Affective symptoms across the life course and the role of adverse childhood experiences

Ellen J. Thompson

University of Sussex

Thesis submitted for the degree of Doctor of Philosophy

April 2018

Declaration

This thesis conforms to an 'article format' in which chapters two, three, four and five contain discrete articles written in a style that is appropriate for publication in peer-reviewed journals. The first and final chapter present synthetic overviews and discussions of the field and the research undertaken.

Chapter 2 (Study 1) is written in the style of an article appropriate for publication. The author contributions are as follows: Ellen Jo Thompson was responsible for all aspects of the data collection, data analysis and writing of the manuscript; Darya Gaysina assisted with second coder rating within the manuscript; Andy Field was responsible for guidance in the data analysis; Marcus Richards provided feedback on the manuscript; Rob Bond provided some guidance on data analysis; Ellen Jo Thompson and Darya Gaysina were collectively responsible for the initial conception and development of the research.

Chapter 3 (Study 2) is written in the style of an article appropriate for publication. The author contributions are as follows: Ellen Jo Thompson was responsible for all aspects of the data analysis and writing of the manuscript and some aspects of the data collection; Oliver Lovick, Diana Falvo and Rebekah Moore were responsible for some aspects of the data collection; Ellen Jo Thompson and Darya Gaysina were collectively responsible for the initial conception and development of the research.

Chapter 4 (Study 3) is written in the style of an article appropriate for publication. The author contributions are as follows: Ellen Jo Thompson was responsible for all aspects of the data preparation, data analysis and writing of the manuscript; Marcus

Richards and Andy Field provided feedback on the manuscript; Ellen Jo Thompson and Darya Gaysina were collectively responsible for the initial conception and development of the research; Darya Gaysina provided feedback on the manuscript.

Chapter 5 (Study 4) is written in the style of an article appropriate for publication. The author contributions are as follows: Ellen Jo Thompson was responsible for all aspects of the data preparation, data analysis and writing of the manuscript; George Ploubidis was responsible for guidance in the data analysis and provided feedback on the manuscript; Marcus Richards provided feedback on the manuscript; Ellen Jo Thompson and Darya Gaysina were collectively responsible for the initial conception and development of the research; Darya Gaysina provided feedback on the manuscript.

George B. Ploubidis was supported by the Economic and Social Research Council - ES/M008584/1

I hereby declare that this thesis has not been, and will not be, submitted in whole or in part to another university for the award of any other degree.

……

Ellen J. Thompson

10th April 2018

Acknowledgments

First and foremost, I would like to acknowledge my excellent primary supervisor – Dr Darya Gaysina. Thank you for giving me the opportunity to undergo this PhD and for all of the valuable academic and training experiences you have enabled me to do over the years. I feel extremely privileged to have had such a brilliant PhD experience and this is solely due to the excellent supervision and support you have given me. Your time, guidance, encouragement and patience has been invaluable throughout my PhD and I am eternally grateful to you.

I would like to acknowledge my second supervisors - Professor Andy Field and Professor Marcus Richards. Thank you both so much for the time you spent reading my papers and providing feedback. I would like to acknowledge and thank Professor George Ploubidis, whose advice on study 4 of this thesis was extremely valuable. I am also grateful to Professor Gordon Harold and Professor Rod Bond for comments on earlier versions of chapter 2 of this thesis and potions of the analysis.

I would like to express my sincerest gratitude to the survey members of the MRC National Survey of Health and Development (1946 British birth cohort). Thank you to the School of Psychology at Sussex University for funding my PhD. I am grateful to all of the faculty, research, technical and administrative staff within the school who have helped and encouraged me over the years. It has been an absolute privilege to be part of the Sussex PhD community and I will always have fond memories of my time as a student. Thank you to the members of the Environment Development Genetics and Epigenetics (EDGE) lab group, and again, to Darya for always facilitating such interesting discussions.

To my fellow PhD students who have been so central to my experience; a huge thanks to Yasin for always being there for me, believing in me and teaching me ‘how to

have fun during my PhD', to Scarlet, Gemma, Helen, Jess, James, Camilla, Olaya, Vlad and Chris for your care, support, encouragement and ongoing friendship. To everyone who shared an office with me over the years; thank you for all of your kind words (and tea bags), and apologies to those who had to do so during my meltdowns and eureka moments!

To all of my non-Sussex University friends. Thanks you so much for your support and kind words over the years; to Julie, Amit, Hannah and Jodie - your personal and professional support over the course of this PhD has been incredible; to Libby - for always being there for me no matter what and never giving up on me; to Sly - for calling me Dr from the very first moment that I started the PhD and for keeping it real; and to Joe - for supporting me unconditionally. To all of my awesome teammates within the Brighton Rockers Roller Derby league - you are all incredible and inspiring individuals who I feel honoured to call my teammates and friends.

A special thank you to Ellen Spall for fighting baddies with me, reminding me to not be so serious in life, and for loving, supporting and encouraging me (always).

To my family. Thank you for just simply being you and for loving and sticking by me no matter what; to Gareth – your humour, love and encouragement has grounded me over the years and I don't know what I would have done without you; to Pace – for your positive spirit and love over the years; to my mum – I can never thank you enough for your emotional support and love you have given me. I love you all.

University of Sussex

Ellen Jo Thompson

Thesis Submitted for the degree of Doctor of Philosophy

Affective symptoms across the life course and the role of adverse childhood experiences

Summary

The primary aim of this thesis is to investigate the effects of single and cumulative family-related adverse childhood experiences (ACEs) on affective problems (disorders and symptoms) across the life course. Chapter 1 represents a general introduction into the prevalence, development and stability of affective problems across the life course, outlines key theories and approaches that address the development of affective problems, and highlights the role of early life risk factors in the onset and stability of these problems. Chapter 2 focuses on systematically reviewing the evidence from prospective studies for the role of single (e.g. parental divorce, parental psychopathology, childhood maltreatment unspecified, sexual abuse and family conflict) and cumulative ACEs in adult affective problems. Through synthesising effect sizes from 42 eligible studies, findings revealed that ACEs were associated with an increased risk of affective symptoms in adulthood. However the strength of the association varied, with sexual abuse, followed by cumulative adversities, being the strongest predictors of affective symptoms in adulthood. These findings show that ACEs pose risk for affective problems beyond childhood and adolescence, and that this risk may vary depending on the type and number of ACEs.

Chapter 3 builds upon this work through exploring the effects of cumulative ACEs on adult affective problems by synthesising the evidence from studies that use various designs (cross-sectional, case-control, and prospective), as well as critically evaluating methodological strengths and limitations of the existing studies, and suggesting new directions for future research. Future studies would benefit from more systematic assessments of ACEs using prospective multi-informant reports, and from utilisation of a developmentally sensitive life course approach to affective symptoms.

Chapter 4 and Chapter 5 extend existing research by utilising longitudinal prospectively collected data from the Medical Research Council (MRC) National Survey of Health and Development (NSHD). These two empirical studies make a novel contribution to the research field by modelling life course profiles of affective symptoms across a period of more than 50 years (from age 13 through 69), and by investigating the effects of single and cumulative ACEs on affective symptoms across the lifespan.

As demonstrated in Chapter 4, a higher cumulative ACE score was associated with affective symptom severity in late adulthood (i.e., at ages 60-64 and 69), but not at earlier ages (i.e., at ages 13, 15, 36, 43, 53). This unexpected finding indicates that the risk of affective symptoms in those who experienced multiple ACEs persists beyond childhood and adolescence, up to late adulthood. Further research is encouraged to explore the effect of cumulative ACEs on affective symptoms across the lifespan using person-centred approaches and to explore risk and resilience mechanisms underlying the association.

