable values were compared between those with and without any CM exposure using Kruskal-Wallis tests for continuous variables and Chi-square tests for categorical variables. To calculate the effect sizes for group differences, we used the reference norm SD=9.47 for MCS and SD=10.82 for PCS from the normative U.S. population of women ages 45-54 years (Ware &Kosinski, 2001). Effect sizes were calculated as group differences in HRQoL scores divided by SD_{norm} (Yost, Haan, Levine, &Gold, 2005). We defined group differences in MCS or PCS with effect sizes <0.2 as small and not clinically meaningful, effect sizes 0.2-0.5 as moderate and potentially meaningful, and effect sizes >0.5 as large and clinically meaningful (Cohen, 1977).

Analytic diagram (**Figure 2-1**) illustrates the relationship between childhood maltreatment (X), potential psychosocial mediators (M), midlife HRQoL outcomes (Y), exposure-outcome confounders (C_{XY}), mediator-outcome confounders (L_{MY}), and other potential unmeasured confounders (U). Age at baseline, race/ethnicity, and childhood socioeconomic circumstances (SES) were considered as a vector of C_{XY} confounders between CM and HRQoL. Race/ethnicity was also considered as a potential effect modifier between CM and HRQoL. A vector of adulthood confounders (L_{MY}) of the association between mediators and HRQoL outcomes included education, marital status, financial strain, lifestyle behaviors, BMI, the number of lifetime medical conditions, menopausal status, vasomotor symptoms, use of exogenous hormones, trait anger and anxiety, and lifetime treatment for emotional problems. Due to the long-term effect of CM, several factors among the adulthood confounders (i.e. education, financial strain, lifestyle behaviors, BMI, trait anger and anxiety, treatment for emotional problems) are associated with CM and could be considered as exposure-induced mediator-outcome confounders (Vanderweele et al., 2014).

Overall associations between CM and HRQoL were assessed by generalized linear models adjusting for age, race, and childhood SES. We evaluated CM in several different ways in separate models: any CM (maltreated versus non-maltreated) as the main predictor, five types of CM not mutually exclusive, a total number of CM (0, 1, 2 and more), and mutually exclusive combined CM subgroups. To assess whether the relationship between CM and HRQoL was the same for blacks and whites, the product of any CM and race and the products of each CM type and race were added in separate main effect models. Due to the small sample size in the current analysis, we did not have sufficient power to detect the significance of effect modification or confidence intervals. We defined effect modification as present if the magnitude of the beta coefficient of CM on HRQoL was changed by more than ± 2 points after adding the interaction product term to the outcome model. Two points difference of HRQoL was determined by the meaningful moderate effect size (ES=0.2) times the standard deviation (SD=10) of MCS and PCS (i.e. moderate effect size*SD=0.2*10=2).

Mediation analysis: We used structural nested mean models (SNMM) estimated via doubly robust g-estimation to quantify the controlled direct association: the extent to which CM would be associated with HRQoL if each mediator were set to a specific value uniformly in the population. This approach properly accounts for confounding due to C_{XY} and L_{MY}, as depicted in Figure 1 (Naimi, Schnitzer, Moodie, & Bodnar, 2016).

$$E[Y(m=0)|X=1] - E[Y(m=0)|X=0] = \psi$$

SNMMs were used to estimate the extent to which a psychosocial mediator explained the relation between any CM and HRQoL in the following steps 2 to 4. We repeated models from [2] to [4] to regress each HRQoL outcome model (i.e. MCS and PCS) against each psychosocial mediator separately with any CM as the main exposure. X denotes any CM, M denotes high

depressive symptoms (1 vs 0) as the mediator, and Y denotes MCS as the outcome to illustrate the following steps.

Step 1: To estimate total association between any CM and MCS

Due to missing data on the L_{MY} confounders, the sample size reduced from 310 to 301 for the mediation analysis. Mediation analysis sample (n=301) did not significantly differ from the original analytic sample (n=338) in terms of age, race, education, marital status, types of childhood maltreatment, and mean scores of MCS and PCS. The total association between any CM and MCS was estimated again in the sample of 301 women by the generalized linear model after adjusting for age, race, and childhood SES:

$$E[Y|X, C_{XY}] = \beta_0 + \psi_0 X + \beta_1' C_{XY}. \qquad [1]$$

The coefficient ψ_0' in model 1 is the total estimated difference in HRQoL scores between maltreated versus non-maltreated women after controlling for C_{XY} confounding.

Step 2: To obtain propensity scores for any CM (exposure) and depressive symptoms (mediator)

First, we obtained the predicted probability (denoted $\hat{p}(X)$) of any CM (X) from a logistic model which included C_{XY} confounders:

$$logit\{E[X|C_{XY}]\} = \theta_0 + \theta' C_{XY}. \qquad [2]$$

Second, we estimated the predicted probability (denoted $\hat{p}(M)$) of the mediator, depressive symptoms, from a logistic model including predictors: exposure of any CM, and confounders $C_{XY,}$ and L_{MY}:

$$logit\{E[m = 1|X, C_{XY}, L_{MY}]\} = \beta_0 + \beta_1' X + \beta_2' C_{XY} + \beta_3' L_{MY}. \qquad [3]$$

Since the predicted probabilities $\hat{p}(X)$ and $\hat{p}(M)$ were included in the following models, this is a doubly-robust version of g-estimation.[cite my paper in AJE, and Daniel and Vansteelandt 2016

Statistics in medicine] The term "doubly-robust" indicates that the controlled direct association (m=0) can be consistently estimated if either (a) the mediator (high depressive symptoms) regression model is correctly specified, (b) the outcome regression models (see below) correctly specified, or both conditions (a and b) hold (Bang & Robins, 2005).

Step 3: To estimate the mediator effect in the structural nested mean model

We regressed MCS outcome (Y) against the high depressive symptoms (mediator), exposure to any CM (exposure), confounders $C_{XY,}$ and L_{MY}, and predicted probability $\hat{p}(X)$ and $\hat{p}(M)$ using least squares regression. Additionally, the product term between any CM and mediator depressive symptoms (X*M) was included in the subsequent model to test if there was X-M interaction effect. Since the magnitude of the beta coefficient of any CM on HRQoL did not change more than ± 2 points after adding the exposure-mediator interaction product term in each outcome model regressed against each mediator, we omitted the interaction term (X*M) from the statistical outcome model:

$$E[Y|M,X,C_{XY},L_{MY}] = \beta_0 + \gamma_1 \ + \beta_1 \ + \beta_2' C_{XY} + \beta_3' L_{MY} + \hat{p}(X) + \hat{p}(M) \qquad [4]$$

The γ_1 in the model 4 gives the desired parameters for the mediator's effect in the structural nested mean model. Next, we created a transformed MCS outcome ($\tilde{Y}$) by subtracting the observed outcome MCS from the product term of estimated γ_1 and the observed mediator (high depressive symptoms= 1 or 0) for each individual:

$\tilde{Y} = Y - \gamma_1$ M ,

where the MCS outcome with mediator effect (high depressive symptoms= 1) is removed.

Figure 2-2 shows the analytic diagrams with a structural transformation of HRQoL outcome $\tilde{Y}$ after the mediator's effect was subtracted from the observed outcome Y in the mediation analysis using a structural nested mean model.

Step 4: To estimate the controlled direct association for any CM on MCS when the effect of high depressive symptoms was removed (m=0):

$$E[Y(m=0)|X=x] - E[Y(m=0)|X=0] = \psi_1 X\,, \qquad [5]$$

where ψ_1 represents the controlled direct association (m=0) when the mediator's effect (high depressive symptoms=1) was removed for a binary exposure X. To estimate the parameter of the interest (ψ_1), the transformed outcome ($\tilde{Y}$) was regressed against the exposure of any CM, $\hat{p}(X)$, and confounders C_{XY} using generalized linear regression:

$$E[\tilde{Y}|X, C_{XY}] = \theta_0 + \psi_1\, X + \hat{p}(X) + \theta' C_{XY}\,, \qquad [6]$$

where ψ_1' is the estimated difference in MCS score between maltreated and non-maltreated women when the mediator's effect was removed for everyone (high depressive symptoms=0 for each individual, i.e. accounting for the mediating role of the mediator). Finally, the proportion of the total association between any CM and HRQoL explained by the mediator (high depressive symptoms) was calculated as:

$$Proportion\,Explained\,(PE)$$

$$= \frac{Overall\ association - \text{Controlled direct association}\ (m=0)}{Overall\ association} \times 100\%$$

Detailed steps of our mediation analysis are illustrated in the Appendix C SAS 9.4 (SAS Institute, Cary NC, USA) was used for statistical analyses.

2.4 RESULTS

Of the 443 participants in SWAN-MHS, 338 women met the two inclusion criteria (**Figure 2-3**) for the current analysis: completion of first full SF-36 at visit 6 or visit 8 and CTQ at visit 8. Mean age was 52 years and 33% of the women in the sample were black (**Table 2-1**). Thirty-eight percent of the participants reported at least one type of CM, before 18 years old. In this study sample, 19% had one type of CM, 15% had 2-3 types, and 5% had 4-5 types. For not mutually exclusive CM types, 21% reported emotional abuse, 18% physical abuse, 16% physical neglect, 15% sexual abuse, and 8% emotional neglect. Based on the mutually exclusive CM experience, 11% of women had emotional and/or physical abuse, 4% emotional and/or physical neglect, 5% sexual abuse, 8% abuse and neglect, and 10% had sexual abuse along with other CM types. A total of 200 (59%) women had a lifetime psychiatric history. High depressive symptoms were observed in 15% of women, sleep problems in 43%, at least one very upsetting life event in 47%, and low social support in 17% (**Table 2-1**).

Mean (SD) midlife HRQoL scores were 51.0 (8.8) for MCS and 51.5 (9.1) for PCS. Both mean MCS and PCS were above the average of the U.S. general population (better health) (John E. Ware et al., 1994). The lowest MCS was reported by women with childhood sexual abuse (mean ± SD: 47.6±10), and the lowest PCS by women with emotional neglect (mean ± SD: 44.8±11.8). When total number of CM types increased, both MCS and PCS mean scores were lower (i.e., 0 vs 1 vs 2+ types: 52.1 vs 51.3 vs 47.4, respectively, for MCS; and 52.2 vs 51.8 vs 48.9, respectively, for PCS). Mean MCS and PCS were both lower than the norm of 50 among women with childhood abuse and neglect or childhood sexual abuse along with other CM types.

The adjusted associations between CM and HRQoL after accounting for age, race, and childhood SES, are shown in **Table 2-2**. Mean MCS was 2.3 points lower (95% CI: -4.3, -0.3) and PCS was 2.5 points lower (95% CI: -4.5, -0.6) in women with any CM compared to those without. MCS was 4.1 points lower (95% CI: -7.3, -1.0) in women with childhood sexual abuse compared to women without childhood sexual abuse. Mean PCS was lower in women with childhood physical abuse [β (95% CI) = -3.8 (-6.9, -0.6)] and childhood emotional neglect [-6.8 (-11.3, -2.4)] than their counterparts. Women with two or more types of CM had lower MCS [-3.6 (-6.4, -0.8)] and PCS [-3.5 (-6.1, -0.8)] than non-maltreated women. Among mutually exclusive CM subtypes, MCS was lower in women with a history of childhood sexual abuse along with other CM types [-5.5 (-9.7, -1.2)] relative to those without any CM. PCS was significantly lower among women with a history of childhood abuse and neglect [-3.1 (-6.1, -0.8)] than non-maltreated women.

Overall, black women had lower MCS [-2.4 (-4.8, -0.02)] and PCS [-1.9 (-4.2, 0.4)] scores than white women, adjusting for any CM, age, and childhood SES. Results for the effect modification by race/ethnicity indicated that the magnitude of physical abuse on PCS differed more than 2 points by racial groups after adding the interaction term. White women with childhood physical abuse reported 5.7 points significantly lower PCS (95% CI: -9.7, -1.7) than white women without childhood physical abuse. PCS was not significantly different in black women with childhood physical abuse [1.0 (-3.1, 5.1)] than black women without childhood physical abuse.

Using SNMM, we evaluated the extent to which each psychosocial mediator explained the relation between CM and HRQoL after adjusting for two sets of confounders C_{XY} and L_{MY} (**Table 2-3**). After accounting for the contribution of psychosocial factors, the difference in MCS

scores between maltreated and non-maltreated women decreased from -2.4 (95% CI: -4.5, -0.4) to -1.6, (95% CI: -3.4, 0.2), -1.9 (95% CI: -3.9, 0.1), or -1.7 (95% CI: -3.8, 0.3) in separate mediation models with high depressive symptoms, very upsetting life events, or low social support, respectively. In contrast, the association between any CM and lower MCS was not greatly affected by lifetime psychiatric history or sleep problems. Psychosocial mediators did not influence the association between CM and PCS.

2.5 DISCUSSION

In this community-based cohort, childhood maltreatment was a robust risk factor for reduced midlife mental and physical HRQoL in women after adjusting for childhood SES variables, race, and age. The association between CM and HRQoL MCS was partially explained by the proximal adulthood psychosocial mediators: depressive symptoms, very upsetting life events, or low social support.

Examination of each type of CM showed childhood sexual abuse had a moderate relationship with lower MCS; childhood physical abuse had a moderate association with lower PCS, and childhood emotional neglect had a strong and clinically meaningful relationship with reduced PCS. Afifi et al. found each type of CM was significantly associated with lower scores in MCS and PCS in a large Dutch population sample of 7,076 males and females (Afifi et al., 2007). However, a large U.S. insurance-based study with men and women found that childhood emotional neglect had the strongest influence on reduced well-being, followed by childhood sexual abuse and childhood physical abuse (Corso et al., 2008). Although these studies did not report results separately for men and women, our results are similar to the previous U.S. findings overall.

Our study confirmed that effect sizes increased as the total number of CM types increased, as reported previously (Afifi et al., 2007; Agorastos et al., 2014; Bonomi et al., 2008; Walker et al., 1999). We also found severe forms of CM types (abuse and neglect, sexual abuse along with other CM types) had moderate to strong associations with reduced PCS and MCS. Studies investigating associations between childhood sexual abuse and HRQoL in women have

reported small to moderate effect sizes ranging from -0.20 to -0.36 (Afifi et al., 2007; Bonomi et al., 2008; Draper et al., 2008; Walker et al., 1999; Weber et al., 2016). We further distinguished the childhood sexual abuse burden on mental HRQoL between sexual abuse only (effect size=-0.25) and sexual abuse along with other CM types (effect size=-0.58). Women with the latter exposures experienced a greater clinical burden on their mental HRQoL.

Plausible mechanisms underlying the relationship between any CM and HRQoL were also investigated in the current study. When accounting for each mediator in separate models, the greatest proportion of the relation between CM and MCS was explained by depressive symptoms (35%), followed by low social support (28%), and very upsetting life events (21%). In contrast, the association between any CM and physical HRQoL was not explained by adult psychosocial factors, but a notable proportion was explained by sleep problems (11%). Interventions targeting these modifiable factors may be beneficial for women to prevent or alleviate the impairment of midlife HRQoL. However, adult psychosocial factors only partially explained the relationship between CM and HRQoL. These findings suggest that childhood maltreatment has a robust and direct association with reduced midlife HRQoL even after adjusting for childhood SES, education, marital status, adult financial strain, and other physical and mental health confounders, emphasizing the importance of interventions earlier in life. There has been a surge of scientific evidence providing both psychosocial and biological explanations for the relationship of child abuse and neglect to reduced quality of interpersonal relationships and self-esteem, increased risk of exposure to life stressors, and altered brain structure, activity, and functioning (Center on the Developing Child at Harvard University 2011; Child Welfare Information Gateway, 2015). The neurobiological alterations associated with CM may affect

stress responses and result in difficulties with emotional regulation of arousing situations, behavioral development, executive functions, and delay of learning (Glaser, 2000).

Several limitations should be mentioned. Childhood maltreatment was assessed retrospectively by the self-report CTQ and the severity or age of CM onset was not assessed. Self-report assessment may potentially result in recall bias and misclassification of the exposure. However, previous evidence showed that the CTQ has high test-retest reliability and strong convergent validity with therapists' ratings and clinical interviews (Bernstein et al., 2003). Adulthood experience of abuse was not assessed and not accounted for in our analyses. Second, our analytic sample was based on data collected at SWAN Visit 6 or Visit 8. Left-truncation bias may exist if the characteristics of the current analysis sample at these visits differ from the cohort at study entry. Women remaining in the current study did not differ substantially from the original sample on age and race/ethnicity but included women were more likely to have a college education or higher, and more likely to be married or living with someone as if married. Third, we did not have sufficient statistical power to examine multiple mediators in one model due to the relatively small analytic sample. However, the controlled direct association of CM on HRQoL accounting for each psychosocial mediator may provide some guidance for targets of future intervention studies to enhance HRQoL in middle-aged women with CM history.

Our study has a number of strengths. First, SWAN-MHS is a community-based cohort sample with better generalizability of results compared with clinical samples. Second, the measurement of CM exposure and HRQoL were assessed by standardized instruments. Third, lifetime psychiatric disorders were ascertained by the SCID, a semi-structured psychiatric interview, which has substantial reliability for lifetime depressive and anxiety disorders (Bromberger et al., 2011). Fourth, mediation analysis was performed by the doubly-robust

structural nested mean model, which is a more general statistical approach requiring less stringent assumptions than the difference or product methods.

In conclusion, childhood maltreatment is a robust social determinant of midlife mental and physical HRQoL in women. Adulthood psychosocial factors (depressive symptoms, very upsetting life events, low social support) partially mediate the association between CM and mental HRQoL. These modifiable factors may be targeted for future intervention studies. Findings from our study provide knowledge to advance research and increase our ability to mitigate the negative impact of early adverse exposures on later HRQoL. It is important to increase the awareness among health professionals that an individual's midlife well-being may be influenced by factors other than medical conditions.