In Chapter 5, advanced modelling techniques – latent class analysis (LCA) – were employed to derive life course profiles of affective symptoms, and the effects of 24 single ACEs and their accumulation, in relation to these life course profiles, were

investigated. Four life course profiles of affective symptoms were identified: no symptoms, adolescent symptoms only, adult symptoms only, and adolescent and adult symptoms. Four ACEs were significantly associated with affective symptom trajectories, with small effect sizes observed: childhood chronic illness was associated with adult symptoms only; whereas growing up in an overcrowded house and parental poor perceived health were associated with symptoms in adolescence and adulthood. However, no associations were found for twenty of the ACEs tested.

The thesis concludes with the Discussion, which aims to synthesise and summarise the evidence from each study, discuss their key findings and implications, before acknowledging the strengths and limitations of the research area in general, along with providing some suggestions for future research.

Table of contents

List of figures

List of tables

List of abbreviations

ACEs	Adverse Childhood Experiences
MRC	Medical Research Council
NSHD	National Survey of Health and Development
NCDS	National Child Development Study
MCS	Millennium Birth Cohort Study
LCA	Latent Class Analysis
APA	American Psychological Association
WHO	World Health Organization
APMS	Adult Psychiatric Morbidity Survey
NICE	National Institute for Clinical Excellence
PSE	Present State Examination
PSF	Psychiatric Symptom Frequency
GHQ	General Health Questionnaire
EFA	Exploratory Factor Analysis
CFA	Confirmatory Factor Analysis

Chapter 1

General introduction

This chapter defines affective disorders and symptoms, presents the prevalence for affective disorders in children, adolescents and adults, and highlights the social and economic costs of these problems. It then considers existing theories for the development of affective disorders and discusses the importance of using the life course approach when investigating the role of early life risk factors in lifelong mental health. It further outlines the importance of examining multiple early life risk factors (adverse childhood experiences, ACEs) and their cumulative effect, and provides some evidence for the association between single and cumulative ACEs and affective disorders across the life course.

1.1. Affective disorders

1.1.1. Definitions

Affective disorders comprise of anxiety and depressive disorders and their affiliated symptoms and behaviours. These disorders lead to marked emotional distress and interference with daily functioning, but do not usually affect insight or cognition (Stansfeld et al., 2014). There are a number of identified anxiety and depressive disorders which are defined using diagnostic manuals, such as the DSM-V (American Psychological Association (APA), 2013) and the ICD-10 (World Health Organization (WHO), 2011), including major depression, bipolar depression, generalised anxiety disorder, panic disorder, agoraphobia, social anxiety, obsessive compulsive disorder, phobias, and post-traumatic stress disorder and health anxiety. Individuals can experience either anxiety or depression symptoms, or comorbid symptoms (McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009). Anxiety disorders often include psychological symptoms, such as worried thoughts, and physical symptoms, such as feelings of tension, sweating, trembling and a rapid heartbeat (APA, 2013). Depressive

disorders often include psychological symptoms (e.g. low mood, irritability) and physical symptoms (e.g. loss of appetite, fatigue) (APA, 2013).

Indeed, affective problems also encompass subclinical symptoms of anxiety and depression (i.e., those that may not meet clinical diagnosis but still interfere with the health and functioning of the individual). There is a distinction between affective symptoms which are measured using a continuous scale, and affective disorders, which are measured using a categorical cut off of symptoms (Solomon, Haaga, & Arnow, 2001). Throughout this thesis the term *affective disorders* is used to refer to clinically defined anxiety and depressive disorders (i.e. those who are assessed with a measurement tool which uses a clinical categorical cut off of symptoms) and the term *affective symptoms* is used to refer to sub-clinical anxiety and depressive symptoms (i.e. those whose symptoms are measured using a continuous scale). The current thesis specifically focuses on affective symptoms across the life course, as opposed to clinically defined affective disorders. A more general term *affective problems* is used when there is no distinction between affective disorders and symptoms. Affective disorders and symptoms are also often referred to as *internalising disorders and symptoms* (particularly, in developmental psychopathology literature) and *common mental disorders* (particularly, in psychiatric epidemiology literature).

1.1.2. Prevalence of affective disorders

Evidence regarding lifetime prevalence and lifetime morbid risk of affective disorders indicate that they are extremely common, with estimates showing that 1 in 4 people worldwide suffer from one or more episodes of affective disorder over the life course (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; Moffitt et al., 2010; Stansfeld et al., 2014). Moreover, affective disorders are among the most debilitating disorders (exceeded only by lower back pain) measured in 'years lived with disability'

and the leading cause of disease burden worldwide (Vos et al., 2012; Whiteford et al., 2013).

In England, adult prevalence rates for affective disorders have been measured through the Adult Psychiatric Morbidity Survey (APMS) (McManus, Bebbington, Jenkins, & Brugha, 2016; McManus et al., 2009). Findings from the most recent APMS reveal that 17% of adults meet the criteria for at least one common mental disorder (i.e., depression or anxiety) at any one time, with almost half of these (i.e., 7.8%) presenting with mixed anxiety and depressive symptoms (McManus et al., 2016; McManus et al., 2009; Stansfeld et al., 2014) (Figure 1.1). These prevalence rates are similar to those in the United States of America. For example, findings from the National Comorbidity Survey – Replication (NCS-R) indicates that the 12-month prevalence estimates of affective disorders (as defined by the DSM-IV) for adults are 18.1% for anxiety disorders, and 9.5% for depressive disorders (Kessler, Demler, et al., 2005; Kessler et al., 2012). Moreover, affective symptoms (i.e., sub-clinical symptoms) are also common throughout adulthood, with 19% of individuals over 16 years of age in the UK indicating they have experienced anxiety and/or depressive symptoms (Beaumont & Lofts, 2013).

Furthermore, comparisons of data from the APMS conducted in 2007 and 2014 have revealed that, over this 7-year period, the prevalence of common mental disorders has significantly increased among middle aged (55-64) men and women (Stanfeld et al., 2014). Furthermore, through comparisons of different age groups, it has been shown that lifetime rates of affective disorders are up to four times higher in young adults compared to those aged 65 or older (Kessler, Berglund, et al., 2005).

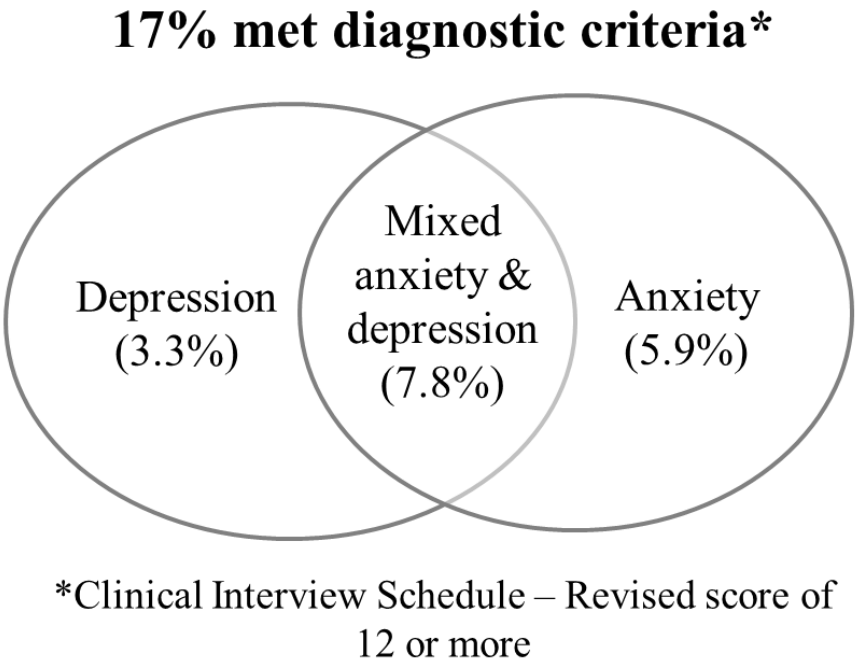


Figure 1.1. Prevalence rates from the 2014 Adult Psychiatric Morbidity Survey (APMS) for morbid and co-morbid affective disorders.

There is also evidence suggesting that prevalence of affective symptoms has a curvilinear shape (i.e., inverted U-shape), with the lowest prevalence of symptoms observed at ages 16-24 and 65-69 and the highest prevalence – in midlife (Beaumont & Lofts, 2013; Spiers et al., 2011).

Furthermore, cohort effects have also been found in the prevalence of affective disorders. For example, a cross-cohort comparison revealed that at age 42, men and women born in 1970 reported higher levels of psychological distress (symptoms of depression and anxiety) compared with those born in 1958 (Ploubidis et al., 2017).

Population prevalence estimates for affective disorders obtained from epidemiological surveys, such as APMS and NCS-R, offer advantages over official mental health records as they include individuals who experience affective disorders but

do not engage in services (Moffitt et al., 2010). Moreover, epidemiological surveys often assess symptoms on a continuous scale, allowing them to identify those at sub-threshold level of affective problems that are known to lead to negative life outcomes (Broadhead, Blazer, George, & Tse, 1990). However cross-sectional assessments of affective symptoms are suggested to be affected by the retrospective ascertainment of symptoms (Kessler, Berglund, et al., 2005). Furthermore, comparing findings from cross-sectional studies may be affected by changes in methodology (e.g. in diagnostic criteria, or interview methods) as suggested by variability in the estimated prevalence of affective disorders across different studies (Roberts, Clifford Attkisson, & Rosenblatt, 1998). Therefore, prospective studies with multiple measures of affective symptoms across the life course may be more accurate at estimating life time prevalence rates and life course trends. Indeed, the prevalence of affective disorders reported through prospective studies has been found to be higher than when reported through cross-sectional reports (Moffitt et al., 2010).

Another important methodological consideration when investigating affective disorders is that affective disorders and symptoms can change dramatically over the life course. It has been estimated that the majority of affective disorders have early onset, with 50% of individuals presenting symptoms by the age of 14 years, and 75% by the age of 24 years (Kessler, Angermeyer, et al., 2007). However, notably, some individuals with early onset affective disorders do not develop recurrent problems, whereas others have repeated affective episodes across the life course, as indicated by prospective studies that followed people from childhood and adolescence through their mid-life (Clark, Rodgers, Caldwell, Power, & Stansfeld, 2007; Colman, Wadsworth, Croudace, & Jones, 2007). Therefore, an individual may fulfil the diagnostic criteria for depression or anxiety at one time point, but may not fulfil this criteria at a later time point.

Furthermore, prospective evidence from studies of children followed into early adulthood, as well as of adult samples with a follow-up of more than ten years, suggests that long-term trajectories of affective disorders are heterogeneous, with trajectories varying in terms of severity (low, medium and high) and stability (stable, increasing, decreasing) (Musliner, Munk-Olsen, Eaton, & Zandi, 2016; Paksarian et al., 2016). This evidence highlights the importance of assessing affective disorders longitudinally as opposed to solely using measures at a single time point in life. Moreover, identifying groups of people who differ in the age of onset and recurrence of affective symptoms across the life course is an important step for studying the aetiology and development of affective disorders.

Prevalence rates of affective disorders have also been considered for children and adolescents. Affective problems account for a large proportion of the mental health burden in children and adolescents, with anxiety disorders being the most common mental health disorder for those under 12 years of age (Cartwright-Hatton, McNicol, & Doubleday, 2006).

In Great Britain, the mental health of children and adolescents have been measured by the office of national statistics (ONS) (Green, McGinnity, Meltzer, & Ford, 2004). Findings from the 2004 survey reveal that 3.5% of 5 – 16 year olds meet the criteria for affective disorders. More recent evidence for the prevalence of affective symptoms in adolescents in the UK population has been obtained from the Millennium Birth Cohort Study (MCS). The MCS reported that the prevalence of depression increased from age 11 to 14 in girls and that at age 14, 24% of girls and 9% of boys reported high symptoms of depression (Patalay & Fitzsimons, 2017).

Moreover, a recent meta-analysis synthesising evidence from 41 studies across 27 countries from every world region has reported similar global prevalence rates of

affective disorders for children and adolescents (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Notably they report that the worldwide prevalence rates for any anxiety and depressive disorders are 6.5% and 2.6%, respectively.

Evidence indicates that diagnosis and treatment of child affective problems in clinical practice has increased in western countries. This increase has been previously attributed to the change in prevalence rates of affective symptoms across generations. Indeed, evidence is provided for the increase in prevalence of affective problems (Collishaw, Maughan, Natarajan, & Pickles, 2010). For example, Collishaw, Maughan, Natarajan, & Pickles (2010) found that twice as many young people in the UK reported frequent feelings of depression and anxiety in 2006 as compared to 1986.

However, more recently findings indicate that prevalence rates for affective symptoms are not increasing (Langley, Collishaw, Williams, & Shelton, 2017; Sellers, Maughan, Pickles, Thapar, & Collishaw, 2015). For example, through a comparison of 7 year old children on the Strengths and Difficulties Questionnaire (SDQ) across three nationally representative British samples assessed in 1999, 2004 and 2008, it was found that perceived levels of emotional distress remained stable (Sellers et al., 2015).

The estimated high prevalence of affective problems in children and adolescents from cross-sectional and prospective studies are of high concern as early onset symptoms are often characterised by greater severity and persistence into adulthood (Pine, Cohen, Gurley, Brook, & Ma, 1998; Raven, Jörg, Visser, Oldehinkel, & Schoevers, 2016).

1.1.3. Social and economic costs of affective disorders

Suffering from depression and/or anxiety has a significant impact on an individual's life and society as a whole. Affective disorders have previously been found to be associated with decreased physical (Roshanaei-Moghaddam, Katon, & Russo,

2009), cognitive (Ahern & Semkovska, 2017; Hatch et al., 2007) and social functioning (Last, Hansen, & Franco, 1997; Wood & Wood, 2006), poorer academic attainment and performance (Veldman, Bultmann, Almansa, & Reijneveld, 2015; Veldman, Reijneveld, Almansa Ortiz, Verhulst, & Bultmann, 2015), greater self-neglect (Abrams, Lachs, McAvay, Keohane, & Bruce, 2002; Dyer et al., 2006), as well as increased risk of morbidity and mortality (Cuijpers & Smit, 2002; Saris, Aghajani, van der Werff, van der Wee, & Penninx, 2017). Affective disorders are the second leading cause of disability worldwide (Ferrari et al., 2013) and have been estimated to cause one fifth of all days lost from work in Great Britain (Das-Munshi et al., 2008).