2.6 TABLES AND FIGURES

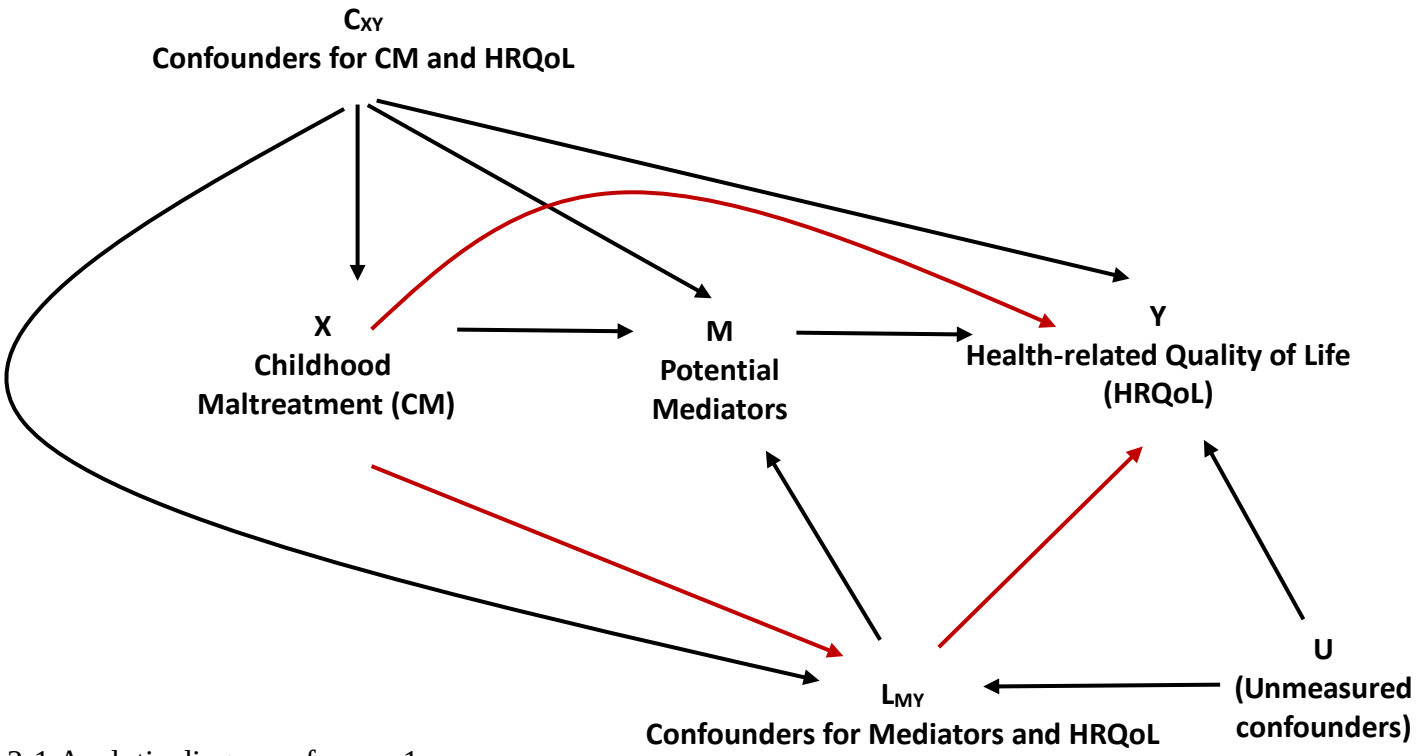

Figure 2-1 Analytic diagram of paper 1.

The relationship between childhood maltreatment (X), potential psychosocial mediators (M), and HRQoL outcomes (Y). Mediator-outcome confounders (L_{MY}) are associated with the early-life exposure X. If conditioning on L_{MY} by standard regression method, collider bias will be induced along the path of $X \rightarrow L_{MY} \leftarrow U \rightarrow Y$, and association of the interest will be blocked through the path of $X \rightarrow L_{MY} \rightarrow Y$. Research of the interest is the extent to which (arrows in red) childhood maltreatment (X) is associated with HRQoL after the mediator's effect is removed.

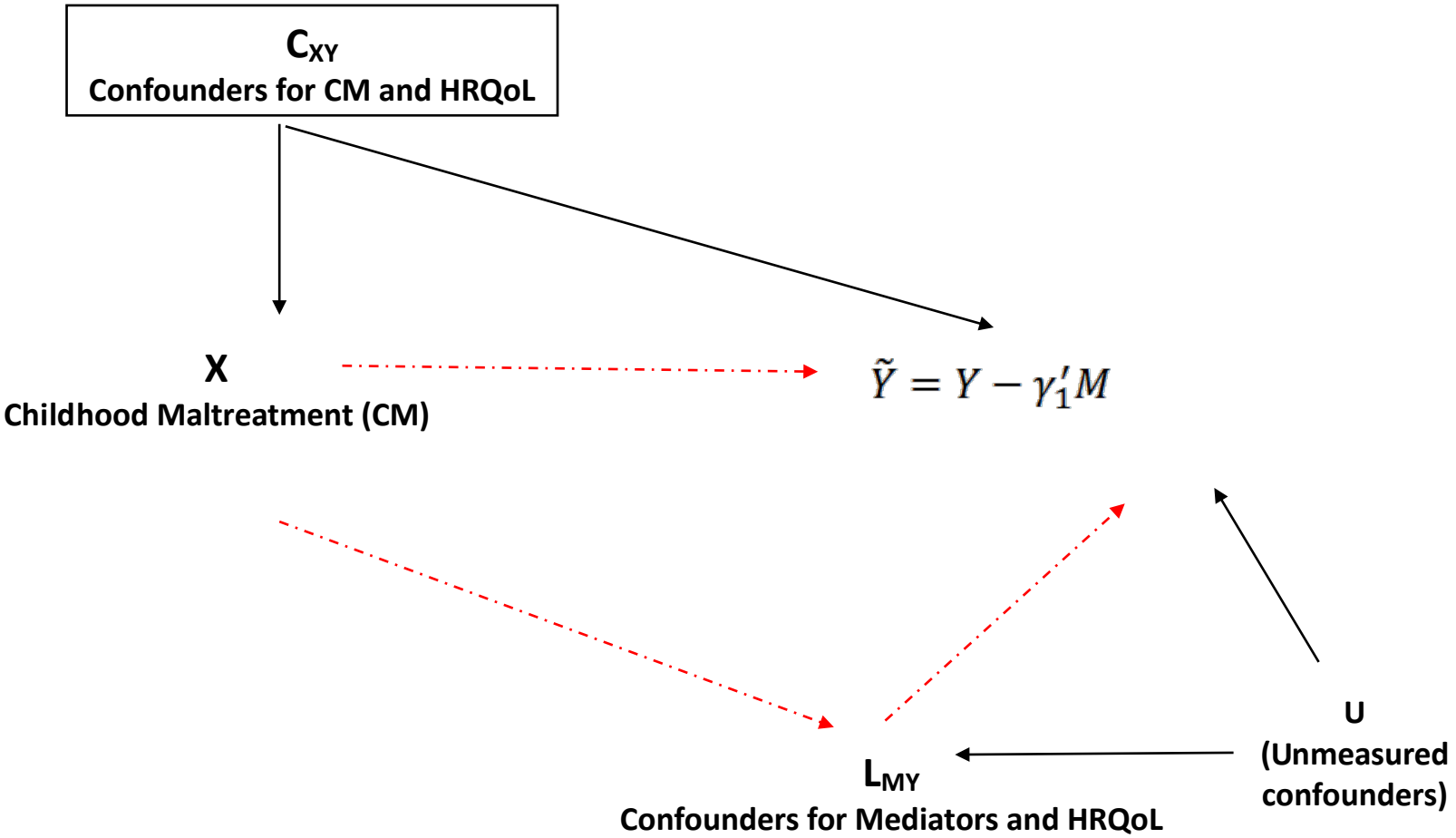

Figure 2-2 Analytic diagrams with a structural transformation of HRQoL outcome.

A structural transformation of HRQoL outcome: the mediator's effect was subtracted from the observed outcome Y in the mediation analysis. A structural nested mean model is used to estimate the controlled direct association between X and transformed outcome when m=0: the extent to which (dashed arrows in red) childhood maltreatment (X) is associated with transformed HRQoL ($\tilde{Y}$).

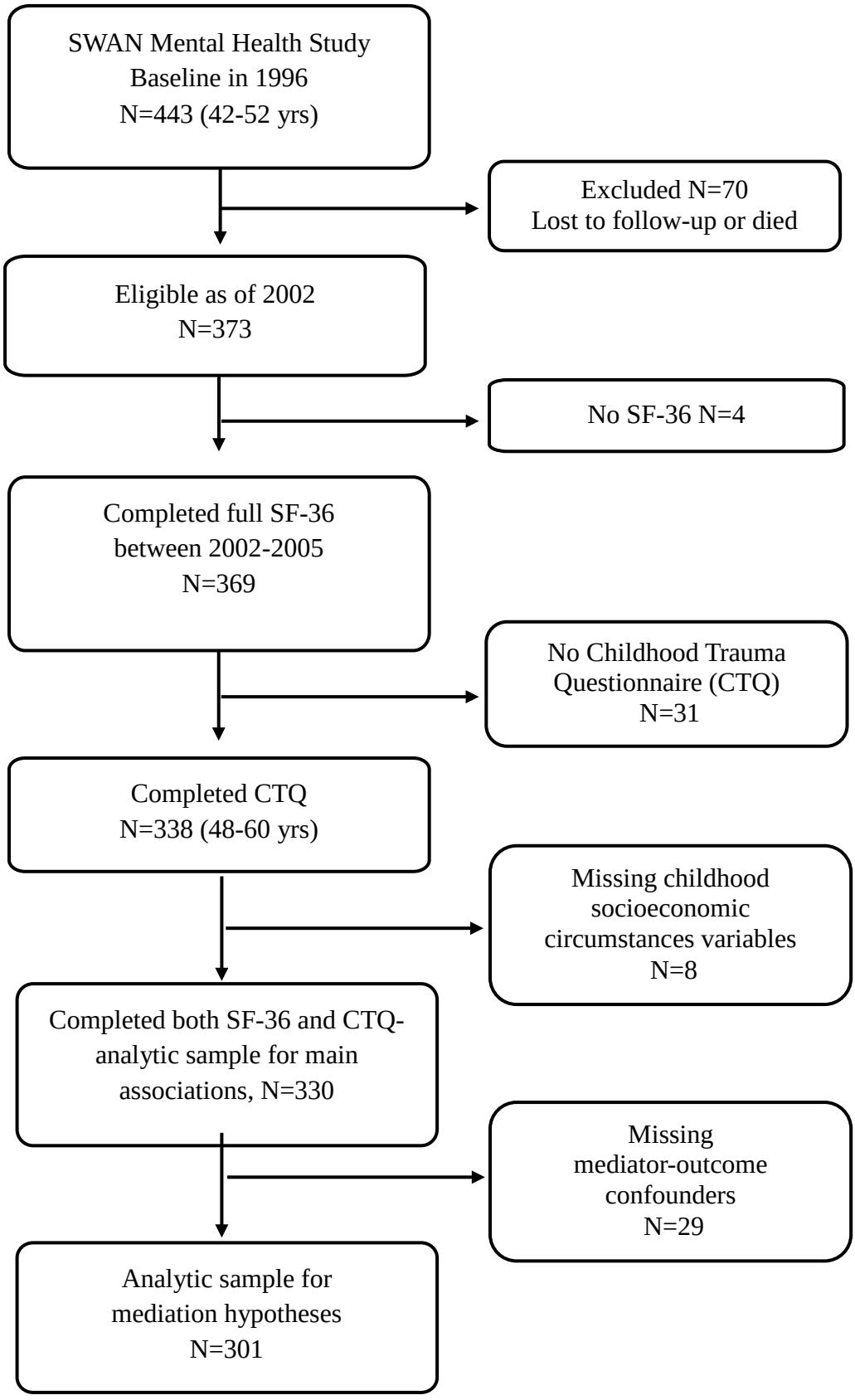

Figure 2-3 Flow diagram of available analytic samples for each hypothesis.

Table 2-1 Characteristics of women by CM exposure in paper 1.

Variables	All N=338	No CM N= 208 (62.5%)	At least one CM N=130 (38.5%)
Exposure-outcome confounders (C_{XY})			
Age at the analysis baseline, Mean (SD)	52.4 (2.6)	52.4 (2.6)	52.3 (2.5)
Median (25^{th}, 75^{th})	52.1 (50.4, 54.3)	52.2 (50.2, 54.3)	51.9 (50.6, 54.2)
Race/Ethnicity			
Black	113 (33)	66 (32)	47 (36)
White	225 (67)	142 (68)	83 (64)
Childhood socioeconomic circumstances			
Maternal Education less than college	261 (78.9)	162 (79.8)	99 (77.3)
Paternal Education less than college	229 (68.8)	145 (70.7)	84 (65.6)
Childhood family…			
…did not own a car	42 (12.5)	26 (12.6)	16 (12.5)
…did not own a home	69 (20.7)	36 (17.5)	33 (25.8)
…ever received public assistance*	51 (15.2)	24 (11.6)	27 (21.1)
…ever had difficulty paying for food or rent**	118 (35.2)	50 (24.2)	68 (53.1)
Exposure: childhood maltreatment (X)			
Total numbers of childhood maltreatment types			
0	208 (61.5)	208 (100.0)	-
1	63 (18.6)	-	63 (48.5)
2	30 (8.9)	-	30 (23.1)
3	19 (5.6)	-	19 (14.6)
4	9 (2.7)	-	9 (6.9)
5	9 (2.7)	-	9 (6.9)
CM types, not mutually exclusive			
Emotional Abuse (≥10)	71 (21.0)	-	71 (54.6)
Physical Abuse (≥8)	60 (17.8)	-	60 (46.2)
Emotional Neglect (≥15)	26 (7.7)	-	26 (20.0)
Physical Neglect (≥8)	53 (15.7)	-	53 (40.8)
Sexual Abuse (≥8)	51 (15.1)	-	51 (39.2)
CM types, mutually exclusive			
No CM	208 (61.5)	208 (100.0)	-
Emotional and/or physical abuse	38 (11.2)	-	38 (29.2)
Emotional and/or physical neglect	15 (4.4)	-	15 (11.5)
Sexual abuse only	16 (4.7)	-	16 (12.3)
Abuse and neglect	26 (7.7)	-	26 (20.0)
Sexual abuse along with other CM types	35 (10.4)	-	35 (26.9)
Potential psychosocial mediators (M)			
Lifetime psychiatric history* (Yes) (i.e., major/minor depression, anxiety disorders, or substance use disorder)	200 (59.3)	114 (55.1)	86 (66.2)
Major/minor depression* (Yes)	160 (47.5)	87 (42.0)	73 (56.2)
Anxiety disorders* (Yes)	76 (22.6)	22 (10.6)	28 (21.5)
Substance use disorder** (Yes)	50 (14.8)	22 (10.6)	28 (21.5)
High depressive symptoms (CES-D ≥16)* (Yes)	50 (15.0)	23 (11.2)	27 (21.1)
Sleep problems (≥ 3 times /week)	142 (42.3)	79 (38.2)	63 (48.8)
Total very upsetting life events** (1+)	159 (47.0)	87 (41.8)	72 (55.4)
Low social support** (Yes)	57 (17.0)	22 (10.7)	35 (26.9)

Table 2-1 Continued			
Mediator-outcome confounders (L_{MY})			
Education attainment less than college	195 (57.7)	128 (61.5)	67 (51.5)
Marital status			
Single	31 (9.2)	17 (8.2)	14 (10.8)
Married or living with someone as if married	240 (71.0)	151 (72.6)	89 (68.5)
Separate/divorced/widowed	67 (19.8)	40 (19.2)	27 (20.8)
Adulthood financial strain- pay for very basics*			
Not hard at all	261 (78.1)	169 (82.4)	92 (71.3)
Somewhat hard	61 (18.3)	31 (15.1)	30 (23.3)
Very hard	12 (3.6)	5 (2.4)	7 (5.4)
Current smoker (Yes)	49 (14.6)	32 (15.6)	17 (13.1)
Weekly alcohol consumption			
None	169 (50.6)	97 (46.9)	72 (56.7)
<2 times	86 (25.7)	58 (28.0)	28 (22.0)
2-7 times	58 (17.4)	39 (18.8)	19 (15.0)
>7 times	21 (6.3)	13 (6.3)	8 (6.3)
Total number of medical conditions			
0	153 (45.5)	98 (47.6)	55 (42.3)
1	98 (29.2)	56 (27.2)	42 (32.3)
2+	85 (25.3)	52 (25.2)	33 (25.4)
Menopausal status			
Premenopausal	14 (4.2)	9 (4.3)	5 (3.8)
Late peri-menopausal or early perimenopausal	129 (38.3)	84 (40.6)	45 (34.6)
Natural postmenopausal	139 (41.2)	83 (40.1)	56 (43.1)
Surgical postmenopausal	30 (8.9)	18 (8.7)	12 (9.2)
Unknown with hormone therapy	25 (7.4)	13 (6.3)	12 (9.2)
Ever use hormone since SWAN study entery* (Yes)	137 (40.7)	75 (36.2)	62 (47.7)
Vasomotor Symptoms			
None	143 (42.7)	95 (46.1)	48 (37.2)
1-5 days/ 2 weeks	116 (34.6)	67 (32.5)	49 (38.0)
≥ 6 days/ 2 weeks	76 (22.7)	44 (21.4)	32 (24.8)
Lifetime medical treatment for emotional problems** (Yes)	70 (20.8)	32 (15.5)	38 (29.2)
Physical activity score excluding work*	7.7 (1.7)	7.8 (1.7)	7.6 (1.7)
Body mass index (kg/m^2)**	30.0 (6.7)	29.1 (6.5)	30.5 (6.8)
Spielberger trait anxiety**	15.2 (4.4)	14.8 (4.5)	15.9 (4.2)
Spielberger trait anger**	14.1 (3.7)	13.5 (3.2)	15.1 (4.3)

N (%) are shown for each level of categorical variables. Mena (standard deviation) is presented for continuous variables.

*$p<0.05$

**$p<0.01$

Table 2-2 Associations between CM and midlife HRQoL.

Models[a]	Childhood Maltreatment		N=330	Mental component score (MCS)		Physical component score (PCS)	
			N (%)	β (95% CI)[b]	Effect Size[c]	β (95% CI)[b]	Effect Size[c]
Model 1	At least one CM	No	202 (61)	reference		reference	
		Yes	128 (39)	-2.29 (-4.29, -0.28)*	-0.24	-2.52 (-4.49, -0.56)*	-0.23
Model 2	Emotional Abuse	No	260 (79)	reference		reference	
		Yes	70 (21)	-2.15 (-4.73, 0.44)	-0.23	-1.22 (-3.63, 1.18)	-0.11
Model 3	Physical Abuse	No	271 (82)	reference		reference	
		Yes	59 (18)	-2.35 (-5.48, 0.77)	-0.25	-3.75 (-6.89, -0.62)*	-0.35
Model 4	Emotional Neglect	No	305 (92)	reference		reference	
		Yes	25 (8)	-1.12 (-4.74, 2.50)	-0.12	-6.85 (-11.26, -2.44)*	-0.63
Model 5	Physical Neglect	No	279 (85)	reference		reference	
		Yes	51 (15)	-0.16 (-2.79, 2.46)	-0.02	-1.66 (-4.16, 0.84)	-0.15
Model 6	Sexual Abuse	No	280 (85)	reference		reference	
		Yes	50 (15)	-4.14 (-7.27, -1.00)*	-0.44	-2.09 (-5.32, 1.15)	-0.19
Model 7	Total number of CM	None	202 (61)	reference		reference	
		1	63 (19)	-1.03 (-3.33, 1.26)	-0.11	-1.60 (-4.11, 0.90)	-0.15
		2+	65 (20)	-3.59 (-6.42, -0.76)*	-0.38	-3.48 (-6.12, -0.84)*	-0.32
Model 8	CM types (mutually exclusive subgroups)	None	202 (61)	reference		reference	
		Emotional and/or physical abuse	38 (12)	-0.29 (-3.13, 2.54)	-0.03	-1.25 (-4.34, 1.84)	-0.12
		Emotional and/or physical neglect	15 (5)	-1.21 (-5.14, 2.72)	-0.13	-3.68 (-7.63, 0.27)	-0.34
		Sexual abuse only	16 (5)	-2.40 (-6.04, 1.24)	-0.25	-1.54 (-6.73, 3.66)	-0.14
		Abuse and neglect	25 (8)	-1.78 (-5.06, 1.50)	-0.19	-3.12 (-6.18, -0.06)*	-0.29
		Sexual abuse along with other CM types	34 (10)	-5.50 (-9.78, -1.22)*	-0.58	-3.49 (-7.67, 0.68)	-0.32

[a] Generalized linear regression was used to estimate the association between CM and HRQoL adjusted for age, race, and childhood socioeconomic circumstances.
[b] If a 95% confidence interval includes 0, then there is no statistically significant difference between the groups. (*$p<0.05$)
[c] Effect sizes are calculated as group differences in HRQoL scores divided by normative SD. We used the reference normative SD=9.47 for MCS and normative SD=10.82 for PCS based on the normative U.S. population in women ages 45-54 years old (21).
|Effect size|: <0.2 small not clinically meaningful, 0.2-0.5 moderate and potentially meaningful, >0.5 large and clinically meaningful.