Currently, only one out of three individuals who suffer from affective disorders receives mental health treatment (McManus et al., 2016). What is more, although evidence demonstrates that current recommended treatments for anxiety and depression are effective (National Institute for Clinical Excellence (NICE), 2009), treatments offered seem to have little impact on the prevalence of affective disorders. This may be because affective disorders tend to be relapsing conditions that often reoccur years after a prior episode. For example, in the case of depression, individuals have been found to relapse ten years from first presentation (Thornicroft & Sartorius, 1993). Due to the increase in prevalence rates for affective disorders, service use, including self-help based treatments, diagnosis and medication treatment, have increased substantially in high income countries over the last decade (Kosidou et al., 2010; Olfson, Blanco, Wang, Laje, & Correll, 2014). This increase has been particularly poignant among adolescents and antidepressant use in young people has continued to increase substantially (Olfson et al., 2014).

However, whilst first line psychological treatments (i.e., CBT) are effective for nearly half of attenders, there remain a substantial number of patients who do not

benefit and require further intervention. This has a significant demand on services within the UK, with estimated costs of depression and anxiety combined predicted to be £5 billion by 2026 (McCrone, Dhanasiri, Patel, Knapp, & Lawton-Smith, 2008). Moreover, although affective disorders are less disabling than major psychiatric disorders, such as psychoses, their higher prevalence in the population results in a higher cumulative cost to society (Zivin et al., 2015).

1.1.4. Theories of development of affective disorders

As highlighted in the previous sections, there are high prevalence rates for youth and adult affective disorders and symptoms and there is a substantial social and economic burden of these problems. Accordingly, there is an urgent need for researchers to identify risk factors for the development of common mental disorders, in order to generate more effective intervention and prevention strategies. A number of factors have been identified in playing an important role in the development of affective problems in childhood, adolescence and adulthood. It is acknowledged that these factors are varied, complex and interacting. They encompass biological factors including genetic variants (Caspi et al., 2003; Lohoff, 2010; Polanczyk et al., 2009), as well as socio-economic and psychosocial factors (McLaughlin et al., 2011), and their interplay (Rutter, Moffitt, & Caspi, 2006).

Indeed, the role of these factors in socio-emotional development and mental health has been a longstanding focus of psychological and psychiatric research (Cicchetti & Toth, 1998; Rutter, 1986). Historically, the influence of psychosocial factors on the development of mental health problems is rooted in psychological theory. Freud (1910) and Bowlby (1952) believed that family influences strongly affected child development and mental health across the lifespan. For example, Freud's psychodynamic theory, primarily developed from case studies of adults relating their

experience to childhood abuse. This theory suggests that affective symptoms can develop as a result of both underlying personality traits and loss of a parent or rejection by a parent (Driessen et al., 2010). Seemingly paradoxically, psychodynamic theory was associated with two contrasting research trends. On the one hand, a focus on underlying personality structures in the development and maintenance of affective symptoms, led to a downplaying of the role of early life experiences. As such psychodynamic psychotherapy aims to treat affective symptoms through focusing on clients' interpersonal relationships, unconscious desires, thoughts and feelings (Driessen et al., 2010). On the other hand, psychodynamic theory concerned with child-rearing practices through the early psychosexual stages led to a focus on the importance of early life experiences, for example, whether the child was breast-fed, timing of weaning and how toilet training was managed (Cuijpers, van Straten, Andersson, & van Oppen, 2008).

Alongside the concern with the specifics of child-rearing practices, there was also a focus on the role of maladaptive parent-child relationships in the development of mental health problems. This line of thought led to the consideration of the parent-child attachment relationship (Bowlby, 1952), as well as the consideration of specific parent practices (Belsky, 1984). Attachment theory asserts that children must feel secure in their belief that a parent will be available when needed and that children may suffer negative mental health consequences from parental neglect, rejection or deprivation.

An alternative explanation offered from the research field of cognitive psychology was the development of the cognitive model of depression. This theory was formerly introduced by Beck (1967) who theorised that when experiencing a stressful life event in childhood, a cognitive schema (core belief/attitude) of the event develops. These depressive schemas then influence the encoding, processing, organisation and retrieval of information (Beck, 1967; Beck, 1987). Subsequently, individuals are

sensitised to respond to similar events in a dysfunctional fashion (Beck, 2008; Ingram, 2003). Furthermore, Beck (1967) proposed that depressive schemas are usually characterised by negative self-referential beliefs. Once these schemas are activated, individuals are vulnerable to develop affective problems (i.e. depression) as information is often processed in terms of negative thoughts about the self, the world, and the future – a process termed the negative cognitive triad (Clark, Beck and Alford, 1999). In addition, it was later proposed that deficits in attention, interpretation and memory occur when depressive self-referential schemas are activated (Clark, Beck and Alford, 1999). This leads to rumination and perpetuates negative thoughts about the self, world and future. Consequently, a 'vicious cycle' within the cognitive system is generated, which maintains and prolongs depressive episodes (Disner, Beevers, Haigh, & Beck, 2011). A criticism of this theory suggests that a description of how cognitions (i.e. the negative cognitive triad) relate to symptoms of affect is offered, but more research is needed to establish a causal link between cognitions and depression and underlying mechanisms (Haaga, Dyck, & Ernst, 1991). Further criticisms of psychological theories for the development of affective problems draw upon the observation that some individuals develop affective disorders and symptoms despite the absence of negative events.

Due to acceptance of the multifactorial nature of human development, it is essential to understand the integration of developmental processes at multiple levels of biological, psychological, and social complexities within individuals over the life course (Cicchetti & Toth, 1998). Thus, multidisciplinary efforts to integrate advances in the field of developmental psychology, clinical psychology, epidemiology, and genetics have addressed critical factors involved in the development of affective disorders. Accordingly, researchers acknowledge and draw upon a biopsychosocial model of

affective problems in order to integrate biological, psychological and social risk factors in their understanding of the development of affective problems (Garcia-Toro & Aguirre, 2007). This model comprises psychobiological vulnerabilities as determined by risk factors (psychological, genetic and neurochemical), and protective factors. Furthermore, it proposes that adverse events interact with these vulnerabilities, which precipitates distress and leads to affective problems (Schotte, Bossche, Doncker, Claes, & Cosyns, 2006). In addition, the biopsychosocial model of affective problems stresses the importance of integrating biological and psychological therapeutic interventions in order to reduce symptoms and prevent relapse. The use of this model in clinical psychology practice allows a psychologist to draw on a variety of theory and data in order to generate a hypothesis of the causes, development and maintaining factors involved in the development of affective problems – a process termed formulation (Johnstone & Dallos, 2006).

The research undertaken for this thesis draws upon developmental psychopathology and life course epidemiology in order to elucidate the role of adverse childhood experiences (ACEs) in the development of affective symptoms across the life course. The developmental psychopathology approach proposes that in order to understand human development, developmental processes such as biological, psychological and environmental mechanisms must be integrated in order to fully understand the complexity involved in the development of these problems (Cicchetti & Toth, 1998). Moreover, a life course epidemiology approach aims to establish how social and biological factors operating at different stages of life, and across generations, contribute to the development of adult health and disease over time. Specifically, life course research seeks to understand influences of early life exposures and development on later disease outcomes and the mechanisms that occur in the intervening years (Kuh,

Lynch, Hallqvist, & Power, 2003; Power, Kuh, & Morton, 2013). Thus, life course epidemiology extends theories of developmental origins by focusing attention on potentially sensitive periods in childhood and adolescence. Specifically, it extends on developmental theories of adult disease through considering the cumulative effect of early life and later life exposures. Conceptual frameworks have been developed to guide this research (Power et al., 2013). For example, Figure 1.2 provides an example of a conceptual model of lifelong health that focuses on three developmental domains - cognitive, emotional, and physical, that are interrelated across the life course and generations. The central feature of the model is that it incorporates environmental influences that act across all the life stages to affect adult health. These environmental influences over the life course can operate in several ways and at many levels (e.g., family, neighbourhood, societal) to affect adult function and disease. In order to test the effects of early life influences on health outcomes across the life span, birth cohort studies have been set up in many countries, including Norway (Krokstad et al., 2013), Australia (Lee et al., 2005), and New Zealand (Morton et al., 2013). In Great Britain, there are four nationally representative birth cohorts that originated in 1946 (Kuh et al., 2011; Wadsworth, Kuh, Richards, & Hardy, 2006), 1958 (Power & Elliott, 2006), 1970 (Elliott & Shepherd, 2006), and 2000 (Connelly & Platt, 2014). Birth cohort studies provide unique data to investigate influences from birth on various health outcomes, including common mental disorders, from childhood through late adulthood. Indeed, these studies have contributed significantly to our current understanding of the role of adverse childhood experiences in lifelong mental health, as outlined in the next section.

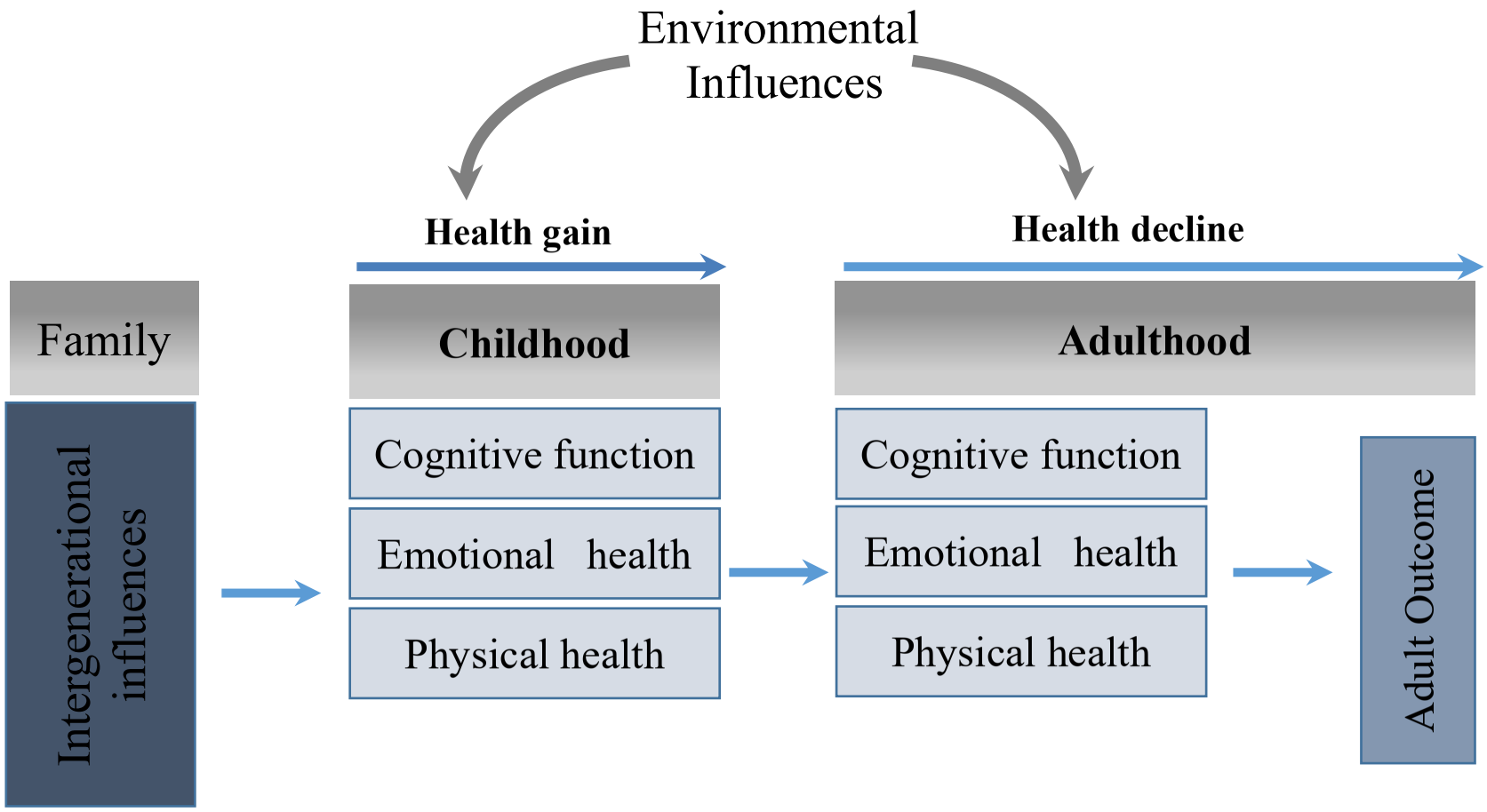


Figure 1.2. Life course framework for mental ageing (adapted from Power et al., 2013).

1.2. Adverse childhood experiences and affective disorders

1.2.1. Definitions

As mentioned earlier, the environment in which children live and learn has a significant impact on their cognitive, social and emotional development. In particular, the home and family environments, as well as the characteristics of parents and other family members with whom children interact on a regular basis, are powerful determinants of emotional and behavioural functioning in later life. Many early life experiences have a positive impact on child development, whereas others can disrupt normal child development and lead to long-term negative consequences (Flouri, Tzavidis, & Kallis, 2010).

Adverse childhood experiences (ACEs), often referred to as childhood adversities, childhood trauma, or early life stress, can occur within the family or social setting, can vary in severity, and can disrupt the child's physical or psychological health and development (Kalmakis & Chandler, 2014; Tiet et al., 1998). ACEs that occur in the family setting include, for example, parental divorce and parental death, whereas ACEs that occur in the social setting include neighbourhood poverty and bullying (See Table 1.1). ACEs can also be classified as acute (e.g., parental death) or chronic (e.g., poverty). Another approach deconstructs ACEs into two domains – deprivation and threat, proposing that different neurodevelopmental mechanisms of action may exist for different types of stressors (McLaughlin & Sheridan, 2016; Sheridan, Peverill, Finn, & McLaughlin, 2017).

Table 1.1. Examples of Adverse Childhood Experiences in family and social settings (adapted from Kalmakis & Chandler, 2014).

Adverse Childhood Experience (ACEs)	
Within the family setting	**Within the social setting**
Physical abuse	Poverty/Socioeconomic status
Sexual abuse	Racial segregation
Emotional abuse	Political conflict
Physical neglect	Hospitalisation
Emotional neglect	Community violence
Physical punishment	School violence/bullying
Witnessing domestic violence	Maltreatment by teacher
Household member's substance misuse	Natural Disaster
Household member's illness	
Household member's incarceration	
Parental separation/divorce	
Child separation from family	

1.2.2. Prevalence of ACEs

Adversities in early life are extremely common. In a recent national survey in England with 3885 adults (aged 18-69) taking part, it was found that 46.4% reported experiencing more than one ACEs, and 8.3% reported experiencing more than four ACEs (Bellis et al., 2014). These prevalence rates are consistent with those from the US, with 46% of children in the US experiencing at least one ACE (Sacks, Murphey, & Moore, 2014). High frequency of ACEs were also reported by adults in other high income countries (38.4%), as well as high-middle income (38.9%) and low-/lower–middle

income (39.1%) countries (Kessler et al., 2010). High prevalence of ACEs and their common co-occurrence provide a strong rationale for a better understanding of the association between ACEs and health outcomes over the life course.