Table 2-3 (a) Associations between CM and each mediator and (b) controlled direct associations between CM and midlife HRQoL.

Mediation models (analyzed respectively)		(a) Associations between CM and each mediator			(b) Controlled direct associations between CM and HRQoL after respectively accounting for each mediator[c]			
		Mediators N (column %)			Mental Component Score		Physical Component Score	
		No	Yes	OR (95% CI)[a] of each mediator predicted by CM	ψ_x (95% CI) [b]	Proportion explained by the mediator[d]	ψ_x (95% CI) [b]	Proportion explained by the mediator[d]
Total association of CM and HRQoL					-2.43 (-4.52, -0.35)*		-2.36 (-4.37, -0.35)*	
Model 1		Lifetime psychiatric history						
CM	No	84 (68)	103 (58)		reference		reference	
	Yes	40 (32)	74 (42)	1.52 (0.91, 2.54)	-2.14 (-4.17, -0.10)*	12%	-2.46 (-4.47, -0.44)*	-4%
Model 2		Depressive symptoms						
CM	No	168 (64)	19 (48)		reference		reference	
	Yes	93 (36)	21 (53)	1.93 (0.92, 4.02)	-1.59 (-3.40, 0.21)	35%	-2.48 (-4.50, -0.45)*	-5%
Model 3		Sleep problems						
CM	No	115 (66)	72 (57)		reference		reference	
	Yes	58 (34)	55 (43)	1.70 (1.02, 2.84)*	-2.35 (-4.38, -0.33)*	3%	-2.10 (-4.08, -0.12)*	11%
Model 4		Very upsetting life events						
CM	No	111 (68)	76 (55)		reference		reference	
	Yes	52 (32)	62 (45)	1.75 (1.05, 2.92)*	-1.92 (-3.92, 0.09)	21%	-2.29 (-4.28, -0.29)*	3%
Model 5		Low social support						
CM	No	167 (67)	20 (39)		reference		reference	
	Yes	83 (33)	31 (61)	2.76 (1.40, 5.44)*	-1.74 (-3.73, 0.26)	28%	-2.34 (-4.34, -0.33)*	1%

[a] ORs for each potential mediator predicted by at least one CM were estimated by logistic regression adjusted for age, race, and childhood socioeconomic circumstances. If a OR 95% confidence interval includes 1, then there is no statistically significant difference between the groups. (*p<0.05)

Table 2-3 Continued

[b] If a 95% confidence interval includes 0, then there is no statistically significant difference between the groups. (*p<0.05)

[c] Controlled direct associations between CM and HRQoL accounting for each potential mediator as 0, respectively, were examined by doubly-robust structural nested mean model after adjusting for age, race, childhood socioeconomic circumstances, education attainment, marital status, adulthood financial strain, smoking, alcohol consumption, total number of medical conditions, menopausal status, hormone therapy use, vasomotor symptoms, physical activity, body mass index, trait anxiety, trait anger, and ever treated for emotional problems.

[d] Proportion explained for MCS = $(-2.43 - \psi_x)/ -2.43 \times 100\%$; proportion explained for PCS = $(-2.36 - \psi_x)/ -2.36 \times 100\%$.

3.0 PAPER 2: CM AND MIDLIFE HRQOL OVER 9 YEARS

Life-course impact of childhood maltreatment on midlife health-related quality of life over a 9-year period in women: Potential pathways through psychosocial factors

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Keywords: childhood maltreatment, abuse, neglect, health-related quality of life, mediation analysis, structural nested mean model, g-estimation

Abbreviations

CM: Childhood maltreatment

HRQoL: Health-related quality of life

SWAN-MHS: The Study of Women's Health Across Nation-Mental Health Study

SNMM: structural nested mean model

3.1 ABSTRACT

Background: It is unknown if childhood maltreatment influences women's health-related quality of life (HRQoL) over time in midlife and what are the potential pathways between them. We investigated the association between childhood maltreatment (CM) and midlife HRQoL over a 9-year period in women and potential psychosocial mediators of this association.

Methods: Analyses were based on a community sample of 443 women enrolled at the Pittsburgh site of the longitudinal Study of Women's Health Across the Nation-Mental Health Study in 1996-97. A total of 342 women (114 Black, 228 White, mean age=52 at analyses baseline) completed the Childhood Trauma Questionnaire and at least one Short Form-36 for HRQoL from 2002 to 2012. Generalized estimating equations were used to estimate the association between CM and HRQoL over time adjusting for years since analysis baseline, race, and childhood socioeconomic circumstances. We sequentially applied structural nested mean models estimated via doubly robust g-estimation to quantify the controlled direct association between CM and midlife HRQoL when each potential time-varying mediator was set to zero uniformly in the population. We addressed missing data using multiple imputations by chained equations.

Results: For a 10-year period of women's midlife, average mental component scores (MCS) increased but physical component scores (PCS) decreased over time. Thirty-eight percent of women reported at least one CM type. The mean MCS and PCS over time were 5.1 points (95%CI: -7.3, -2.9) and 3.9 points (95%CI: -6.2, -1.5) lower in women with 2 or more CM types than those without. After accounting for each psychosocial mediator, 2+ CM types was still significantly associated with midlife HRQoL over time. Low levels of optimism, high depressive

symptoms, sleep problems, and low social support explained a notable proportion (≥10%) of the relation between 2+ CM types and HRQoL in separate mediation models.

Conclusions: CM has a significant life-course impact on midlife HRQoL over time in women. Low levels optimism, high depressive symptoms, sleep problems, and low social support may be targeted as potentially modifiable factors to improve midlife HRQoL for women with 2+ CM types history.

3.2 INTRODUCTION

Health-related quality of life (HRQoL) is a vital measure to capture multidimensional aspects of health perceived by individuals (Fayers & Machin, 2016). Studying HRQoL over time is important to increase understanding of the interrelationships among physical health, mental health, and HRQoL, as well as the influence of early-life childhood maltreatment (CM) exposure on these health outcomes. CM, including abuse or neglect experiences before 18 years old, has long-lasting adult health consequences and substantial social and health cost in economics (Fang, Brown, Florence, & Mercy, 2012). Unfortunately, CM is not uncommon. Based on a U.S. health survey in 2010, about 37.6% of a midlife population age 50+ reported adverse childhood experiences with rates higher in females than males (Brown, Thacker, & Cohen, 2013). However, little is known about the impact of CM on midlife HRQoL over time in women. This association has been mostly investigated in clinical settings with one-time measurement of HRQoL, however, with limited generalizability of the results (Weber et al., 2016). More longitudinal community studies are needed to examine if CM is associated with the level of HRQoL over time in general populations.

From our previous investigation (Lin et al., 2017a), we found that one CM relative to none was not significantly associated with midlife HRQoL in women at an average age of 52, but two or more CM types were associated with 3.6 points lower mental HRQoL (95%CI: -6.4, -0.8) and 3.5 points lower physical HRQoL (95%CI: -6.1, -0.8), which was consistent with the literature (Afifi et al., 2007; Agorastos et al., 2014; Bonomi et al., 2008; Walker et al., 1999). We also found that depressive symptoms, very upsetting life events or low social support partially

explained the differences in MCS, but not PCS. Another important question is whether CM has a direct negative impact on HRQoL over time or CM influences midlife HRQoL via potential time-varying psychosocial factors that have been associated with CM, such as depressive symptoms or social support during adulthood (Gilbert et al., 2009).

The current investigation aims to extend our previous findings to evaluate whether 2+ CM types is directly associated with midlife mental and physical related HRQoL components over a 9-year period (mean age from 52 to 62 years) using data from the community-based cohort of 443 women recruited into the Pittsburgh site of the Study of Women's Health Across Nation. We also evaluated whether time-fixed and time-varying psychosocial factors mediated the association using a series of structural nested mean models to estimate controlled direct associations between 2+ CM types and midlife HRQoL over time.

3.3 METHODS

Study design and participants

The Study of Women's Health Across the Nation (SWAN) is a multi-site, community-based, cohort study of midlife women enrolled in seven sites across the U.S. between 1996-97. The goal of SWAN was to investigate women's mental and physical health during the menopause transition. Further detailed explanation of the SWAN study design is available elsewhere (Sowers M, 2000). Briefly, study inclusion criteria included aged 42 to 52 years, with at least one menstrual period in the previous three months, not currently using exogenous hormones, no surgical removal of the uterus and/or both ovaries, not pregnant, and not breastfeeding. The current investigation was based on 443 women who were also enrolled in the Mental Health

ancillary study (MHS) in Pittsburgh. Women in SWAN-MHS study completed the Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders (SCID) (Spitzer et al., 1992) at baseline and annual follow-up visits in addition to extensive questionnaires about physical, psychosocial, lifestyle, and psychological characteristics. Participants provided written informed consent at each visit and the study was approved by the University of Pittsburgh Institutional Review Board.

For the current analyses, women had to have completed the Childhood Trauma Questionnaire at Visit 8 and at least one Short Form-36 measurement for HRQoL from 2002 to 2012. Because the full Medical Outcomes Survey Short Form 36 (SF-36) was first administered at follow-up Visit 6, and subsequently at Visits 8, 10, 12, and 13 from 2002 to 2012, other than study entry demographics, we used data from these visits. We refer to the SWAN baseline visit as "the study entry", Visit6 as "the analysis baseline, time 1", Visit 8 as time 2, Visit 10 as time 3, Visit 12 as time 4, Visit 13 as time 5 hereafter.

Measures

Exposure (X): *Childhood maltreatment* experienced before 18 years old was self-reported by women using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The 28-items were summed to derive scores on five types of CM. Each type of childhood maltreatment was classified as present using validated clinical cut-offs: emotional abuse (≥10), physical abuse (≥8), sexual abuse (≥8), physical neglect (≥8), and emotional neglect (≥15) (Bernstein et al., 2003; Walker et al., 1999). The CTQ has high test-retest reliability and strong convergent validity with therapists' ratings and clinical interviews. (Bernstein et al., 1994), In the Pittsburgh SWAN, the CTQ showed strong internal consistency with Cronbach's α=0.80-0.94 for each of the CTQ subscales. We summed CM types above clinical cutoffs as total number of CM types ranging

from 1 to 5 for maltreated women. CTQ scores below all five clinical cutpoints were classified as women without CM. Different types of CM were further collapsed as 5 mutually exclusive CM subgroups: 1) abuse only, 2) neglect only, 3) sexual abuse only, 4) abuse and neglect, and 5) sexual abuse and other CM types (Lin et al., 2017a).

Outcome (Y): *Midlife HRQoL* was assessed by the SF-36, a generic measure of the interviewee's health profiles in physical health, mental health, and social functioning (Ware et al., 1993). The SF-36 includes eight subdomains and two component T-scores: mental component score (MCS) and physical component score (PCS). MCS and PCS were calculated by standardizing each of the eight SF-36 scales using a z-score transformation, computing an aggregate component score from weighted z-scores, and then transforming the aggregate score to a norm-based score with a mean of 50 and standard deviation of 10 in the 1998 general U.S. population (Ware & Kosinski, 2001). Higher scores indicate better mental or physical health related quality of life. MCS or PCS below or above 50 is considered below or above the average in the general U.S. population.

Time-invariant mediators (M): *Lifetime and current psychiatric history* were initially diagnosed at study entry and past year and current at each follow-up by trained mental health clinicians using the SCID (Spitzer et al., 1992). The SCID is a semi-structured psychiatric interview and in SWAN-MHS has shown substantial reliability for lifetime depressive and anxiety disorders (kappa=0.81-0.82) (Bromberger et al., 2011). In the current study, lifetime psychiatric disorders were defined as occurring up to the Visit 6 or Visit 8 for any of the following disorders: major depression; minor depression; any anxiety disorder; alcohol use disorder, abuse or dependence; and non-alcohol use disorder, abuse or dependence. *Lifetime post-traumatic stress disorder (PTSD)* was diagnosed at visit 12 using the SCID and for the

purpose of this study, defined as lifetime if the age of onset was within three years of the analysis baseline (Visit 6). *Low levels of optimism* were ascertained by the Life Orientation Test (LOT) (Scheier, Carver, & Bridges, 1994) at the SWAN study entry. The LOT indicates the degree to which a woman tends to have a favorable outlook on life. A lower score indicates a lower level of optimism. Because SWAN reduced the 5-point Liker scale to 4-point Liker scale, a score below the 25^{th} percentile (<10) in our sample was defined as lower levels of optimism.

Time-varying mediators (M) measured at each follow-up visit included depressive symptoms, sleep problems, very upsetting life events, and social support. *Depressive symptoms* were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D) at baseline and each follow-up visit. The CES-D is a widely used measure of depressive symptom levels with well-established reliability (Roberts, 1980), and a cut-off score ≥ 16 is used as an indicator of potential clinical depression (Radloff, 1977). *Sleep problems were self-reported by w*omen and defined as at least three nights with one or more of three sleep problems in each of the past two weeks. *Very upsetting life events* were assessed by the Psychiatric Epidemiology Research Interview scale (Dohrenwend et al., 1978), modified to include events relevant to midlife women or those living in low socioeconomic environments. Women checked the life events they experienced since the last study visit and indicated how upsetting each was. Life events rated as "very upsetting" or "very upsetting and still upsetting" were totaled and categorized as 1 or more versus none. *Social support*, both instrumental and emotional support was assessed by four items from the Medical Outcomes Study Social Support Survey (Sherbourne & Stewart, 1991). Participants were asked how often each of 4 kinds of support is available to them when they need it: someone listens to you; someone takes you to the doctor; someone to confide in or talk to, and

someone helps with daily chores. The total score ranged from 0 to 16. A score below the 25th percentile (<12) was defined as low social support since a standard cut-point is not available.

Exposure-Outcome Confounders (C_{XY}) included age at each visit, race, and childhood socioeconomic circumstances (SES). Childhood SES before 19 years old was self-reported at Visit 7 and was assessed with questions about maternal and paternal education, and participant's childhood financial circumstances such as family owned their own home or a car, family ever received public assistance, or family ever had a hard time paying for rent or food. Previous work in SWAN has reported that childhood SES measures are moderately reliable (Montez et al., 2016).

Mediator-Outcome Confounders (L_{MY}): Adulthood sociodemographic factors include educational attainment, marital status, and adulthood financial strain (i.e., difficulty paying for basics as somewhat hard or very hard). Lifestyle behavioral variables (i.e., current smoking, weekly alcohol consumption, and physical activity) and body mass index (BMI) (kg/m^2) were included as confounders. A total number of lifetime medical conditions were summed from the self-report questionnaire inquiring about 12 pre-specified medical conditions, and we categorized the total number of lifetime medical conditions as 0, 1 and 2 or more. Menopausal status was included and was categorized based on menstrual bleeding patterns in the previous 12 months (WHO, 1996). The presence of vasomotor symptoms (hot flashes and night sweats) in the past two weeks, was ascertained as part of a symptom checklist frequently used in studies of menopause. Ever use of hormones since SWAN study baseline entry and lifetime treatment for emotional problems were self-reported. Trait anger and trait anxiety were assessed by the Spielberger Trait Anger and Trait Anxiety Scales, respectively, at visit 7 (Spielberger & Reheiser, 2009).

Statistical analysis

We compared characteristics of the women with and without any CM exposure using Kruskal-Wallis tests for continuous variables and Chi-square tests for categorical variables. To calculate the effect sizes for group differences, we used the reference norm SD=9.47 for MCS and norm SD=10.9 for PCS from the normative U.S. population in women ages 54-64 years (Ware et al., 1994). Effect sizes are calculated as group differences in HRQoL scores divided by SD_{norm} (Yost et al., 2005). We defined group differences in MCS or PCS with effect sizes <0.2 as small and not clinically meaningful, effect sizes 0.2-0.5 as moderate and potentially meaningful, and effect sizes >0.5 as large and clinically meaningful (Norman, Sloan, & Wyrwich, 2003; Yost et al., 2005). A two points difference of HRQoL was defined as a meaningful moderate effect size (ES=0.2) times the standard deviation (SD=10) of MCS and PCS (i.e. moderate effect size*SD=0.2*10=2).

Analytic diagram (**Figure 3-1**) illustrates the relationship between childhood maltreatment (X), time-varying potential psychosocial mediators (M_1 to M_5), HRQoL outcomes over five visits (Y_1 to Y_5), exposure-outcome confounders (C_{XY}), and time-varying mediator-outcome confounders (L_1 to L_5). Age at baseline, race, and childhood SES variables were considered as a vector of C_{XY} confounders between CM and HRQoL. A vector of time-varying adulthood confounders (L_1 to L_5) of the association between mediators and HRQoL outcomes included financial strain, lifestyle behaviors, BMI, the number of lifetime medical conditions, menopausal status, vasomotor symptoms, and use of hormones since SWAN study baseline entry. Education, marital status, trait anger and trait anxiety, and lifetime treatment for emotional problems at analysis baseline were time-invarying adulthood confounders. Due to the long-term effect of CM, several factors among the adulthood confounders are associated with CM and could be

considered as exposure-induced mediator-outcome confounders (Vanderweele et al., 2014), including time-varying adulthood confounders (financial strain, current smoking, weekly alcohol consumption, physical activity, BMI) and time-invarying confounders (education, trait anger, trait anxiety, treatment for emotional problems).

Main associations between CM and midlife HRQoL over time was assessed by generalized estimating equation models with exchangeable working correlation adjusting for years since analysis baseline, race, and childhood socioeconomic circumstances. To assess whether the relationship between CM and HRQoL was the same for blacks and whites, the product of any CM and race and the products of each CM type and race were added in separated main effect models. Due to the small sample size in the current analysis, we did not have sufficient power to detect the significance of effect modification and confidence intervals. We defined effect modification as present if the magnitude of the beta coefficient of CM on HRQoL was changed by more than ± 2 points after adding the interaction product term to the outcome model.

Mediation analysis: Traditional meditation methods cannot be applied to estimate the direct effect of life-course CM exposure on adult HRQoL over time due to the challenges in time-varying mediators, time-varying outcomes, and time-varying confounders (i.e. BMI, financial strain, trait anger, trait anxiety lifestyle behaviors, etc.) that are potentially affected by CM exposure (VanderWeele & Tchetgen Tchetgen, 2016). We applied structural nested mean model estimated via doubly robust g-estimation in our previous work (Lin et al., 2017a) for one time-point mediator and one time-point outcome and this approach properly accounts for confounding due to C_{XY} and L_{MY}, (Naimi et al., 2016). In the present analysis, we sequentially applied a series of SNMM estimated via doubly robust g-estimation to quantify the controlled direct effect of CM and midlife HRQoL over time: the extent to which CM would be associated with HRQoL if

each time-varying mediator was set to zero uniformly in the population after accounting for confounders C_{XY} and L_{MY} and previous HRQoL outcomes. Confidence intervals for controlled direct estimates were obtained using 1000 bootstrap samples for each imputation data set in R. The proportion of the total association between any CM and HRQoL explained by the mediator was calculated as (overall association – controlled direct associations) divided by overall associations*100%. Detailed steps of our mediation analysis are illustrated in **Figure 3-2**. The overall proportion of missing data was 12% for the 342 participants for all the analytic variables across five visits. The proportion of missing for HRQoL outcomes from time 1 to time 5 were 6%, 7%, 11%, 16%, and 16%, respectively. Missing data for outcomes, time-varying mediators, and adulthood confounders were imputed using multivariate imputations by chained equations in R (mice package) to generate 20 completed analysis data sets with 25 iterations. We compared the distributions of imputed and observed values to inspect implausible values and convergence figures of MICE algorithm. SAS 9.4 (SAS Institute, Cary NC, USA) and R 3.2.3 were used for statistical analyses.

3.4 RESULTS

Of the 443 participants in SWAN-MHS, a total of 342 women (114 Black, 228 White, mean age=52 at follow-up Visit 6) were included in the current analysis (**Table 3-1**). Thirty-eight percent reported at least one type of CM: 21% reported emotional abuse, 18% physical abuse, 16% physical neglect, 15% sexual abuse, and 8% emotional neglect. Nineteen percent had one type of CM, 15% had 2-3 types, and 5% had 4-5 types. Based on the mutually exclusive combined CM subtypes, 11% of women had emotional and/or physical abuse, 4% had emotional and/or physical neglect, 5% had sexual abuse, 8% had abuse and neglect, and 10% had sexual abuse along with other CM types. See **Table 3-1** for a description of the characteristics of the sample overall and those with and without CM.

Mean (SD) scores for MCS increased and were above the norm score of 50 throughout the five time-points: 50.6 (9.3), 51.3 (9.0), 50.7 (10.2), 51.6 (9.3), 52.3 (9.1). However, mean (SD) scores for PCS decreased and were below the norm score of 50 at time 4 and time 5: 49.8 (9.2), 48.1 (10.3). When the total number of CM types increased, both MCS and PCS mean scores decreased (**Table 3-2** and **Figure 3-3**). Mean MCS and PCS were both lower than the norm of 50 among women who reported childhood abuse and neglect or childhood sexual abuse and other CM types. Both subgroups also had the lowest PCS at time point 5: abuse and neglect (mean ± SD: 46.8±10.1) and sexual abuse with other CM types (mean ± SD: 44.8±12) (**Table 3-2**). These two subgroups reported PCS below the norm of 50 throughout the five time-points.

The associations between CM and midlife HRQoL over time after adjusting for years since baseline, race, and childhood SES are shown in **Table 3-3**. Overall, MCS increased 0.1 points (95% CI: -0.02, 0.2) per year over time, while PCS significantly decreased 0.3 points (95% CI: -0.4, -0.2) per year over time (data not shown in tables). The change in mean HRQoL over time did not differ between women with and without CM. Each type of CM was significantly associated with lower MCS and PCS over time in separate analyses (**Table 3-3**). Emotional neglect had the largest impact on both MCS [β (95% CI) = -7.3 (-10.8, -3.8)] and PCS [β (95% CI) = -6.1 (-10.1, -2.0)] over time. Women with two or more types of CM reported significantly lower MCS [-5.1 (-7.3, -2.9)] and PCS [-3.9 (-6.2, -1.5)] than women without CM. For mutually exclusive CM subgroups (Table 3-3, Model 8), abuse and neglect or sexual abuse along with other CM types were both associated with lower MCS and PCS over time. Overall, black women had lower MCS [-1.9 (-3.7, 0.0)] and lower PCS [-1.9 (-3.8, 0.1)] than white women adjusting for the total number of CM types, age, and childhood SES. The association between CM and MCS or PCS over time did not differ by race after adding an interaction term between CM and race for each type of CM.

Two or more types of CM were associated with time-invarying mediators (lifetime psychiatric history, lifetime PTSD, low levels of optimism) and time-varying mediators (high depressive symptoms, sleep problems, very upsetting life event, low social support) (**Table 3-4**-a). After sequentially applying a series of structural nested mean models estimated via doubly robust g-estimation across five time-points, we evaluated the extent to which each psychosocial mediator explained the relation between CM and HRQoL after adjusting for years since baseline, race, childhood SES variables, prior time-point HRQoL outcome, and adulthood confounders (**Table 3-4**-b). After accounting for the mediating contribution of each psychosocial factor,

multiple CM types remained significantly associated with both lower MCS and PCS over a 9-year period. However, a notable proportion of the association between multiple CM types and MCS was explained by low levels of optimism (20%), high depressive symptoms (31%), sleep problems (24%), and low social support (20%) in separate mediation models. A notable proportion for the association between multiple CM types and PCS was explained by low levels of optimism (51%), sleep problems (38%), and low social support (35%) in separate mediation models.

3.5 DISCUSSION

The current investigation is one of the first studies to assess the long-lasting effect of childhood maltreatment on the longitudinal quality of life in midlife women from a community-based cohort study. We found that women with 2 or more types of CM had impaired mental and physical HRQoL over a 9-year follow-up (52 to 62 years old) compared to women without CM or a single CM after adjusting for years since baseline, race, and childhood SES variables. Psychosocial factors did not completely mediate the associations between multiple forms of CM and impaired mental or physical HRQoL over time even accounting for important childhood and adulthood confounders.

Our results indicated that CM is a robust life-course social determinant for women's impaired midlife HRQoL over time, which is associated with increased mortality and morbidity (Ware & Kosinski, 2001) and are consistent with our previous baseline analysis with one-time HRQoL (Lin et al., 2017a). Women with childhood abuse and neglect or sexual abuse along with other CM types before 18 years old had reduced HRQoL during their mid-50's over time with moderate effect sizes from 0.3 to 0.4.

The association between multiple forms of CM and reduced HRQoL were identified in the previous literature with only one-time measurement of HRQoL. A population study in Netherlands with adults aged 18-64 years reported graded associations between total numbers of CM and both SF-36 MCS and PCS (Afifi et al., 2007). A military study with males aged 22 years identified that multiple CM types increased the likelihood of poor mental and physical HRQoL measured by SF-12 (Agorastos et al., 2014). Women aged 18-64 with both childhood

physical and sexual abuse reported significantly lower scores on both MCS and PCS in a randomly sampled insured female population (Bonomi et al., 2008). A Swedish study with children aged 15 years old also suggested a dose-response relationship between the total number of CM types and child quality of life (Jernbro, Tindberg, Lucas, & Janson, 2015). Our data showed that midlife women reporting multiple types of CM (abuse and neglect or sexual abuse and other types) would be especially important to target for interventions to mitigate the long-lasting impact of CM on well-being from midlife through older adulthood.

We performed a novel longitudinal mediation analysis method to identify potential mechanisms underlying the relationship between multiple forms of CM and midlife HRQoL over a 9-year follow-up. However, adult psychosocial factors only partially explained the relationship between CM and HRQoL. After accounting for each mediator in separate models, low levels of optimism, time-varying depressive symptoms, time-varying sleep problems, and time-varying low social support individually explained more than 20% of the relationship between multiple CM types and both MCS and PCS HRQoL over time.

Social support, particularly, was identified as an important explanatory factor for the poor disease-specific HRQoL among 132 breast cancer female survivors with CM history (Fagundes, Lindgren, Shapiro, & Kiecolt-Glaser, 2012). Data from the 2009 Behavioral Risk Factors Surveillance System (BRFSS) (Barile, Edwards, Dhingra, & Thompson, 2015) indicated that lower emotional support partially contributed to the poor HRQoL measured by two items among 29,212 female and male adults with adverse childhood experiences (ACE). Lower scores of mental and physical HRQoL measured by SF36 were also observed among patients with non-cardiac chest pain who had CM history and a lack of social support (n=10) compared to those with available social support and with CM (n=39) or without CM (n=84) (Biggs, 2004).

The literature has found several characteristics that may protect women from the deleterious effect of CM. Although optimism is considered a trait with 25% heritability and is relatively stable over time, there is some evidence that levels of optimism can be increased and changed by interventions (Heinonen, Räikkönen, & Keltikangas-Järvinen, 2005; Meevissen, Peters, & Alberts, 2011; Peters, Flink, Boersma, & Linton, 2010). A longitudinal study found that the increased levels of optimism over four years were associated with better overall well-being and fewer chronic illness over time among older adults aged from 51 to 97 years old (Chopik, Kim, & Smith, 2015). Among a sample of 266 postpartum mothers with CM history from a longitudinal cohort found that positive parenting, family functioning, and resilience were significant predictors of a mother's perceptions of quality of life independent of psychiatric symptoms and income (Irwin, Beeghly, Rosenblum, & Muzik, 2016). Better health was also reported by young adults with strengths in emotion regulation, community support, social support, and practicing of forgiveness compared to those without these protective factors independent of CM history in a rural community sample of 2565 young adults (Banyard, Hamby, & Grych, 2017).

The implications of our longitudinal mediation findings suggest that prevention or intervention efforts to improve maltreated women's well-being may focus on promoting a broad spectrum of protective factors such as developing positive emotion toward the meaning of life, strengthening the social support network, increasing levels of resilience, reducing depressive symptoms, or alleviating sleep problems. Chandler et al. (2015) conducted a short-term pilot intervention study to evaluate the feasibility and potential efficacy of the Empower Resilience Intervention (ERI) among 28 female undergraduate students who had adverse childhood experiences. The ERI framework including active coping, building strength, cognitive flexibility,

and social support can potentially increase health-promoting behaviors and build resilience for young adult maltreated female survivors (Chandler, Roberts, & Chiodo, 2015). Perhaps, such an intervention may be helpful for older women as well.

There are limitations in our study. First, self-report childhood maltreatment was assessed by CTQ retrospectively. The severity, duration, and age of CM onset were not assessed. Self-report assessment may potentially result in recall bias for the misclassification of the CM exposure. However, previous evidence showed that the CTQ has high test-retest reliability and strong convergent validity with therapists' rating and clinical interview (Bernstein et al., 2003). Second, adulthood experiences of abuse or neglect were not assessed and not accounted for in our analyses.

There are a number of strengths in the current study. First, we used data from SWAN-MHS which is a community-based cohort sample with better generalizability compared with clinical samples. Second, the measurement of CM exposure, longitudinal HRQoL, and psychosocial mediators were all assessed by standardized and validated instruments. Third, we performed novel time-varying mediation analysis using a series of structural nested mean models estimated via doubly robust g-estimation, which is a more general statistical approach to accounting for time-varying mediators, time-varying outcomes, and time-varying confounders that are potentially affected by the exposure. Fourth, we comprehensively controlled for childhood SES variables and many adulthoods' mental or physical health-related confounders in the mediation analyses to assess the controlled direct effect of multiple CM on midlife HRQoL.

Our findings consistently suggest that childhood maltreatment has a lifelong impact on the midlife mental and physical HRQoL over a 9-year period in women. Adulthood psychosocial factors (i.e. low levels of optimism, depressive symptoms, sleep problems, or low social support)

appear to partially explain the association between CM and midlife HRQoL. As noted above, future intervention studies may target these modifiable factors among maltreated women to improve overall well-being from midlife to older adulthood.

3.6 TABLES AND FIGURES

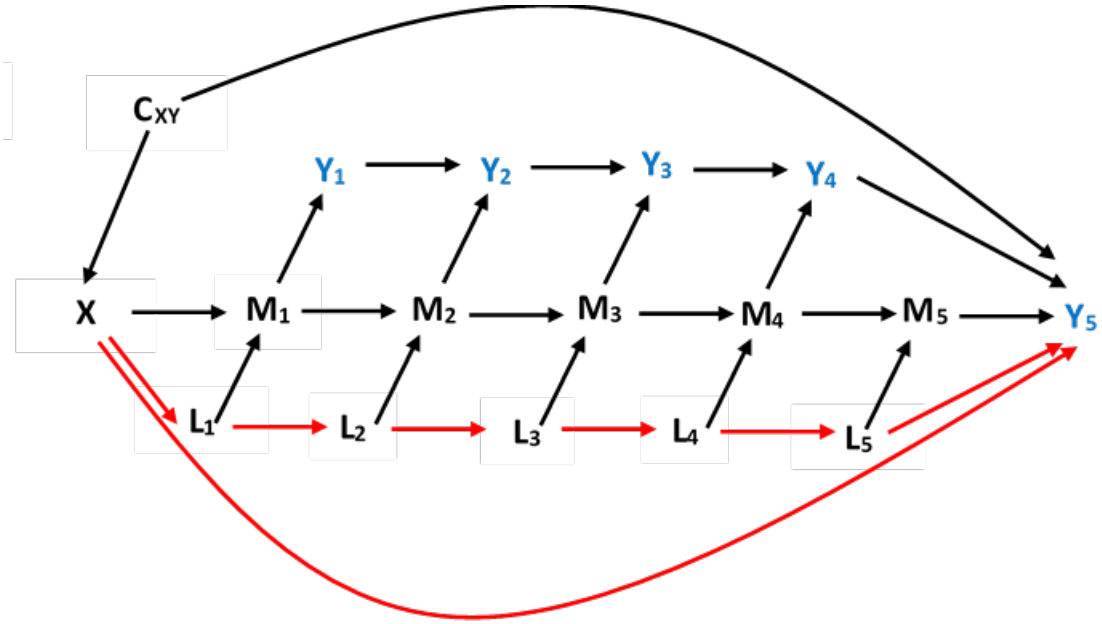


Figure 3-1 Analytic diagram of paper 2.

The analytic diagram illustrates the relationship between childhood maltreatment (X), time-varying potential psychosocial mediators (M_1 to M_5), QALY outcomes over five visits (Y_1 to Y_5), exposure-outcome confounders (C_{XY}), and time-varying mediator-outcome confounders (L_1 to L_5).

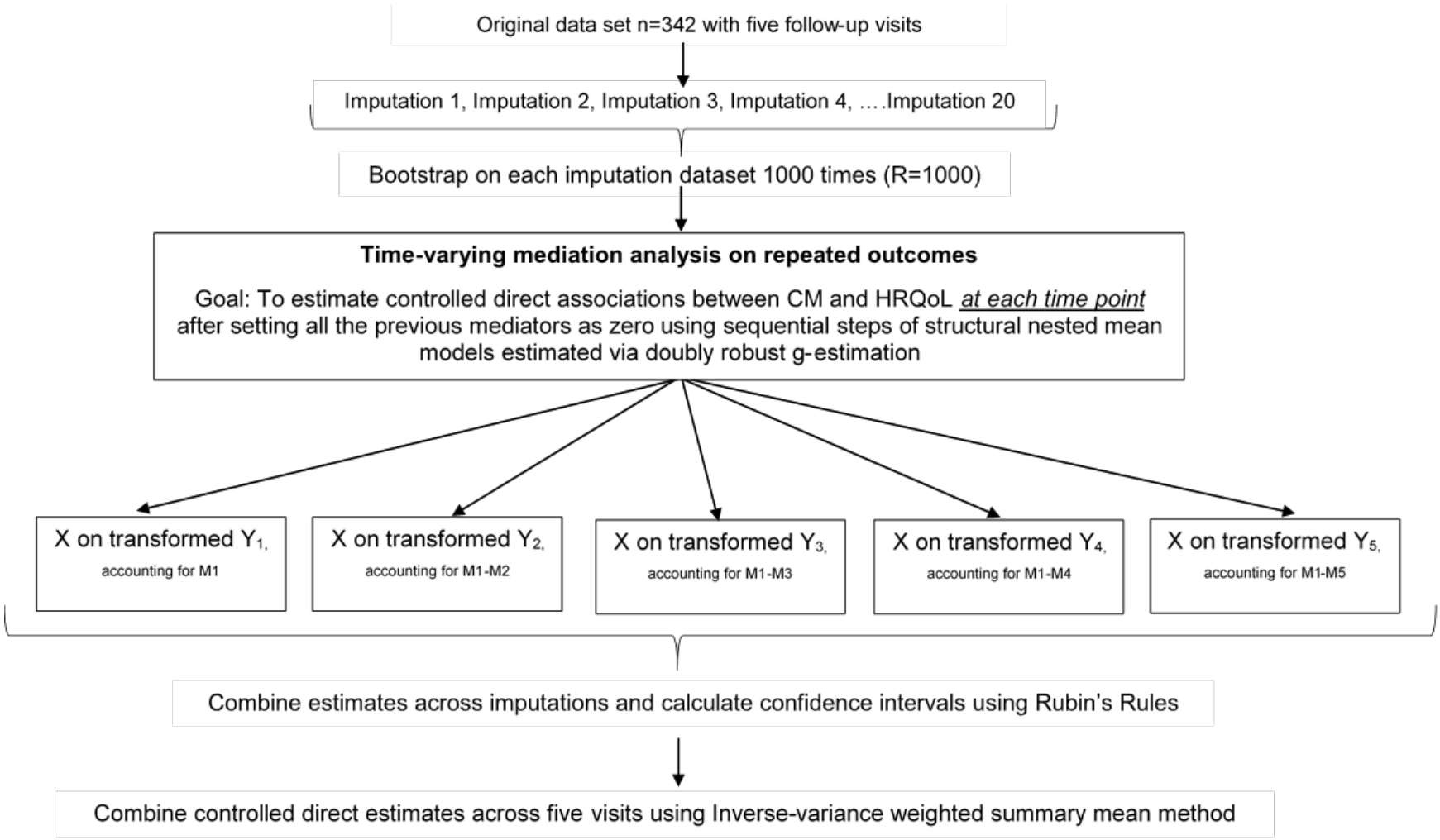


Figure 3-2 Time-varying mediation analysis flowchart**.**

Table 3-1 Characteristics of women by CM exposure at the analysis baseline.