1.2.3. Associations between ACEs and affective symptoms: state of the art and methodological limitations

A risk factor is a measurable individual or environmental factor that is associated with an increased likelihood of developing a negative outcome over the population base rate (Garber, 2006; Kraemer et al., 1997). The study of risk factors is extremely useful in identifying individuals who may have an increased vulnerability to developing maladaptive outcomes.

ACEs are known risk factor for the development of various health problems, including affective disorders. It is well established that ACEs pose risk for the development of affective disorders in childhood, adolescence and adulthood (Evans, Li, & Whipple, 2013; Hughes et al., 2017). This evidence includes the long-term effects of ACEs on affective problems, across the life course as outlined below.

Significant evidence has emerged for the association between a range of individual ACEs and subsequent psychopathology, including affective disorders among adults (Clark, Caldwell, Power, & Stansfeld, 2010). For example, the Adverse Childhood Experiences Study in the United States demonstrated an association between single and multiple ACEs and poor health behaviours and outcomes in adulthood, including depressive disorder (Felitti et al., 1998).

Since this study, many ACEs, such as childhood maltreatment (Brown et al., 2009; Lindert et al., 2014; Norman et al., 2012), parental divorce (Richards, Hardy, & Wadsworth, 1997; Sands, Thompson, & Gaysina, 2017), parental loss and separation (Otowa, York, Gardner, Kendler, & Hettema, 2014; Tyrka, Wier, Price, Ross, &

Carpenter, 2008), and parental psychopathology (Wickramaratne & Weissman, 1998) have been extensively examined in this context and the accumulating evidence is mainly consistent in relation to the long-term negative effects of these ACEs. For example, evidence from a recent systematic review and meta-analysis suggests that parental divorce was significantly associated with offspring depression in adulthood, with the odds ratio of 1.56. (Sands et al., 2017). A meta-analysis of studies investigating the association between childhood maltreatment (physical abuse, emotional abuse, and neglect) and adulthood depression reported a doubling of risk, with the odds ratio of 2.27 (Nanni, Uher, Ph, & Danese, 2012).

As demonstrated by these systematic reviews and meta-analyses, the majority of the existing research in relation to the effects of ACEs on adult affective disorders is cross-sectional and relies on retrospective reports of early life experience. The validity of retrospective, self-reported measures of ACEs has been widely criticised, as depressed individuals are more likely to recall negative events (Williams & Scott, 2009). It has recently been proposed that the memory of an ACE, rather than the ACE itself, can be differentially associated with affective symptoms in adulthood (Afifi, Boman, Fleisher, & Sareen, 2009; Henry, Moffitt, Caspi, Langley, & et al, 1994a; Newbury et al., 2018).

Nevertheless, a number of prospective studies have been conducted to illuminate the role of childhood adversities in lifelong mental health and illness. Historically, mixed findings have been found for the role of ACEs in the development of anxiety and depression (Rodgers, 1990). For example, using data from the British 1946 birth cohort, Rodgers (1990) investigated the association between single and cumulative ACEs and anxiety and depression at ages 36. In order to do this, prospectively measured ACEs across six domains, including perinatal factors (e.g. breastfeeding), socio-economic

circumstance (e.g. father's social class), family structure and disruption (e.g. family size), childhood illness (serious illness between ages 0-15 years), parental behaviour, attitudes and health (e.g. parent's interest in child's education), and schooling (education progress by age 15 years), were used as individual and cumulative predictors for associations with anxiety and depression at age 36 years. This study revealed that individual ACEs did not significantly predict adult affective disorder, although multiple ACEs had an accumulative deleterious effect. Furthermore, previous studies using data from British birth cohorts have provided comprehensive evidence for the role of childhood socio-economic position (SEP) (Poulton et al., 2013; Stansfeld, Clark, Rodgers, Caldwell, & Power, 2008; Wood et al., 2017), parental divorce/separation (Lacey et al., 2012; Lacey, Bartley, Pikhart, Stafford, & Cable, 2014; Richards et al., 1997), and bullying (Takizawa, Maughan, & Arseneault, 2014) in adult mental health. As mentioned earlier, birth cohort studies are particularly powerful to explore this link due to availability of prospectively collected data on ACEs in large samples. Great Britain is particularly well positioned in this area as there are multiple birth cohorts that have been set up in the last decades. These birth cohort studies provide longitudinal data on affective symptoms from childhood through late adulthood, and therefore allow us to investigate prospective associations between childhood adversities and lifelong mental health.

Studies using birth cohort resources have made a significant contribution to better understanding of pathways and mechanisms underlying the links between ACEs and lifelong mental health. For example, they have tested for the timing of effects and whether ACEs experienced in a particular period of childhood lead to more negative mental health outcomes (Done, Crow, Johnstone, & Sacker, 1994; Rodgers, 1990). They have investigated the chain of effects to test whether ACEs can lead to negative

health outcomes later in life via mediation by stressful life experiences (SLEs) in adulthood and/or via accumulation with SLEs across different periods of life (Colman et al., 2014). For example, one study has identified an indirect effect of childhood economic deprivation on adult depression: childhood economic deprivation was only found to be significantly associated with adulthood depression when mediated by low SES in adulthood (Colman et al., 2014).

Additionally, birth cohort studies provide information from multiple generations (e.g., from birth cohort members and their parents and/or offspring) and can test for intergenerational effects of ACEs (Collishaw, Dunn, O'Connor, & Golding, 2007).

For example, a study using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), examined the intergenerational transmission of psychosocial risk associated with maternal childhood abuse. It was found that maternal childhood abuse was associated with poorer behavioural trajectories between ages 4 and 7 years (Collishaw et al., 2007).

To summarize, previous studies, including those that utilise birth cohort resources, have provided valuable insights into the role of specific individual ACEs in lifelong mental health. However, investigating single types of risk factors can be problematic as this approach assumes that ACEs occur independently from one another, whereas multiple early life risk factors tend to co-occur (Bellis, Hughes, Leckenby, Perkins, & Lowey, 2014; Dong et al., 2004; Fallon et al., 2010). For example, children from families with low SEP are more likely to live in poor and overcrowded houses (Evans, Wells, & Moch, 2003). Further to this, a recent study has shown that 89% of cases involving childhood sexual abuse were accompanied by non-sexual types of childhood maltreatment (Vachon, Krueger, Rogosch, & Cicchetti, 2015). As such, the elevated odds associated with sexual abuse, as compared to other types of ACEs, could

be the result of co-occurring ACEs (e.g., other types of maltreatment) and therefore the impact of a single risk factor under investigation may be overestimated (Evans & Cassells, 2013).

Moreover, inconsistent findings have been observed between studies that focused on specific types of ACEs. It has been suggested that this stems from considerable variation across studies, such as: (i) the number of adversity types assessed; (ii) the analytic strategy employed; and (iii) the types of covariates included (Arata et al., 2005; Higgins & McCabe, 2001)**.** Furthermore, as affective disorders are multifactorial, it is unlikely that a single risk factor will give rise to the development of a disorder, or that targeting of a single risk factor will be sufficient to prevent the development of a disorder (Garber, 2006).