Characteristics	All N=342	No CM N= 212 (62.0%)	At least one CM N=130 (38.0%)
Exposure-outcome confounders (C_{XY})			
Age at the analysis baseline, Mean (SD)	52.2 (2.5)	52.3 (2.6)	52.1 (2.4)
Race/Ethnicity			
Black	114 (33.3)	67 (31.6)	47 (36.2)
White	228 (66.7)	145 (68.4)	83 (63.8)
Childhood socioeconomic circumstances			
Maternal Education less than college	272 (79.5)	171 (80.7)	101 (77.7)
Paternal Education less than college	236 (69.0)	150 (70.8)	86 (66.2)
Childhood family…			
…did not own a car	43 (12.6)	27 (12.7)	16 (12.3)
…did not own a home*	72 (21.1)	37 (17.5)	35 (26.9)
…ever received public assistance*	52 (15.2)	25 (11.8)	27 (20.8)
…ever had difficulty paying for food or rent**	120 (35.1)	51 (24.1)	69 (53.1)
Exposure: Childhood maltreatment (X)			
Total numbers of childhood maltreatment types			
0	212 (62.0)	212 (100.0)	0 (0.0)
1	63 (18.4)	-	63 (48.5)
2+	67 (19.6)	-	67 (51.5)
CM types, not mutually exclusive			
Emotional Abuse (≥10)	71 (20.8)	-	71 (54.6)
Physical Abuse (≥8)	60 (17.5)	-	60 (46.2)
Emotional Neglect (≥15)	26 (7.6)	-	26 (20.0)
Physical Neglect (≥8)	53 (15.5)	-	53 (40.8)
Sexual Abuse (≥8)	51 (14.9)	-	51 (39.2)
CM types, mutually exclusive			
No CM	212 (62.0)	212 (100.0)	0 (0.0)
Abuse only	38 (11.1)	-	38 (29.2)
Neglect only	15 (4.4)	-	15 (11.5)
Sexual abuse only	16 (4.7)	-	16 (12.3)
Abuse and neglect	26 (7.7)	-	26 (20.0)
Sexual abuse and other CM types	35 (10.4)	-	35 (26.9)
Potential psychosocial mediators (M)			
Lifetime psychiatric history* (i.e., major/minor depression, anxiety disorders, or substance use disorder)	201 (58.8)	115 (54.2)	86 (66.2)
Lifetime post-traumatic stress disorder**	56 (16.4)	21 (9.9)	35 (26.9)
Low levels of optimism (<25th percentile=10)*	82 (24.0)	41 (19.3)	41 (31.5)
High depressive symptoms**	63 (18.4)	30 (14.2)	33 (25.4)
Sleep problems (≥ 3 times /week)	139 (40.6)	79 (37.3)	60 (46.2)
Total very upsetting life events* (1+)	164 (48.0)	91 (42.9)	73 (56.2)
Low social support**	61 (17.8)	27 (12.7)	34 (26.2)

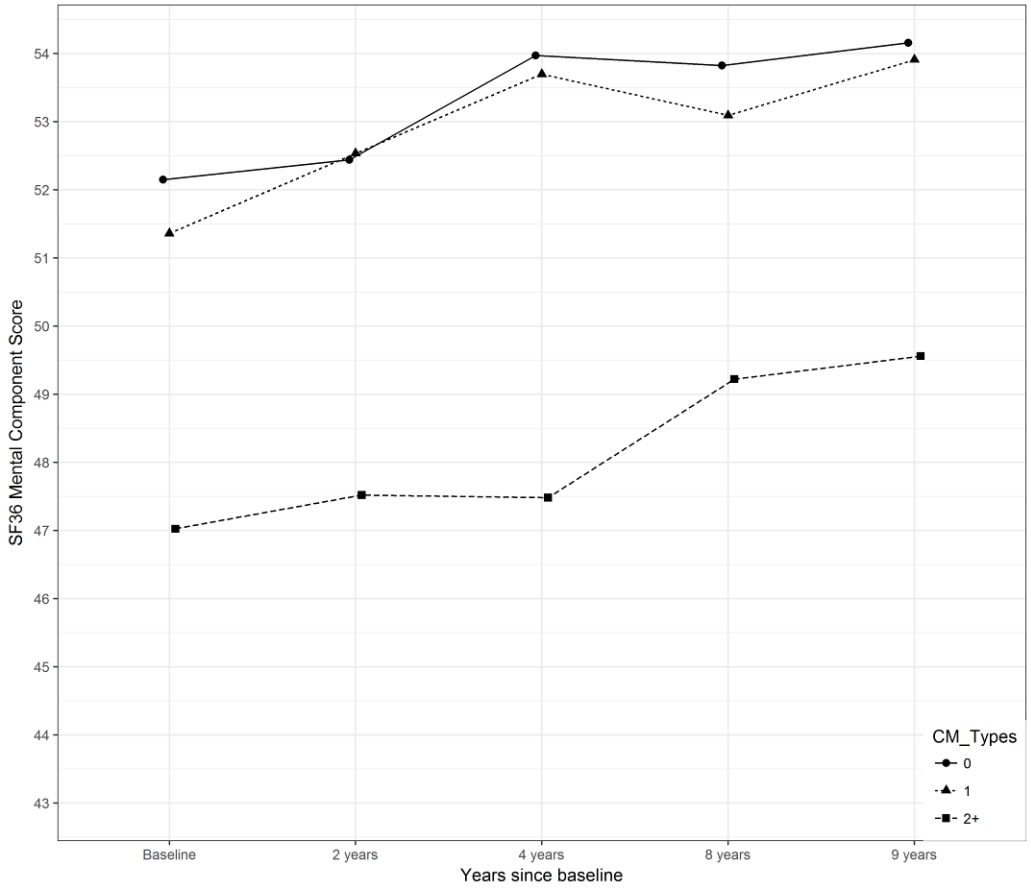
Table 3-1 Continued

Mediator-outcome confounders (L_{MY})			
Education attainment less than college	198 (57.9)	131 (61.8)	67 (51.5)
Marital status			
Single	35 (10.2)	21 (9.9)	14 (10.8)
Married or living with someone as if married	238 (69.6)	150 (70.8)	88 (67.7)
Separate/divorced/widowed	69 (20.2)	41 (19.3)	28 (21.5)
Adulthood financial strain* (somewhat or very hard to pay for very basics)	83 (24.3)	43 (20.3)	40 (30.8)
Current smoker	60 (17.5)	38 (17.9)	22 (16.9)
Weekly alcohol consumption			
None	172 (50.3)	99 (46.7)	73 (56.2)
<2 times	89 (26.0)	60 (28.3)	29 (22.3)
2-7 times	59 (17.3)	39 (18.4)	20 (15.4)
>7 times	22 (6.4)	14 (6.6)	8 (6.2)
Total number of medical conditions			
0	157 (45.9)	100 (47.2)	57 (43.8)
1	93 (27.2)	54 (25.5)	39 (30.0)
2+	92 (26.9)	58 (27.4)	34 (26.2)
Menopausal status			
Premenopausal	17 (5.0)	9 (4.2)	8 (6.2)
Late peri-menopausal or early perimenopausal	129 (37.7)	87 (41.0)	42 (32.3)
Natural postmenopausal	134 (39.2)	81 (38.2)	53 (40.8)
Surgical postmenopausal	35 (10.2)	21 (9.9)	14 (10.8)
Unknown with hormone therapy	27 (7.9)	14 (6.6)	13 (10.0)
Vasomotor Symptoms			
None	148 (43.3)	101 (47.6)	47 (36.2)
1-5 days/ 2 weeks	117 (34.2)	67 (31.6)	50 (38.5)
≥ 6 days/ 2 weeks	77 (22.5)	44 (20.8)	33 (25.4)
Ever use hormone since SWAN study entry*	135 (39.5)	74 (34.9)	61 (46.9)
Lifetime medical treatment for emotional problems** (Yes)	71 (20.8)	33 (15.6)	38 (29.2)
Physical activity score excluding work*	7.6 (1.7)	7.8 (1.7)	7.4 (1.7)
Body mass index (kg/m^2)**	30.1 (6.8)	29.2 (6.5)	31.6 (6.9)
Spielberger trait anxiety**	15.3 (4.5)	14.9 (4.5)	16.1 (4.3)
Spielberger trait anger**	14.1 (3.8)	13.5 (3.1)	15.1 (4.5)

N (%) are shown for each level of categorical variables. Mean (standard deviation) is presented for continuous variables.
*$p<0.05$
**$p<0.01$

Table 3-2 Mean (SD) scores of SF-36 over time by CM.

HRQoL	N	Baseline	2 years since baseline	4 years since baseline	8 years since baseline	9 years since baseline
		Time 1	Time 2	Time 3	Time 4	Time 5
Mental component score (MCS), All	342	50.6 (9.3)	51.3 (9.0)	50.7 (10.2)	51.6 (9.3)	52.3 (9.1)
Total numbers of CM types						
No CM	212	51.8 (8.8)	52 (8.7)	52.3 (9.0)	52.5 (8.7)	53.1 (8.7)
1 CM type	63	50.3 (9.1)	52.5 (8.3)	51.3 (9.4)	52.4 (7.0)	53.7 (6.6)
2+ CM types	67	47.2 (10.5)	48 (10.0)	45.1 (12.5)	48.1 (11.9)	48.4 (11.1)
CM types, mutually exclusive						
No CM	212	51.8 (8.8)	52.0 (8.7)	52.3 (9.0)	52.5 (8.7)	53.1 (8.7)
Abuse only	38	50.1 (10.1)	53.0 (7.2)	49.2 (12.1)	52.3 (7.7)	54.2 (6.8)
Neglect only	15	49.5 (10.4)	52.1 (8.3)	51.9 (10.3)	50.7 (9.2)	49.2 (11.3)
Sexual abuse only	16	49.8 (7.0)	49.3 (11.0)	51 (7.8)	52.6 (4.9)	51.8 (7.3)
Abuse and neglect	26	48.6 (9.6)	47.7 (10.6)	46.8 (11.3)	46.4 (14.5)	49.2 (10.9)
Sexual abuse and other CM types	35	46.5 (11.0)	48.5 (9.9)	45 (12.4)	49.4 (9.9)	49.2 (10.7)
Physical component score (PCS), All	342	51.6 (9.0)	50.8 (9.3)	50.6 (9.0)	49.8 (9.2)	48.1 (10.3)
Total numbers of CM types						
No CM	212	52.3 (8.4)	51.7 (8.9)	51.8 (8.1)	51.1 (8.8)	48.8 (10.2)
1 CM type	63	51.9 (9.1)	50.9 (8.9)	49.9 (8.9)	49.9 (8.1)	48.0 (9.5)
2+ CM types	67	49.0 (10.2)	47.9 (10.4)	47.4 (10.7)	45.8 (10.3)	45.7 (11.1)
CM types, mutually exclusive						
No CM	212	52.3 (8.4)	51.7 (8.9)	51.8 (8.1)	51.1 (8.8)	48.8 (10.2)
Abuse only	38	52.6 (8.8)	51.3 (8.1)	49.8 (9.4)	49.4 (9.1)	46 (10.2)
Neglect only	15	48.4 (8.7)	46.1 (9.9)	49.3 (7.8)	50.1 (6.4)	50.8 (5.7)
Sexual abuse only	16	51.1 (11.1)	49.9 (13.2)	50.5 (9.8)	50.5 (7.8)	49.5 (10.6)
Abuse and neglect	26	49.0 (8.8)	48.1 (8.4)	46.8 (10.5)	46.5 (9.2)	46.8 (10.1)
Sexual abuse and other CM types	35	49.6 (11.2)	49.2 (10.5)	47.5 (11.2)	44.7 (11.2)	44.8 (12.0)



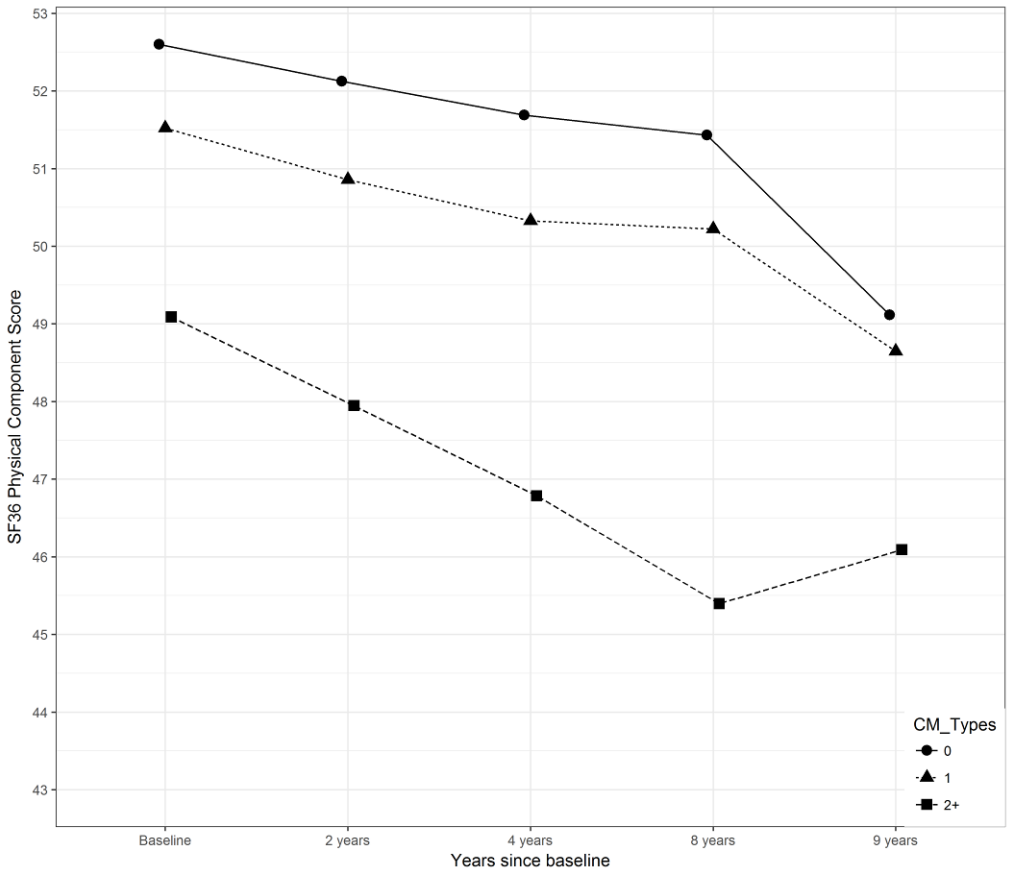


Figure 3-3 Mean SF-36 mental component score (MCS) and physical component score (PCS) over time by total numbers of childhood maltreatment types.

Table 3-3 Associations between CM and HRQoL over 9 years.

Models[a]	Childhood Maltreatment		Mental component score (MCS)		Physical component score (PCS)	
			β (95% CI)[b]	Effect Size[c]	β (95% CI)[b]	Effect Size[c]
Model 1	At least one CM	No	reference		reference	
		Yes	-2.80 (-4.37, -1.24)*	-0.29	-2.36 (-4.04, -0.68)*	-0.22
Model 2	Emotional Abuse	No	reference		reference	
		Yes	-3.82 (-5.93, -1.71)*	-0.39	-2.21 (-4.33, -0.08)*	-0.20
Model 3	Physical Abuse	No	reference		reference	
		Yes	-3.83 (-6.15, -1.50)*	-0.39	-3.61 (-6.25, -0.98)*	-0.33
Model 4	Emotional Neglect	No	reference		reference	
		Yes	-7.30 (-10.79, -3.82)*	-0.75	-6.08 (-10.12, -2.04)*	-0.56
Model 5	Physical Neglect	No	reference		reference	
		Yes	-3.79 (-6.24, -1.34)*	-0.39	-2.20 (-4.39, -0.00)*	-0.20
Model 6	Sexual Abuse	No	reference		reference	
		Yes	-3.42 (-5.50, -1.34)*	-0.35	-2.34 (-5.12, 0.45)	-0.21
Model 7	Total number of CM	No CM	reference		reference	
		1 CM type	-0.45 (-2.15, 1.26)	-0.05	-0.84 (-2.81, 1.13)	-0.08
		2+ CM types	-5.12 (-7.31, -2.93)*	-0.53	-3.86 (-6.20, -1.52)*	-0.35
Model 8	CM groups	No CM	reference		reference	
		Abuse only	-0.20 (-2.30, 1.90)	-0.02	-0.77 (-3.27, 1.74)	-0.07
		Neglect only	-1.34 (-5.15, 2.48)	-0.14	-2.75 (-5.85, 0.36)	-0.25
		Sexual abuse only	-2.45 (-5.30, 0.40)	-0.25	-0.79 (-5.08, 3.51)	-0.07
		Abuse & neglect	-5.18 (-8.92, -1.43)*	-0.53	-3.46 (-6.22, -0.69)*	-0.32
		Sexual abuse & other CM	-4.80 (-7.45, -2.14)*	-0.49	-3.96 (-7.49, -0.42)*	-0.36

[a] Generalized estimating equation (GEE) with an exchangeable working correlation matrix was used to estimate the association between CM and HRQoL over time adjusting for years since analysis baseline, race, and childhood socioeconomic circumstances.

[b] If a 95% confidence interval includes 0, then there is no statistically significant difference between the groups. (*p<0.05)

[c] Effect sizes are calculated as group differences in HRQoL scores divided by normative SD. We used the reference normative SD=9.47 for MCS and normative SD=10.90 for PCS based on the normative U.S. population in women ages 54-64 years old (Ware and Kosinski, 2009).

|Effect size|: <0.2 small not clinically meaningful, 0.2-0.5 moderate and potentially meaningful, >0.5 large and clinically meaningful.

Table 3-4 (a) Associations between CM and each mediator and (b) controlled direct associations between CM and HRQoL over 9 years.

Mediation models (analyzed respectively)		Associations between CM and each mediator: Mediators N (row %) at baseline			(b) Controlled direct associations ($\overline{\varphi_x}$) between CM and HRQoL over time after respectively accounting for each time-varying mediator across 5 timepoints[c]			
					Mental Component Score (MCS)		Physical Component Score (PCS)	
		No	Yes	OR (95% CI)[a] of each mediator predicted by CM	$\overline{\varphi_x}$ (95% CI)[b]	Proportion Explained	$\overline{\varphi_x}$ (95% CI)[b]	Proportion Explained
Overall association between 2+ CM types and HRQoL					-4.53 (-5.68, -3.39)*		-3.87 (-4.98, -2.77)*	-
Model 1		Lifetime psychiatric history		(time-fixed)				
CM	No	127 (46.2)	148 (53.8)	1.80 (1.30, 2.49)*	reference		reference	
	Yes	14 (20.9)	53 (79.1)		-4.47 (-6.19, -2.75)*	1%	-4.29 (-5.88, -2.70)*	-11%
Model 2		Lifetime post-traumatic stress disorder		(time-fixed)				
CM	No	243 (88.4)	32 (11.6)	2.16 (1.51, 3.09)*	reference		reference	
	Yes	43 (64.2)	24 (35.8)		-5.33 (-7.17, -3.49)*	-18%	-4.91 (-6.54, -3.29)*	-27%
Model 3		Low levels of optimism		(time-fixed)				
CM	No	221 (80.4)	54 (19.6)	1.75 (1.28, 2.40)*	reference		reference	
	Yes	39 (58.2)	28 (41.8)		-3.63 (-5.01, -2.24)*	20%	-1.89 (-3.08, -0.71)*	51%
Model 4		High depressive symptoms		(time-varying)				
CM	No	235 (85.5)	40 (14.5)	2.45 (1.69, 3.55)*	reference		reference	
	Yes	44 (65.7)	23 (34.3)		-3.14 (-4.57, -1.72)*	31%	-4.05 (-5.44, -2.67)*	-5%
Model 5		Sleep problems		(time-varying)				
CM	No	173 (62.9)	102 (37.1)	1.43 (1.00, 2.04)*	reference		reference	
	Yes	30 (44.8)	37 (55.2)		-3.45 (-5.1, -1.81)*	24%	-2.4 (-3.89, -0.90)*	38%
Model 6		Very upsetting life events		(time-varying)				
CM	No	154 (56.0)	121 (44.0)	1.94 (1.44, 2.62)*	reference		reference	
	Yes	24 (35.8)	43 (64.2)		-4.45 (-6.26, -2.65)*	2%	-3.63 (-5.29, -1.96)*	6%
Model 7		Low social support		(time-varying)				
CM	No	238 (86.5)	37 (13.5)	3.71 (2.33, 5.92)*	reference		reference	
	Yes	43 (64.2)	24 (35.8)		-3.62 (-5.04, -2.20)*	20%	-2.52 (-3.86, -1.18)*	35%

Table 3-4 Continued

[a] ORs for each time-fixed mediator predicted by 2+ CM (vs 0 or 1 CM) were estimated by logistic regression adjusted for age, race, and childhood socioeconomic circumstances. ORs for each time-varying mediator predicted by 2+ CM (vs 0 or 1 CM) were estimated by generalized estimating equation (GEE) with logit link adjusted for years since baseline, race, and childhood socioeconomic circumstances. If an OR 95% confidence interval includes 1, then there is no statistically significant difference between the groups. (*$p<0.05$)

[b] If a 95% confidence interval includes 0, then there is no statistically significant difference between the groups. (*$p<0.05$)

[c] Controlled direct associations between 2+ CM types and HRQoL accounting for each potential mediator as 0, respectively, were examined by doubly-robust structural nested mean model after adjusting for age, race, childhood socioeconomic circumstances, education attainment, marital status, adulthood financial strain, smoking, alcohol consumption, total number of medical conditions, menopausal status, hormone therapy use, vasomotor symptoms, physical activity, body mass index, trait anxiety, trait anger, and ever treated for emotional problems.

[d] Proportion explained by each mediator for MCS = (Overall association - ψ_x)/ Overall association × 100%

4.0 PAPER 3: CM AND MIDLIFE QALY OVER 9 YEARS

The long-term impact of childhood maltreatment on quality-adjusted life years in midlife women: potential pathways through psychosocial factors

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Keywords: childhood maltreatment, abuse, neglect, quality-adjusted life years, SF-36, SF-6D, QALY, longitudinal mediation analysis, structural nested mean model, g-estimation

Abbreviations

CM: Childhood maltreatment

QALY: Quality-adjusted life years

SWAN-MHS: The Study of Women's Health Across Nation-Mental Health Study

SNMM: structural nested mean model

4.1 ABSTRACT

Background: Few studies have assessed the long-term impact of childhood maltreatment (CM) on quality-adjusted life years (QALY) in women. We investigated if multiple forms of CM is associated with lower QALY during a 10-year follow-up in midlife women and the explanatory role of each potential adulthood psychosocial mediator for this association.

Methods: We used data from a community sample of 443 women enrolled in the Pittsburgh site of the longitudinal Study of Women's Health Across the Nation-Mental Health Study in 1996-97. The analyses included 342 women who completed the Childhood Trauma Questionnaire and at least one Short Form-36 (SF-36) from 2002 to 2012. QALY per year (i.e. SF-6D health index) was generated by Brazier's algorithm based on six dimensions of the SF-36. We used generalized estimating equations to examine the total association between CM and QALY, expressed as yearly healthy days, over time adjusting for years since analysis baseline, race, and childhood socioeconomic circumstances. The mediation role of each psychosocial factor in the relationship between CM and QALY was investigated by a series of sequential structural nested mean models estimated via doubly robust g-estimation after accounting for confounders. Missing data were addressed using multiple imputations by chained equations.

Results: A single CM was reported by 63 (18%) women, and 2+ CM types were reported by 67 (20%) women. Compared to women without CM, women with 2+ CM types reported a clinically meaningful difference of 28.3 fewer healthy days (95%CI: -37.2, -19.5) per year. After accounting for the mediating role of each psychosocial factor, multiple CM types remained statistically associated with midlife QALY over time. A notable proportion (≥10%) of multiple

CM and QALY over time were explained by low levels of optimism, time-varying sleep problems, and time-varying low social support in separate mediation models.

Conclusions: Our findings suggest that childhood maltreatment directly influences midlife QALY over time (52-62 years old) in women. Optimism, sleep problems, and social support are potentially modifiable psychosocial factors that may mitigate the effect of CM on the reduced midlife yearly healthy days.

4.2 INTRODUCTION

A generic measure of health-related quality of life such as 36-item Short-Form Health Survey (SF-36) assesses individuals' subjective health profiles in specific domains of health (mental or physical HRQoL) (Fayers & Machin, 2016), while quality-adjusted life years (QALY) further integrates psychosocial, mental, and physical health domains as a health index. A QALY reflects the proportion of the individual's perception of the impact of diseases or conditions on her health-related functioning during her life (Brazier, Usherwood, Harper, & Thomas, 1998). A health index is anchored at 1.0 indicating good health and at 0 that is equivalent to death. For example, a QALY of 0.7 indicates an individual has an estimated 0.7 year of good health per year of life (i.e. quality-adjusted life years), which is equivalent to yearly 256 healthy days (0.7*365.25). QALY is an important patient-reported HRQoL outcome and it can be used as one of the references for prioritizing management or interventions (Fayers & Machin, 2016).

Assessing midlife QALY over time is important to increase understanding of the interrelationships among proximal physical-, mental-, and psychosocial-related factors on long-term quality of life. Early life exposure, such as childhood maltreatment (CM) may also influence QALY. CM includes childhood abuse or neglect experienced before 18 years old. CM has long-lasting adult health consequences and substantial social and health cost. The estimated lifetime cost is $210,012 for one nonfatal victim in 2010 dollars. The costs include childhood health care, child welfare, adult medical care, productivity losses, special education, and criminal justice (Fang et al., 2012). Overall, CM is estimated to cost $124 billion in the US each year (Fang et al., 2012).

According to a U.S. health survey in 2010, about 37.6% of a midlife population age 50+ reported adverse childhood experiences with rates higher in females than males (Brown et al., 2013). Female adult survivors are also more vulnerable to the substantial burden of long-lasting health consequences resulting from abuse or neglect than males (Cutler & Nolen-Hoeksema, 1991; Greenfield, 2010; Weiss et al., 1999). To date, only two studies (Corso et al., 2008; Cuijpers et al., 2011) found that CM is associated with lower QALY using a one-time measure. Longitudinal community studies are needed to examine if CM is associated with impaired midlife QALY over time in maltreated women.

We previously found that multiple CM types significantly influenced midlife mental and physical HRQoL at one point in time as well as over 9 years among women (Lin et al., 2017a, 2017b),. While these are important findings in and of themselves, in the current investigation we aimed to quantify this association. Specifically, we evaluated the association of multiple CM types with an estimated number of healthy days of quality-adjusted life year (QALY) over a 9-year period (52 to 62 years old) using the data collected from the 443 participants in the community-based cohort at the Pittsburgh site of the Study of Women's Health Across Nation-Mental Health Study (SWAN-MHS). We further evaluated the extent to which adulthood psychosocial factors explained the relationship between multiple CM types and the reduced midlife QALY over time.

4.3 METHODS

Study design and participants

The Study of Women's Health Across the Nation (SWAN) is a multi-site, community-based, cohort study of midlife women enrolled at seven sites across the U.S. between 1996-97. The goal of SWAN was to investigate women's mental and physical health during the transition through menopause. Further detailed explanation of the SWAN study design is available elsewhere (Sowers, 2000). Briefly, study eligibility included aged 42 to 52 years, with at least one menstrual period in the previous three months, not currently using exogenous hormones, no surgical removal of the uterus and/or both ovaries, not pregnant, and not breastfeeding. The current investigation was based on 443 women who were also enrolled in the Mental Health ancillary study (MHS) in Pittsburgh. Participants provided written informed consent at each visit and the study was approved by the University of Pittsburgh Institutional Review Board.

Women were assessed at baseline and approximately annually with extensive questionnaires about physical, psychosocial, lifestyle, and psychological characteristics and anthropometric measures were obtained. Women also completed the Structured Clinical Interview for the Diagnosis of DSM-IV Axis I Disorders (SCID) (Spitzer et al., 1992). To be included in the current analyses women had to complete the Childhood Trauma Questionnaire and at least one Short Form-36 HRQoL questionnaire from 2002 to 2012. Of the 443 participants in SWAN-MHS, 342 (114 Black, 228 White, mean age=52 at follow-up Visit 6 or 8) completed both measures. The full Medical Outcomes Survey Short Form 36 (SF-36) was administered at follow-up Visit 6, 8, 10, 12, and 13 from 2002 to 2012. Because the full Medical

Outcomes Survey Short Form 36 (SF-36) was first administered at follow-up Visit 6 or 8, other than study entry demographics, we used data from these visits only. We refer to the SWAN baseline visit as "the study entry", Visit 6 as "the analysis baseline, time 1", Visit 8 as time 2, Visit 10 as time 3, Visit 12 as time 4, Visit 13 as time 5 hereafter.

Measures

Exposure (X): *Childhood maltreatment* experienced before 18 years old was self-reported by women using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). The 28-items were summed to derive scores on five types of CM. Each type of childhood maltreatment was classified as present using validated clinical cut-offs: emotional abuse (≥10), physical abuse (≥8), sexual abuse (≥8), physical neglect (≥8), and emotional neglect (≥15) (Bernstein et al., 2003; Walker et al., 1999). The CTQ has high test-retest reliability and strong convergent validity with therapists' ratings and clinical interviews. (Bernstein et al., 1994), In the Pittsburgh SWAN, the CTQ showed strong internal consistency with Cronbach's $\boldsymbol{\alpha}$=0.80-0.94 for each of the CTQ subscales. We summed CM types above clinical cutoffs as total number of CM types ranging from 1 to 5 for maltreated women. CTQ scores below all five clinical cutpoints were classified as women without CM. Different types of CM were further collapsed as 5 mutually exclusive CM subgroups: 1) abuse only, 2) neglect only, 3) sexual abuse only, 4) abuse and neglect, and 5) sexual abuse and other CM types (Lin et al., 2017a).

Outcome (Y): *Midlife QALY* was calculated by a validated scoring algorithm which derives the SF-6D health index from a subset of SF-36 items (Brazier, Roberts, & Deverill, 2002; Brazier et al., 1998). A health index is anchored at 1.0 indicating good health and at 0 that is equivalent to death. We primarily expressed QALY as yearly healthy days (QALY*365.25) for a simple interpretation of the current findings. The age-specific norm of the SF-6D is 0.7 for the mean and

the norm SD is 0.158 based on the normative U.K. population in women ages 55-59 years old (van den Berg, 2012). A U.S. SF-6D validation study showed that UK and US predictions of QALY were very similar (Craig, Pickard, Stolk, & Brazier, 2013).

Time-invariant mediators (M): *Lifetime and current psychiatric history* were initially diagnosed at study entry and past year and current at each follow-up by trained mental health clinicians using the SCID (Spitzer et al., 1992). The SCID is a semi-structured psychiatric interview and in SWAN-MHS has shown substantial reliability for lifetime depressive and anxiety disorders (kappa=0.81-0.82) (Bromberger et al., 2011). Lifetime psychiatric disorders were defined as occurring up to the Visit 6 or Visit 8 for any of the following disorders: major depression; minor depression; any anxiety disorder; alcohol use disorder, abuse or dependence; and non-alcohol use disorder, abuse or dependence. *Lifetime post-traumatic stress disorder (PTSD)* was diagnosed at visit 12 using the SCID and for the purpose of this study, defined as lifetime if the age of onset was within three years of the analysis baseline (Visit 6). *Low levels of optimism* were ascertained by the Life Orientation Test (LOT) (Scheier et al., 1994) at the SWAN study entry. The LOT indicates the degree to which a woman tends to have a favorable outlook on life. A lower score indicates a lower level of optimism. Since SWAN reduced the 5-point liker scale to 4-point liker scale in the LOT questionnaire, a score below the 25^{th} percentile (<10) was defined as lower levels of optimism.

Time-varying mediators (M) measured at each follow-up visit included depressive symptoms, sleep problems, very upsetting life events, and social support. *Depressive symptoms* were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D) at baseline and each follow-up visit. The CES-D is a widely used measure of depressive symptom levels with well-established reliability (Roberts, 1980), and a cut-off score $\geq$ 16 is used as an indicator of

potential clinical depression (Radloff, 1977). *Sleep problems were self-reported by w*omen and defined as at least three nights with one or more of three sleep problems in each of the past two weeks. *Very upsetting life events* were assessed by the Psychiatric Epidemiology Research Interview scale (Dohrenwend et al., 1978), modified to include events relevant to midlife women or those living in low socioeconomic environments. Women checked the life events they experienced since the last study visit and indicated how upsetting each was. Life events rated as "very upsetting" or "very upsetting and still upsetting" were totaled and categorized as 1 or more versus none. *Social support*, both instrumental and emotional support was assessed by four items from the Medical Outcomes Study Social Support Survey (Sherbourne & Stewart, 1991). Participants were asked how often each of 4 kinds of support is available to them when they need it: someone listens to you; someone takes you to the doctor; someone confides in or talk to, and someone helps with daily chores. The total score ranged from 0 to 16. A score below the 25th percentile (<12) was defined as low social support since a standard cut-point is not available.

Exposure-Outcome Confounders (C_{XY}) included age at each visit, race, and childhood socioeconomic circumstances (SES). Childhood SES before 19 years old was self-reported at Visit 7 and was assessed with questions about maternal and paternal education, and participant's childhood financial circumstances such as family owned their own home or a car, family ever received public assistance, or family ever had a hard time paying for rent or food. Previous work in SWAN has reported that childhood SES measures are moderately reliable (Montez et al., 2016).

Mediator-Outcome Confounders (L_{MY}): Adulthood sociodemographic factors include educational attainment, marital status, and adulthood financial strain (i.e., difficulty paying for basics as somewhat hard or very hard). Lifestyle behavioral variables (i.e., current smoking,

weekly alcohol consumption, and physical activity) and body mass index (BMI) (kg/m^2) were included as confounders. A total number of lifetime medical conditions were summed from the self-report questionnaire inquiring about 12 pre-specified medical conditions, and we categorized the total number of lifetime medical conditions as 0, 1 and 2 or more. Menopausal status was included and categorized based on menstrual bleeding patterns in the previous 12 months (WHO, 1996). The presence of vasomotor symptoms (hot flashes and night sweats) in the past two weeks, was ascertained as part of a symptom checklist frequently used in studies of menopause. Ever use of oral contraceptives or hormone replacement therapy during SWAN follow-ups, and lifetime treatment for emotional problems was self-reported. Trait anger and trait anxiety were assessed by the Spielberger Trait Anger and Trait Anxiety Scales, respectively, at visit 7 (Spielberger & Reheiser, 2009). Higher scores indicate higher levels of trait anger or trait anxiety.

Statistical analysis

We compared characteristics of the women with and without any CM exposure using Kruskal-Wallis tests for continuous variables and Chi-square tests for categorical variables. To calculate the effect sizes for group differences, we used the norm SD=0.158 for QALY (i.e. 57.7 yearly healthy days) in women aged 55-59 years old (van den Berg, 2012). Effect sizes are calculated as group differences in QALY divided by SD_{norm}. We defined group differences in QALY with effect sizes <0.2 as small and not clinically meaningful, effect sizes 0.2-0.5 as moderate and potentially meaningful, and effect sizes >0.5 as large and clinically meaningful (Norman et al., 2003; Yost et al., 2005). Half of the SD (0.158*0.5=0.079 or 0.079 *365.25=28.8 days) is defined as the clinically meaningful difference in QALY per year between two groups in the current study.

Analytic diagram (**Figure 3-1**) illustrates the relationship between childhood maltreatment (X), time-varying potential psychosocial mediators (M_1 to M_5), QALY outcomes over five visits (Y_1 to Y_5), exposure-outcome confounders (C_{XY}), and time-varying mediator-outcome confounders (L_1 to L_5). Age at baseline, race, and childhood SES variables were considered as a vector of C_{XY} confounders between CM and QALY. A vector of time-varying adulthood confounders (L_1 to L_5) of the association between mediators and HRQoL outcomes included financial strain, lifestyle behaviors, BMI, the number of lifetime medical conditions, menopausal status, vasomotor symptoms, and use of hormone therapy since SWAN study entry. Education, marital status, trait anger and trait anxiety, and lifetime treatment for emotional problems at analysis baseline were time-invarying adulthood confounders. Due to the long-term effect of CM, several factors among the adulthood confounders are associated with CM and could be considered as exposure-induced mediator-outcome confounders (Vanderweele et al., 2014), including time-varying adulthood confounders (financial strain, current smoking, weekly alcohol consumption, physical activity, BMI) and time-invarying confounders (education, trait anger, trait anxiety, treatment for emotional problems).

Main associations between CM and midlife QALY over time was assessed by generalized estimating equation models with exchangeable working correlation adjusting for years since analysis baseline, race, and childhood socioeconomic circumstances.

Mediation analysis: Longitudinal mediation analysis was similar to our previous work (Lin et al., 2017b). A series of structural nested mean models (SNMM) estimated via doubly robust g-estimation was used to quantify the extent to which CM would be associated with QALY if each time-varying mediators were set to zero uniformly in the population after accounting for confounders C_{XY} and L_{MY} and previous QALY outcomes. Confidence intervals for ψ were

obtained using 1000 bootstrap samples for each imputation data sets in R. The proportion of the total association between any CM and QALY explained by the mediator was calculated as (overall association – controlled direct associations) divided by overall associations*100%. Detailed steps of our mediation analysis are illustrated in the Appendix Figure 2 flowchart. The overall proportion of missing data was 12% for the 342 participants for all the analytic variables across five visits. The proportion of missing for QALY outcomes from time 1 to time 5 were 6%, 7%, 11%, 16%, and 16%, respectively. Missing data for outcomes, time-varying mediators, and adulthood confounders were imputed using multivariate imputations by chained equations in R (mice package) to generate 20 completed analysis data sets with 25 iterations. We compared the distributions of imputed and observed values to inspect implausible values and convergence figures of MICE algorithm. SAS 9.4 (SAS Institute, Cary NC, USA) and R 3.2.3 were used for statistical analyses.

4.4 RESULTS

Mean (SD) age was 52 (2.5) years at the analysis baseline and 66% of the women in the sample were white (**Table 4-1**). Single CM was reported by 63 (18%) women, and 2+ CM types were reported by 67 (20%) women. **Table 4-1** shows a description of the characteristics of the sample overall and those with and without CM. Mean (SD) for QALY were above the norm of 255.7 healthy days per year (i.e. norm QALY=0.7*365.25 days) throughout the five time-points: 268.4 (43.2), 268.5 (42.0), 267.7 (42.0), 264.2 (45.8), and 261.7 (43.2). However, the lowest yearly healthy days at time 5 was observed among women with multiple CM types, particularly in women who were abused and neglected (mean ± SD: 243.9 ± 39.4) or sexually abused with other CM types (mean ± SD: 239.6 ± 43.4) (**Table 4-2** and **Figure 4-1**).