Accordingly, it is now widely acknowledged that the accumulation of risk factors plays a much greater role in the development of affective psychopathology. The accumulation of risk model in psychopathology was initially proposed and demonstrated by Rutter (1979). This theory postulates that it is not just a single risk factor, but a number of risk factors that leads to maladaptive outcomes – often referred to as a dose-response relationship. This model is based on the Rutter's seminal Isle of Wight study (1979), whereby a significant association was found between a number of risk factors, including low parental SEP, large family size, severe marital discord, parental criminality, maternal mental illness, and foster placement, and the likelihood of presenting with a psychiatric disorder in childhood. Notably, it was found that not only did this probability increase with each risk factor experienced, but the type of risk factor did not influence the cumulative pattern (Rutter, 1979). This finding has been replicated by multiple studies that have been reviewed by Evans (2013). These findings indicate that multiple risk factors are detrimental to mental health in early life, and accordingly

the more children are exposed to ACEs the higher risk for negative mental health outcomes in childhood. However, as affective disorders are often found to persist across the life course, it is important to consider the impact of cumulative ACEs on mental health outcomes beyond childhood.

A growing number of studies have tested the hypothesis of the accumulation of multiple ACEs and the dose-response relationship with adult anxiety (Park, Pyo, et al., 2014; Reiser, McMillan, Wright, & Asmundson, 2014) and depression (Chapman et al., 2004; Turner & Butler, 2003). In these studies, cumulative risk is identified by using a set of known risk factors (e.g. parental divorce, parental psychopathology). Specifically, researchers use binary variables for these risk factors (as present '1' or not present '0'), and tallying them in order to derive a risk score (or risk index) for each individual that can range from 0 (no risk factors present) to an upper limit (based on the number of risk factors considered). This risk index can be derived from multiple risk factors measured either across a period of time (e.g. from age 5 to 18), or at a specific time point (e.g. at age 10).

Horan & Widom (2014) highlight three benefits of using an aggregated score: (1) a cumulative risk index allows researchers to capture the co-variation of different ACEs; (2) previous research indicates that mental health outcomes are often explained by multiple, as opposed to single, ACEs (Evans & Cassells, 2014); and (3) aggregated variables increase the methodological power to detect effects as individual risk factors are summed (leading to a decrease in measurement error), thus preserving degrees of freedom (Flouri, Tzavidis, & Kallis, 2010).

However, a conceptual drawback of summing the total number of childhood social risk factors is that is does not account for the respective severity of individual risk factors, nor does it account for the fact that certain risk factors may co-occur more

often than others (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Evans et al., 2013). Therefore, it has been suggested that modelling approaches can be applied to identify specific profiles of ACEs (Caleyachetty et al., 2017; Oliver, Kretschmer, & Maughan, 2014). For example, one study used three approaches: conceptual, exploratory factor analysis (EFA), and latent class analysis (LCA) in order to investigate patterns of exposure to multiple ACEs and their associations with physical capability and common affective disorders in later life (Caleyachetty et al., 2017). This study showed that, when modelling cumulative ACEs using a cumulative summary score approach or EFA approach, a greater accumulation of ACEs was associated with higher risk of affective symptoms.

To summarise, there is a growing body of evidence for long-term effects of single types of ACEs and their accumulation on affective disorders. However, most of this evidence has been based on cross-sectional data. For the majority of existing prospective studies, data on affective symptoms are limited to a single time point, often in young adulthood. Therefore, our knowledge of these influences on the course of affective disorders, including onset, recurrence, and severity across the life course, is still limited. The current thesis aims to address these limitations by investigating the role of single and multiple family-related ACEs in the development of affective symptoms at different time points across the life course.

1.3. The current thesis

Given the high individual, social and economic burden of affective disorders, attention needs to be drawn to identifying early life risk factors for these problems. The overarching aim of this thesis is to investigate multiple adverse childhood experiences (ACEs) that occur in the family context in relation to affective symptoms at different stages of the life course. There are four key research objectives of the thesis.

The first research objective is to review in a systematic way and synthesize using a meta-analytical approach the evidence from existing prospective studies on the role of single and multiple ACEs in adult affective problems.

The second research objective is to provide an overview of studies that focus on accumulation of ACEs in relation to adult affective problems, and to critically evaluate the methodology of these studies, and to suggest some novel directions for research in this area.

The third research aim is to derive a cumulative ACE score (based on 24 ACEs) and to test its effect on affective symptoms severity across the life course using prospective data from the British 1946 birth cohort (MRC National Survey of Health and Development; NSHD).

The final research objective is to derive life course profiles of affective symptoms using Latent Class Analyses, and to investigate the effects of individual ACEs and a cumulative ACE score on these profiles using data from the NSHD.

Chapter 2

Study 1: Family-related adverse childhood experiences and internalising psychopathology in adulthood: a systematic review and meta-analysis of prospective longitudinal studies

2.1. Abstract

Background: A majority of the evidence for the link between family-related adverse childhood experiences (ACEs) and internalising psychopathology (i.e., depression and anxiety) in adulthood is often based on single types of retrospectively reported childhood adversities.

Aim: To systematically review prospective evidence for the link between different types of family-related ACEs (before age 18) and internalising disorders and symptoms in adulthood (at age 18 or older).

Method: An electronic database search was conducted using 'MEDLINE', 'Web of Science', 'EMBASE', 'psycARTICLES' and 'PsycINFO'. A random effects multivariate meta-analysis was used to synthesise effects from prospective longitudinal studies.

Results: The multivariate meta-analysis showed a significant positive association between any single type of ACEs and adult internalising symptoms (42 studies; n = 83,920; OR = 1.83, 95% CI (1.57, 2.15)). Subgroup meta-analyses revealed significant associations with specific single ACEs: childhood maltreatment (4 studies; n = 3,303; OR = 1.91, 95% CI (1.04, 3.49) p = 0.03); sexual abuse (3 studies; n = 10,974; OR = 2.56, 95% CI (1.32, 4.97) p < 0.01); parental psychopathology (5 studies; n = 3,078; OR = 1.75, 95% CI (1.11, 2.76) p = 0.02); parental divorce / separation (9 studies; n = 29,739; OR=1.49; 95% CI: 1.18, 1.89) p < 0.01; family conflict (3 studies; n = 2,232; OR = 1.40; 95% CI: 1.23, 1.60) p < 0.01), and multiple ACEs (5 studies; n = 13,872; OR = 2.28, 95% CI (1.11, 4.72), p = 0.02).

Conclusion: Overall, associations were found between different types of family-related ACEs and internalising psychopathology in adulthood. As the majority of studies focused on the effect of single types of ACEs in young adult populations, future

research should focus on investigating the influence of multiple ACEs on internalising psychopathology in older adults.

2.2. Introduction

Internalising or affective psychopathology comprises a set of symptoms and behaviours characterised by negative mood states and inhibition, and includes depression and anxiety (See 1.1.1). Both internalising disorders and symptoms are common in childhood and adolescence (Merikangas et al., 2011), often persist into adulthood (Kessler, Angermeyer, et al., 2007), and are associated with substantial social and economic costs (Last et al., 1997; Pine et al., 1998; Wood & Wood, 2006). Epidemiological and clinical studies have consistently identified exposures to adverse experiences during early period of life as a major influence on adult risk for depression and anxiety (see 1.2.3).