The overall associations between CM and midlife QALY over time after adjusting for years since baseline, race, and childhood SES are shown in **Table 4-3**. Each type of CM was significantly associated with fewer yearly healthy days over time in separate analyses. Compared to women without CM, women with 2+ CM types reported a clinically meaningful difference of 28.3 fewer yearly healthy days (95%CI: -37.2, -19.5). For mutually exclusive CM subgroups, childhood sexual abuse alone, abuse and neglect or sexual abuse along with other CM types were both associated with impaired midlife QALY over time. On average, QALY decreased only 0.7 healthy days (95% CI: -1.3, -0.2) per year over time in our study sample. The change in QALY per year over time did not differ between women with and without CM. Overall, black women had 11.8 fewer yearly healthy days (95% CI: -20.1, -3.4) than white women adjusting for the total number of CM types, age, and childhood SES. The association between CM and QALY over time did not differ by race after adding an interaction term between CM and race for each type of CM.

In separate mediation analyses (**Table 4-4**), low levels of optimism, time-varying sleep problems, and time-varying low social support explained a notable proportion (≥10%) of the relation between 2+ CM types and QALY in separate mediation models; however, multiple CM types remained stable association with midlife QALY over time.

4.5 DISCUSSION

To our knowledge, this is the first study to assess the life-course impact of childhood maltreatment on the longitudinal QALY among midlife women using data from a community-based cohort study. We found that women with multiple forms of CM had 28 fewer healthy days per year over a 9-year follow-up (mean 52 to 62 years old) than those without CM after adjusting for years since baseline, race, and childhood SES variables. The associations between multiple forms of CM and impaired QALY remained stable after accounting for the mediating role of each psychosocial factors.

Cuijpers et al. (2011) found that childhood abuse and neglect were strongly associated with impaired QALY using a one-time measure even after accounting for mental disorders in a population sample of 7,076 with a mean age of 41 years in the Netherlands. Corso et al. (2008) reported that individuals with CM aged 50-59 years old had 8.4 fewer healthy days per year (0.023 QALY) compared to those without CM using data collected from the Kaiser Permanent's Health Appraisal Clinic in San Diego in 1997.

Our longitudinal results also suggested a substantial burden on quality-adjusted life years resulted from childhood maltreatment. Particularly, abuse and neglect or sexual abuse along with other CM types before 18 years old had significantly impaired QALY during mid-50's over time with moderate effect sizes from 0.4 to 0.5. Childhood sexual abuse alone is also related to 12 fewer healthy days per year compared to those without CM. Multiple types of CM (abuse and neglect or sexual abuse and other types) and childhood sexual abuse alone would be important

subgroups among maltreated women, who may be targeted for interventions to mitigate the long-lasting impact of CM on overall well-being from midlife through older adulthood.

After applying a series of longitudinal mediation analysis, we found that adult psychosocial factors only partially explained the relationship between CM and QALY. Low levels of optimism, time-varying sleep problems, and time-varying low social support respectively explained 19%, 23%, and 14% of the relationship between multiple CM types and QALY over time. Our findings consistently suggested that CM is an important life-course social determinant for fewer yearly healthy days during midlife in women.

Our findings have better generalizability compared to clinical samples because we used data from a community-based cohort study with extensive demographic, behavioral, and HRQoL data. The assessments of the CM exposure, longitudinal QALY, and psychosocial mediators were ascertained by validated and standardized instruments. Third, we performed time-varying mediation analysis on the longitudinal outcomes using novel mediation statistical approach to accounting for time-varying mediators, time-varying outcomes, and time-varying confounders that are potentially affected by the exposure. Fourth, we comprehensively controlled for childhood SES variables and many adulthoods' mental or physical health-related confounders in the mediation analyses to assess the controlled direct effect of multiple CM on midlife QALY. Fifth, we addressed missing data by multiple imputations and the results are similar between observed data and imputed data.

Regarding limitations, we retrospectively assessed childhood maltreatment so recall bias for the misclassification of the CM exposure may occur. However, CTQ has been validated with good test-retest reliability and strong convergent validity with therapists' rating and clinical

interview (Bernstein et al., 2003). The severity of CM, age onset of CM, and adulthood abuse or neglect were not assessed and not accounted for in our analyses.

Our results suggest that women with multiple forms of CM had a clinically meaningful burden of fewer yearly healthy days over a 9-year period compared to those without CM in women. Adulthood psychosocial factors (i.e. low levels of optimism, sleep problems, or low social support) partially explain the association between CM and midlife QALY. These modifiable factors may be targeted to improve overall well-being among maltreated women in the future intervention studies.

4.6 TABLES AND FIGURES

Table 4-1 Characteristics of women by CM exposure at the analysis baseline.

Characteristics	All N=342	No CM N= 212 (62.0%)	At least one CM N=130 (38.0%)
Exposure-outcome confounders (C_{XY})			
Age at the analysis baseline, Mean (SD)	52.2 (2.5)	52.3 (2.6)	52.1 (2.4)
Race/Ethnicity			
Black	114 (33.3)	67 (31.6)	47 (36.2)
Childhood socioeconomic circumstances			
Maternal Education less than college	272 (79.5)	171 (80.7)	101 (77.7)
Paternal Education less than college	236 (69.0)	150 (70.8)	86 (66.2)
Childhood family…			
…did not own a car	43 (12.6)	27 (12.7)	16 (12.3)
…did not own a home*	72 (21.1)	37 (17.5)	35 (26.9)
…ever received public assistance*	52 (15.2)	25 (11.8)	27 (20.8)
…ever had difficulty paying for food or rent**	120 (35.1)	51 (24.1)	69 (53.1)
Exposure: Childhood maltreatment (X)			
Total numbers of childhood maltreatment types			
0	212 (62.0)	212 (100.0)	0 (0.0)
1	63 (18.4)	-	63 (48.5)
2+	67 (19.6)	-	67 (51.5)
CM types, not mutually exclusive			
Emotional Abuse (≥10)	71 (20.8)	-	71 (54.6)
Physical Abuse (≥8)	60 (17.5)	-	60 (46.2)
Emotional Neglect (≥15)	26 (7.6)	-	26 (20.0)
Physical Neglect (≥8)	53 (15.5)	-	53 (40.8)
Sexual Abuse (≥8)	51 (14.9)	-	51 (39.2)
CM types, mutually exclusive			
No CM	212 (62.0)	212 (100.0)	0 (0.0)
Abuse only	38 (11.1)	-	38 (29.2)
Neglect only	15 (4.4)	-	15 (11.5)
Sexual abuse only	16 (4.7)	-	16 (12.3)
Abuse and neglect	26 (7.7)	-	26 (20.0)
Sexual abuse and other CM types	35 (10.4)	-	35 (26.9)
Potential psychosocial mediators (M)			
Lifetime psychiatric history*	201 (58.8)	115 (54.2)	86 (66.2)
Lifetime post-traumatic stress disorder**	56 (16.4)	21 (9.9)	35 (26.9)
Low levels of optimism (<25th percentile=10)*	82 (24.0)	41 (19.3)	41 (31.5)
High depressive symptoms**	63 (18.4)	30 (14.2)	33 (25.4)
Sleep problems (≥ 3 times /week)	139 (40.6)	79 (37.3)	60 (46.2)
Total very upsetting life events* (1+)	164 (48.0)	91 (42.9)	73 (56.2)
Low social support**	61 (17.8)	27 (12.7)	34 (26.2)

Table 4-1 Continued

Mediator-outcome confounders (L_{MY})			
Education attainment less than college	198 (57.9)	131 (61.8)	67 (51.5)
Marital status			
Single	35 (10.2)	21 (9.9)	14 (10.8)
Married or living with someone as if married	238 (69.6)	150 (70.8)	88 (67.7)
Separate/divorced/widowed	69 (20.2)	41 (19.3)	28 (21.5)
Adulthood financial strain* (somewhat or very hard to pay for very basics)	83 (24.3)	43 (20.3)	40 (30.8)
Current smoker	60 (17.5)	38 (17.9)	22 (16.9)
Weekly alcohol consumption			
None	172 (50.3)	99 (46.7)	73 (56.2)
<2 times	89 (26.0)	60 (28.3)	29 (22.3)
2-7 times	59 (17.3)	39 (18.4)	20 (15.4)
>7 times	22 (6.4)	14 (6.6)	8 (6.2)
Total number of medical conditions			
0	157 (45.9)	100 (47.2)	57 (43.8)
1	93 (27.2)	54 (25.5)	39 (30.0)
2+	92 (26.9)	58 (27.4)	34 (26.2)
Menopausal status			
Premenopausal	17 (5.0)	9 (4.2)	8 (6.2)
Late peri-menopausal or early perimenopausal	129 (37.7)	87 (41.0)	42 (32.3)
Natural postmenopausal	134 (39.2)	81 (38.2)	53 (40.8)
Surgical postmenopausal	35 (10.2)	21 (9.9)	14 (10.8)
Unknown with hormone therapy	27 (7.9)	14 (6.6)	13 (10.0)
Vasomotor Symptoms			
None	148 (43.3)	101 (47.6)	47 (36.2)
1-5 days/ 2 weeks	117 (34.2)	67 (31.6)	50 (38.5)
≥ 6 days/ 2 weeks	77 (22.5)	44 (20.8)	33 (25.4)
Ever use hormone since SWAN study entry*	135 (39.5)	74 (34.9)	61 (46.9)
Lifetime medical treatment for emotional problems** (Yes)	71 (20.8)	33 (15.6)	38 (29.2)
Physical activity score excluding work*	7.6 (1.7)	7.8 (1.7)	7.4 (1.7)
Body mass index (kg/m^2)**	30.1 (6.8)	29.2 (6.5)	31.6 (6.9)
Spielberger trait anxiety**	15.3 (4.5)	14.9 (4.5)	16.1 (4.3)
Spielberger trait anger**	14.1 (3.8)	13.5 (3.1)	15.1 (4.5)

N (%) are shown for each level of categorical variables. Mean (standard deviation) is presented for continuous variables.
*$p<0.05$
**$p<0.01$

Table 4-2 Mean (SD) of QALY expressed as a proportion (SF-6D) or yearly healthy days over time by CM.

HRQoL		N	Baseline	2 years since baseline	4 years since baseline	8 years since baseline	10 years since baseline
			Time 1	Time 2	Time 3	Time 4	Time 5
QALY (SF-6D)	All	342	0.735 (0.118)	0.735 (0.115)	0.733 (0.115)	0.723 (0.125)	0.717 (0.118)
Total numbers of CM types							
	No CM	212	0.753 (0.119)	0.749 (0.117)	0.760 (0.111)	0.743 (0.120)	0.733 (0.121)
	1 CM type	63	0.732 (0.097)	0.740 (0.101)	0.727 (0.104)	0.727 (0.114)	0.722 (0.100)
	2+ CM types	67	0.681 (0.120)	0.686 (0.111)	0.654 (0.102)	0.659 (0.131)	0.659 (0.110)
CM types, mutually exclusive							
	No CM	212	0.753 (0.119)	0.749 (0.117)	0.760 (0.111)	0.743 (0.120)	0.733 (0.121)
	Abuse only	38	0.740 (0.097)	0.756 (0.103)	0.707 (0.116)	0.732 (0.129)	0.703 (0.106)
	Neglect only	15	0.689 (0.157)	0.698 (0.122)	0.719 (0.112)	0.727 (0.101)	0.736 (0.105)
	Sexual abuse only	16	0.714 (0.092)	0.707 (0.101)	0.733 (0.107)	0.721 (0.093)	0.724 (0.080)
	Abuse and neglect	26	0.718 (0.107)	0.687 (0.114)	0.676 (0.087)	0.661 (0.132)	0.668 (0.108)
	Sexual abuse and other CM types	35	0.663 (0.107)	0.693 (0.102)	0.647 (0.104)	0.643 (0.128)	0.656 (0.119)
Yearly healthy days (QALY*365.25 days)	All	342	268.4 (43.2)	268.5 (42.0)	267.7 (42.0)	264.2 (45.8)	261.7 (43.2)
Total numbers of CM types							
	No CM	212	275.0 (43.4)	273.5 (42.6)	277.5 (40.4)	271.2 (44.0)	267.7 (44.1)
	1 CM type	63	267.3 (35.5)	270.5 (37.0)	265.5 (38.0)	265.4 (41.5)	263.7 (36.5)
	2+ CM types	67	248.8 (43.8)	250.7 (40.4)	238.7 (37.1)	240.8 (47.9)	240.7 (40.3)
CM types, mutually exclusive							
	No CM	212	275.0 (43.4)	273.5 (42.6)	277.5 (40.4)	271.2 (44.0)	267.7 (44.1)
	Abuse only	38	270.4 (35.4)	276.1 (37.8)	258.4 (42.4)	267.4 (47.0)	256.7 (38.8)
	Neglect only	15	251.7 (57.4)	255.1 (44.5)	262.7 (41.0)	265.5 (37.1)	268.7 (38.3)
	Sexual abuse only	16	260.7 (33.7)	258.3 (36.8)	267.8 (38.9)	263.4 (34.0)	264.6 (29.2)
	Abuse and neglect	26	262.3 (39.0)	250.9 (41.8)	246.8 (31.7)	241.5 (48.3)	243.9 (39.4)
	Sexual abuse and other CM types	35	242.1 (39.1)	253.3 (37.1)	236.2 (38.0)	234.8 (46.7)	239.6 (43.4)

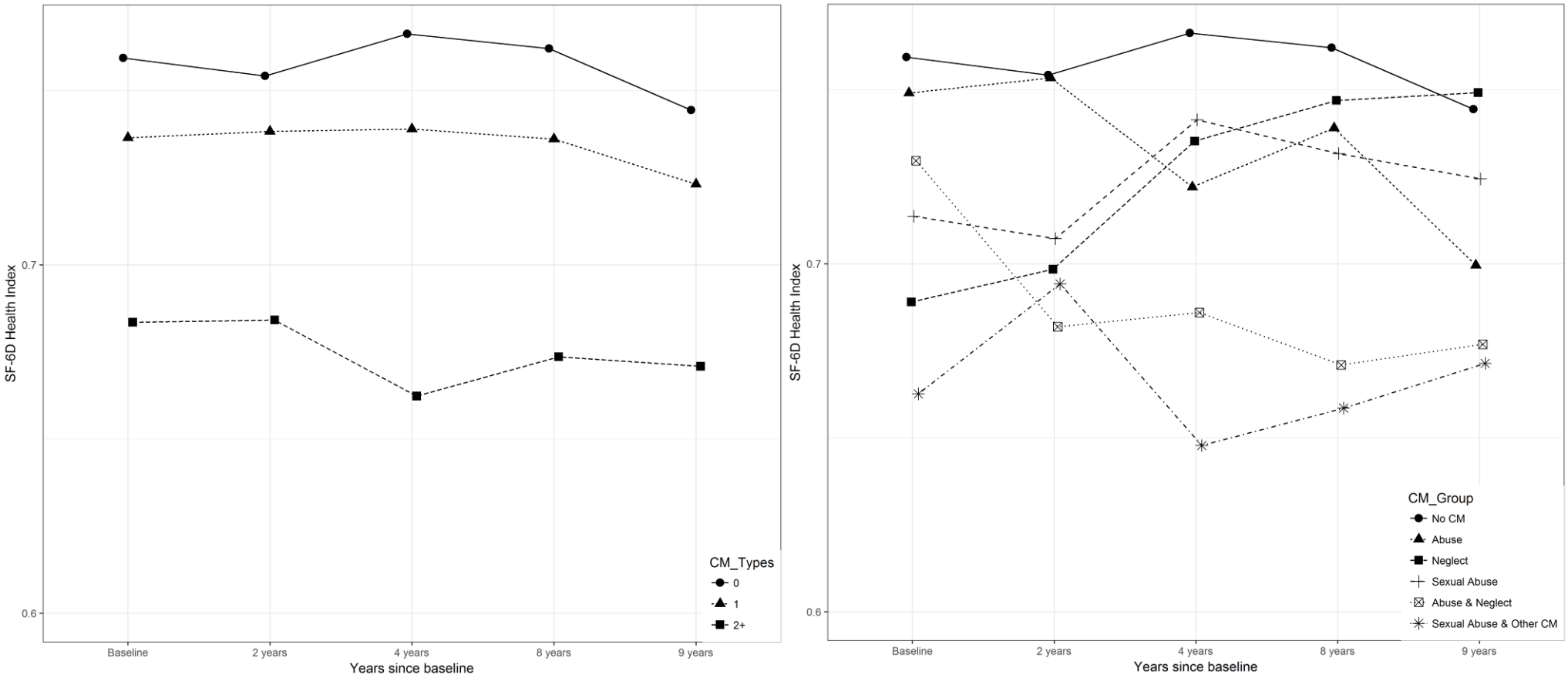

Figure 4-1 Mean yearly quality-adjusted life (SF-6D) over time by total numbers of childhood maltreatment types and CM subgroups.

Table 4-3 Associations between CM and quality-adjusted life years over 9 years.

Models[a]	**Childhood Maltreatment**		**Quality-adjusted life year (QALY) Difference of yearly healthy days**	
			β (95% CI)[b]	Effect Size[c]
Model 1	Any Childhood Maltreatment	No	reference	
		Yes	-17.3 (-24.4, -10.2)*	-0.30
Model 2	Emotional Abuse	No	reference	
		Yes	-19.0 (-27.5, -10.4)*	-0.33
Model 3	Physical Abuse	No	reference	
		Yes	-22.3 (-32.2, -12.4)*	-0.39
Model 4	Emotional Neglect	No	reference	
		Yes	-36.1 (-50.5, -21.8)*	-0.62
Model 5	Physical Neglect	No	reference	
		Yes	-18.1 (-27.4, -8.8)*	-0.31
Model 6	Sexual Abuse	No	reference	
		Yes	-21.2 (-30.4, -12.0)*	-0.37
Model 7	Total number of CM	No CM	reference	
		1 CM type	-6.1 (-14.5, 2.3)	-0.11
		2+ CM types	-28.3 (-37.2, -19.5)*	-0.49
Model 8	CM groups	No CM	reference	
		Abuse only	-4.4 (-15.4, 6.6)	-0.08
		Neglect only	-13.4 (-30.4, 3.7)	-0.23
		Sexual abuse only	-12.4 (-24.1, -0.7)*	-0.21
		Abuse & neglect	-24.4 (-37.0, -11.7)*	-0.42
		Sexual abuse & other CM	-31.0 (-42.6, -19.3)*	-0.54

[a] Generalized estimating equation (GEE) with an exchangeable working correlation matrix was used to estimate the association between CM and HRQoL over time adjusting for years since analysis baseline, race, and childhood socioeconomic circumstances.

[b] If a 95% confidence interval includes 0, then there is no statistically significant difference between the groups. (*p<0.05)

[c] Effect sizes are calculated as group differences in yearly healthy days divided by normative SD. The reference norm SD=0.158 for SF-6D index (i.e. 57.7 yearly healthy days) was based on the normative U.K. population in women aged 55-59 years old (van Den Berg, 2012). A U.S. SF-6D validation study showed that UK and US predictions of QALY were extremely similar (Craig et al., 2013).

|Effect size|: <0.2 small not clinically meaningful, 0.2-0.5 moderate and potentially meaningful, >0.5 large and clinically meaningful.

Table 4-4 (a) Associations between CM and each mediator and (b) controlled direct associations between CM and QALY over 9 years.

Mediation models (analyzed respectively)		**(a) Associations between CM and each mediator**			**(b) Controlled direct associations (ψ) between CM and QALY after respectively accounting for each time-varying mediator across 5 time points[c]**	
		Mediators N (row %) at baseline		OR (95% CI)[a] of each mediator predicted by CM	Quality-adjusted life year (QALY) Difference of yearly healthy days	
		No	Yes		ψ (95% CI)	Proportion Explained%
Overall association between 2+ CM types and QALY					**-25.70 (-28.26, -23.14)***	
Model 1		Lifetime psychiatric history		(time-fixed)		
CM	No	127 (46.2)	148 (53.8)	1.80 (1.30, 2.49)*	reference	
	Yes	14 (20.9)	53 (79.1)		-29.31 (-33.32, -25.31)*	-14%
Model 2		Lifetime post-traumatic stress disorder		(time-fixed)		
CM	No	243 (88.4)	32 (11.6)	2.16 (1.51, 3.09)*	reference	
	Yes	43 (64.2)	24 (35.8)		-35.96 (-40.2, -31.72)*	-40%
Model 3		Low levels of optimism		(time-fixed)		
CM	No	221 (80.4)	54 (19.6)	1.75 (1.28, 2.40)*	reference	
	Yes	39 (58.2)	28 (41.8)		-20.73 (-23.92, -17.54)*	19%
Model 4		High depressive symptoms		(time-varying)		
CM	No	235 (85.5)	40 (14.5)	2.45 (1.69, 3.55)*	reference	
	Yes	44 (65.7)	23 (34.3)		-25.79 (-29.19, -22.39)*	0%
Model 5		Sleep problems		(time-varying)		
CM	No	173 (62.9)	102 (37.1)	1.43 (1.00, 2.04)*	reference	
	Yes	30 (44.8)	37 (55.2)		-19.88 (-24.40, -15.35)*	23%
Model 6		Very upsetting life events		(time-varying)		
CM	No	154 (56.0)	121 (44.0)	1.94 (1.44, 2.62)*	reference	
	Yes	24 (35.8)	43 (64.2)		-33.34 (-37.60, -29.08)*	-30%
Model 7		Low social support		(time-varying)		
CM	No	238 (86.5)	37 (13.5)	3.71 (2.33, 5.92)*	reference	
	Yes	43 (64.2)	24 (35.8)		-22.17 (-25.64, -18.70)*	14%

a ORs for each time-fixed mediator predicted by 2+ CM (vs 0 or 1 CM) were estimated by logistic regression adjusted for age, race, and childhood socioeconomic circumstances. ORs for each time-varying mediator predicted by 2+ CM (vs 0 or 1 CM) were estimated by generalized estimating equation (GEE) with logit link adjusted for years since baseline, race, and childhood socioeconomic circumstances. If an OR 95% confidence interval includes 1, then there is no statistically significant difference between the groups. (*p<0.05)

b If a 95% confidence interval includes 0, then there is no statistically significant difference between the groups. (*p<0.05)

Table 4-4 Continued

c Controlled direct associations between 2+ CM types and HRQoL accounting for each potential mediator as 0, respectively, were examined by doubly-robust structural nested mean model after adjusting for age, race, childhood socioeconomic circumstances, education attainment, marital status, adulthood financial strain, smoking, alcohol consumption, total number of medical conditions, menopausal status, hormone therapy use, vasomotor symptoms, physical activity, body mass index, trait anxiety, trait anger, and ever treated for emotional problems.
d Proportion explained by each mediator for QALY = (Overall association - ψ)/ Overall association × 100%

5.0 GENERAL SUMMARY

5.1 FINDINGS FROM THREE PAPERS

Paper 1: Childhood maltreatment and midlife HRQoL (baseline analyses)

Thirty-eight percent of women in SWAN-MHS reported at least one type of CM experienced before 18 years old. After accounting for age, race, and childhood SES, the mean mental (MCS) and physical (PCS) component scores were 2.3 points (95% CI: -4.3, -0.3) and 2.5 points (95% CI: -4.5, -0.6) lower in women with CM than those without, respectively. The examination of each type of CM showed childhood sexual abuse had a moderate relationship with lower MCS; childhood physical abuse had a moderate association with lower PCS, and childhood emotional neglect had a strong and clinically meaningful relationship with reduced PCS. Compared to women with no CM at the analysis baseline, there was no clinically meaningful difference (< 2 points) in MCS or PCS among women with single CM. Women with multiple CM types reported moderately lower mean scores of MCS [β (95% CI): -3.6 points (-6.4, -0.8)] and PCS [-3.5 points (-6.1, -0.8)]. In analyses comparing subgroups of different types of CM exposures, the subgroup reporting childhood sexual abuse and other CM types was associated with a clinically meaningful difference of -5.5 points (95% CI: -9.8, -1.2) in MCS. In the baseline mediation analyses, upsetting life events, high depressive symptoms, and low social support were found to explain more than 20% of the relationship between any CM and MCS only, not in PCS.

Paper 2: Childhood maltreatment and midlife HRQoL over 9 years

Overall, the MCS increased but PCS decreased over 9 years regardless the CM history. The opposite direction of MCS and PCS outcomes is consistent with the previous findings (Jokela et al., 2010). The rate of the change (regression slopes) in HRQoL over time did not differ by any CM versus no CM. However, women with multiple CM types started with lower HRQoL from the analysis baseline and remained low scores over a 9-year follow-up compared to women without CM or single CM type. In the adjusted longitudinal analyses with a 9-year follow-up, any CM was associated with 2.8 points (95% CI: -4.4, -1.2) lower MCS and 2.4 points (95% CI: -4.0, -0.7) lower PCS compared to no CM. Multiple CM types were associated with a clinically meaningful difference in MCS [-5.1 (-7.3, -2.9)] and a moderate difference in PCS [-3.9 (-6.2, -1.5)] compared to no CM. The examination of each type of CM showed emotional neglect had a clinically meaningful difference in both MCS and PCS, while other each CM type was moderately associated with reduced MCS and PCS in separate analyses. In analyses comparing subgroups of different types of CM exposures, the subgroup reporting childhood abuse and neglect was associated with a clinically meaningful difference of 5.2 fewer points (95% CI: -8.9, -1.4) in MCS and moderately meaningful difference of 3.5 fewer points (95% CI: -6.2, -0.7) in PCS compare to no CM. The subgroup reporting childhood sexual abuse and other CM types was also associated with a moderately meaningful difference of -4.8 points (95% CI: -7.5, -2.1) in MCS and -4.0 points (95% CI: -7.5, -0.4) in PCS. Results of longitudinal mediation analyses showed that low levels of optimism, time-varying sleep problems, and time-varying low social support were consistently found to explain more than 20% of the relationship between multiple CM and both MCS and PCS over time. Time-varying high depressive symptoms explained more than 20% of the association between multiple CM and MCS only, not in PCS.

Paper 3: Childhood maltreatment and midlife QALY over 9 years

QALY was expressed as yearly healthy days reported by women in the paper 3. The QALY per year is quite stable during the 9-year follow-up since QALY is the overall health index combining both MCS and PCS. The rate of the change (regression slopes) in QALY over time did not differ by any CM versus no CM. However, women with multiple CM types started with lower QALY from the analysis baseline and remained low scores over 9 years compared to women without CM or single CM type. In the adjusted longitudinal QALY analysis, women with at least one CM had an average of 17 fewer healthy days per year than those without CM. There was a clinically meaningful difference of 28.3 fewer yearly healthy days (95% CI: -37.2, -19.5) in women with multiple CM than without CM. The examination of each type of CM showed emotional neglect had a clinically meaningful difference of 36.1 fewer yearly healthy days (95% CI: -50.5, -21.8) in QALY over time, while other each CM type was moderately associated with reduced QALY over time in separate analyses. In analyses comparing subgroups of different types of CM exposures, the subgroup reporting childhood sexual abuse only was associated with 12.4 fewer yearly healthy days (95% CI: -24.1, -0.7); the subgroup reporting childhood abuse and neglect was associated with a moderately difference of 24.4 fewer yearly healthy days (95% CI: -37.0, -11.7); and the subgroup reporting childhood sexual abuse and other CM types was associated with a clinically meaningful difference of 31.0 fewer yearly healthy days (95% CI: -42.6, -19.3). In the separate longitudinal mediation analyses, low levels of optimism and time-varying low social support explained >10% while sleep problems explained >20% for the relationship between multiple CM and yearly QALY outcome over 9 years.

5.2 DISCUSSION

The prevalence of CM in our study was consistent with the U.S. health survey in 2010, which also found that 38% of midlife women and men aged 50 years older with at least one adverse childhood experiences (Brown et al., 2013). The association between multiple forms of CM and reduced HRQoL were identified in the previous literature with one-time measurement of HRQoL. A population study in Netherlands with adults aged 18-64 years reported graded associations between total numbers of CM and both SF-36 MCS and PCS (Afifi et al., 2007). Women aged 18-64 with both childhood physical and sexual abuse reported significantly lower scores on both MCS and PCS in a randomly sampled insured female population (Bonomi et al., 2008). A Swedish study with children aged 15 years old also suggested a dose-response relationship between the total number of CM types and child quality of life (Jernbro et al., 2015). Our investigation found a gradient relationship between the total number of CM types and midlife HRQoL/QALY not only in the analysis baseline but also in the longitudinal analyses.

Afifi et al. found each type of CM was significantly associated with lower scores in MCS and PCS in a large Dutch population sample of 7,076 males and females (Afifi et al., 2007). However, a large U.S. insurance-based study with men and women found that childhood emotional neglect had the strongest influence on reduced well-being, followed by childhood sexual abuse and childhood physical abuse (Corso et al., 2008). Findings from our baseline and longitudinal analyses also indicated that childhood emotional neglect had a strong and clinically meaningful relationship with reduced MCS, PCS, and QALY. Overall, we found that childhood abuse and neglect and sexual abuse along with other CM types are more salient compared to single CM types in terms of long-term outcomes of midlife HRQoL and QALY.

We performed a novel mediation analysis method to identify potential pathways underlying the relationship between multiple forms of CM and midlife HRQoL/QALY over a 9-year follow-up. Adult psychosocial mediators (high, depressive symptoms, low levels of optimism, sleep problems, and low social support) partially explained the relationship between CM and HRQoL/QALY. It was not surprising that adult depressive symptom levels were mediators of the link between CM and HRQoL as they are strongly associated with compromised quality of life. Social support was identified as an important explanatory factor for the poor disease-specific HRQoL among 132 breast cancer female survivors with CM history (Fagundes et al., 2012). Data from 2009 Behavioral Risk Factors Surveillance System (BRFSS) (Barile et al., 2015) reported that lower emotional support partially contributed to the poor HRQoL measured by two items among 29,212 female and male adults with adverse childhood experiences (ACE). Lower scores of mental and physical HRQoL measured by SF36 were also observed among patients with non-cardiac chest pain who had CM history and a lack of social support compared to those with available social support and with CM or without CM (Biggs, 2004).

The literature has reported that several characteristics may protect women from the deleterious effect of CM. Although optimism is considered to be a trait with 25% heritability and is relatively stable over time, there is some evidence that level of optimism can be increased and changed by interventions (Heinonen et al., 2005; Meevissen et al., 2011; Peters et al., 2010). A longitudinal study found that the increased levels of optimism over four years were associated with better overall well-being and fewer chronic illness over time among older adults aged from 51 to 97 years old (Chopik et al., 2015). Among a sample of 266 postpartum mothers with CM history from a longitudinal cohort, positive parenting, family functioning, and resilience were

significant predictors of a mother's perceptions of quality of life independent of psychiatric symptoms and income (Irwin et al., 2016). Better health was also reported by young adults with strengths in meaning making, emotion regulation, community support, social support, and practicing of forgiveness compared to those without these protective factors independent of CM history in a rural community sample of 2565 young adults (Banyard et al., 2017).

Our mediation findings suggest that prevention or intervention efforts to improve well-being in midlife victims of childhood maltreatment focus on promoting a broad spectrum of protective factors such as developing positive emotion toward the meaning of life, strengthening the social support network, increasing levels of resilience, reducing depressive symptoms, or alleviating sleep problems. Chandler et al. (2015) conducted a short-term pilot intervention study to evaluate the feasibility and potential efficacy of the Empower Resilience Intervention (ERI) among 28 female undergraduate students who had adverse childhood experiences. The ERI framework including active coping, building strength, cognitive flexibility, and social support can potentially increase health-promoting behaviors and build resilience for young adult maltreated female survivors (Chandler et al., 2015). Perhaps, such an intervention may be helpful for older women as well.

5.3 STRENGTHS AND LIMITATIONS

The findings from this comprehensive investigation addressed gaps in the current literature in the following way. 1) We examined each type of CM in all three papers while only 5 out of 19 prior studies examined specific types. 2) Our findings were based on a community-based cohort sample with better generalizability of results compared with clinical samples that predominate the current literature. 3) We are one of the first longitudinal studies to assess the temporal relationship of CM and HRQoL/QALY over an extended period of time. 4) Total numbers of CM types and mutually exclusive CM subgroups were assessed in our investigation. 5) Child neglect which has been overlooked in the literature was examined in our investigation. 6) We accounted for many possible confounders from childhood to adulthood (e.g. childhood family SES, adulthood medical conditions, marital status, medication use for mental problems) for CM and HRQoL/QALY. 7) We considered both risk and protective modifiable factors in the mediation analyses including time-fixed psychosocial factors (e.g. lifetime psychiatric history, lifetime post-traumatic stress disorder, low levels of optimism) and time-varying psychosocial factors (e.g. depressive symptoms, sleep problems, very upsetting life events, low social support). 8) Time-fixed and time-varying mediation analyses were performed using the doubly-robust structural nested mean model, which is a more general statistical approach requiring less stringent assumptions than the difference or product methods. and should be evaluated with appropriate analytic approaches. 9) We addressed missing data by multiple imputations and the results are similar between observed data and imputed data. 10) The measurement of CM exposure, HRQoL/QALY outcomes, covariates, and mediators were assessed by standardized and validated instruments.

Several limitations of our studies should be mentioned. First, childhood maltreatment was assessed retrospectively by the self-report CTQ and the age of CM onset was not assessed. Retrospective self-report information may potentially result in recall bias and misclassification of the exposure. However, it has previously been shown that the CTQ has high test-retest reliability and strong convergent validity with therapists' ratings and clinical interviews (Bernstein et al., 2003). Second, adulthood experience of abuse was not assessed and not accounted for in our analyses. Third, our analytic sample was based on data collected at the study 6th or 8th Visit which may have introduced left-truncation bias if the characteristics of the current analysis sample at these visits differ from those of the cohort at study entry. However, women remaining in the current study did not differ substantially from the original sample on age and race/ethnicity but included women were more likely to have a college education or higher, and more likely to be married or living with someone as if married. Fourth, we did not have sufficient statistical power to examine multiple mediators in one model due to the relatively small analytic sample. Nevertheless, the controlled direct association of CM on HRQoL accounting for each psychosocial mediator in separate analyses may still provide some guidance for targets of future intervention studies to enhance HRQoL in middle-aged women with CM history.

5.4 PUBLIC HEALTH SIGNIFICANCE

Our results indicated that CM is a robust life-course social determinant for women's impaired midlife HRQoL and QALY over time, which is associated with increased mortality and morbidity (Ware & Kosinski, 2001). Women who experienced childhood abuse and neglect or sexual abuse along with other CM types before 18 years old had significantly impaired HRQoL/QALY during their mid-50's over time. The findings from our studies increased the understanding of the impact of childhood maltreatment on HRQoL and QALY in women at midlife. Intervention for childhood maltreated female survivors may be beneficial for healthy aging. The QALY estimation results from our study can be used for future cost-effective analyses to help allocate resources of programs or interventions for maltreated female victims in the U.S.

The modifiable mediators (optimism, sleep problems, and social support) identified in our novel longitudinal mediation analyses for the relationship of CM with HRQoL/QALY over time may be targeted for future intervention studies. Additionally, previous research has suggested that good social support and positive emotions may potentially promote resilience among women with maltreatment histories and are also important for overall well-being for adults (Banyard et al., 2017; Barile et al., 2015; Biggs, 2004; Fagundes et al., 2012; Irwin et al., 2016). Therefore, it is feasible and beneficial to improve the well-being of women who have been maltreated as children by promoting a broad spectrum of protective factors such as developing positive feelings about and satisfaction with life, strengthening social support networks, or increasing levels of resilience (Chandler et al., 2015). It is also important to increase

the awareness among health professionals that in addition to medical conditions an individual's midlife well-being may be influenced by early childhood adversities.

5.5 FUTURE RESEARCH DIRECTIONS

We examined important research questions for the relationship between CM and HRQoL/QALY based on a longitudinal study over a 9-year follow-up but it was still a relatively small community sample. A larger longitudinal study with more than 1000 participants is still needed to replicate our findings. Future studies should also include more diverse race/ethnicity and both female and male to enhance the generalizability of study results. We also suggested that future studies collect the childhood abuse and neglect information from both self-report and agency report records when possible to enhance the reliability and validity of self-report CM history.

Additionally, future studies will benefit from collecting data on important risk factors such as the age of onset of CM, adulthood abuse/neglect experiences or participants' maternal abuse/neglect experiences. The current study primarily focused on adulthood psychosocial mediators; therefore, future studies of mediation analyses should also take into account potential adulthood physical factors (e.g., medical conditions, smoking, BMI, physical activity), biomarkers of psychological stress (e.g. elevated levels of C-reactive protein,), environmental factors, brain functions, and genetic data. A larger sample size will allow for a more comprehensive analytic approach to examining multiple mediators including psychosocial, physical, biological, and genetic factors at the same time will also contribute to the current literature and provide the knowledge for future intervention studies to mitigate the life-course impact of CM on midlife HRQoL/QALY.

5.6 CONCLUSIONS

Our investigations through this dissertation consistently identified that 1) early exposure to childhood maltreatment is robustly associated with reduced subjective well-being, life functioning, and quality-adjusted life years in midlife. 2) Multiple forms of CM (abuse and neglect or sexual abuse along with other types) are most salient to the midlife HRQoL and QALY over 9 years among middle-aged women. 3) Low levels of optimism, sleep problems, and social support are important modifiable factors identified in our mediation analyses for the relationship of CM with HRQoL/QALY over time. Findings from our study provide knowledge to advance research and increase our ability to mitigate the negative impact of early adverse exposures on later HRQoL/QALY.

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