Adverse childhood experiences (ACEs) often occur within the child's family settings, vary in severity, commonly co-occur, and can disrupt the child's physical or psychological health and development (Kalmakis & Chandler, 2014; Tiet et al., 1998). Moreover, it has been demonstrated that they are highly prevalent around the world (see 1.2.2). Therefore, there is a strong rationale for a better understanding of the link between ACEs and mental health outcomes across the life course. This research is crucial in aiding the development of preventive intervention strategies aimed at both children and adults. Specific types of family-related ACEs, such as childhood maltreatment (Brown et al., 2009; Lindert et al., 2014; Nanni et al., 2012; Norman et al., 2012), parental divorce (Amato & Keith, 1991; Rodgers, 1994), parental loss or separation (Otowa et al., 2014; Tyrka et al., 2008), and parental psychopathology (Wickramaratne & Weissman, 1998), have been extensively examined in this context. Moreover, another line of the existing research has focused on the multiple types of ACEs and their effects on adult psychopathology. For example, a large-scale study by Kessler et al. (2010) has provided evidence for the differential influence of twelve

different types of ACEs (retrospectively reported by adults from 21 countries) on the first onset of several mental disorders. Different types of ACEs differentially predicted the incidence and chronicity of psychopathology in adults. More specifically, ACEs associated with maladaptive family functioning (e.g. childhood maltreatment, parental mental health) were found to be the strongest predictor of onset of DSM-IV disorders.

As emphasised earlier (see 1.2.3), the majority of studies that investigate the influence of ACEs on adult affective psychopathology have used retrospectively reported data on ACEs that are known to be subject to recall bias (Henry, Moffitt, Caspi, Langley, & et al, 1994b; Prescott et al., 2000). Nevertheless, a number of prospective studies have been conducted more recently using cohort data. One of the most recent meta-analyses of prospective studies focused on the association between different types of childhood maltreatment (i.e., physical abuse, emotional abuse, and neglect) and risk of adult depression and anxiety, however this review did not take into account the influence or co-occurrence of other forms of ACEs (Li, D'Arcy, & Meng, 2016). No study to date has systematically reviewed and synthesised the evidence from existing studies for the association between a wide range of ACEs and adult internalising outcomes.

The present study systematically reviews and synthesises the evidence from longitudinal prospective studies for the effects of family-related ACEs on adult depression and anxiety, with the aims to determine: 1) the overall association between any family-related ACEs and adult internalising psychopathology (i.e. anxiety, depression, and unspecified internalising symptoms); 2) the specific associations between different single types of ACEs, such as childhood maltreatment, sexual abuse, physical abuse, emotional abuse, parental psychopathology, parental death, parental

divorce/separation, family conflict and multiple (3 or more) ACE, and internalising psychopathology in adulthood.

2.3. Method

A systematic review and meta-analysis of longitudinal prospective studies of the association between family-related ACEs and adult internalising disorders or symptoms, was conducted using the Meta-analysis Of Observational Studies and Epidemiological guidelines (MOOSE) (Stroup et al., 2015),

2.3.1. Search strategy

Five databases were searched, including 'MEDLINE' (National Library of Medicine), 'Web of Science' (Thomson Reuters), 'EMBASE' (Elsevier), 'psycARTICLES' and 'PsycINFO'. These databases were chosen based on their inclusion of relevant publications and the greatest access to a wide array of accessible journals. Due to the wide range of family-related ACEs reported in the literature (Kalmakis & Chandler, 2014), a series of search terms were initially piloted in order to: (1) identify search terms which represented the most widely studied family-related ACEs in the psychopathology literature, and (2) identify 'sensitive' and 'specific' search terms which generate an appropriate number of sources to be screened.

All databases were systematically searched from January 1980 up to, and including November 2014, using the following search terms: *early OR child* OR famil**, combined with: *advers* OR neglect* OR maltreat* OR "parental loss" OR separat* OR "parental ill*" OR "parental mental ill*"*, combined with: *anxi* OR depress* OR mood OR internalising*. The Boolean operator "AND" was used to combine search terms.

A series of steps were taken to conduct a comprehensive search of relevant studies and to reduce 'file drawer effect' (publication bias based on statistical

significance). Firstly, reference lists of previous reviews and eligible articles were screened to ensure that unidentified studies were considered for the current meta-analysis (forward- and backward searching). Further to this, the authors of eligible reports, who were recognised experts in the field, were contacted about eligible peer-reviewed data which may not have been picked up by the specified search terms (see appendix 2D for details).

2.3.2. Inclusion and exclusion criteria

Sources. Sources were limited to: (1) papers written in English; (2) peer reviewed papers. Only studies published between January 1980 and November 2014, were included as the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), was published in 1980 and was shortly followed by the publication of the DSM-III – revised (DSM-III-R), improving the consistency of diagnosis for internalising disorders.

Study design. Studies were confined to those with a prospective design, and investigated the association between family-related ACEs and depressive or anxiety symptoms/disorders in adulthood.

Participants. Participants were required to be younger than 18 years of age at the time of exposure and older than 18 years of age at the time of follow up. If studies contained overlapping samples, or if samples were reported in multiple articles, the most appropriate articles were selected based on the following criteria: (1) a definition of ACEs that most closely resembled the search terms used, (2) whether the articles had a specific focus on ACEs as a main variable, and (3) the longest follow up period.

ACEs. Single and multiple types of ACEs were included in the current review and meta-analysis. Studies were included if they reported on one or more family-related ACE that reflected the search terms specified. Studies were excluded if they solely

reported on poverty, socio-economic status, substance misuse, racial segregation, community violence, school violence, separation due to evacuation, or natural disaster.

Adult depression and anxiety. Studies reporting current diagnosis or symptoms of anxiety or depression were considered for inclusion. Diagnostic outcomes of major depressive disorder, generalised anxiety disorder, social anxiety disorder, panic disorder, agoraphobia, obsessive compulsive disorder or post-traumatic stress disorder were deemed to be eligible for inclusion. Diagnoses were required to be consistent with DSM-III (APA, 1980), DSM-III-R (APA, 1987), DSM-IV (APA, 1994), DSM-IV-TR (APA, 2000), DSM-5 (APA, 2013), Research Diagnostic Criteria or the International Classification of Disease (ICD-9), ICD-10. Dimensional outcomes of depressive or anxious symptoms using standardised instruments, such as the Beck Depression Inventory (BDI), were also included. Studies with heterogeneous psychiatric samples, e.g., with participants with comorbid symptoms of psychosis, personality disorders, or only those diagnosed with bipolar disorder, were excluded from the analysis.

2.3.3. Eligibility check

Following the systematic search, all sources were imported into EndNote, and duplicates were removed. Article screening was conducted in three separate phases: (1) title screening; (2) abstract screening; and (3) full text screening. Before phases 2 and 3 began, 10% of the abstracts and full-texts were selected at random using a random numbers generator, and were assessed independently by two separate researchers (E.T. & D.G.). Percent agreement was calculated to assess inter-rater agreement. In the abstract screening phase, if one or both of the coders deemed an abstract to be eligible for further screening, this was included for further examination. The percentage agreement between E.T. & D.G. was 86% for the abstracts screened and 88% for the

full-texts screened. Eligibility discrepancies were discussed during regular consensus meetings.

2.3.4. Data extraction

For all eligible papers the following information was extracted from each study: basic data (author, project name, year of publication, study design, country); socio-demographic data (number of participants, gender, age at exposure, age at follow up, and length of follow up); information about the predictor (ACE type and ACE measure); information about the outcome (type and measure); covariates; and statistical information. All statistical information was extracted twice in order to increase coding accuracy; 10% of eligible reports were also randomly selected and coded independently by two separate researchers (E.T. and D.G.), and any coding discrepancies were discussed and resolved.

All studies were required to provide sufficient statistical information (e.g., beta-values, standard errors or 2×2 contingency tables) which allowed for the computation of effect sizes. If sufficient statistical information for computing effect sizes was not available, studies were excluded from the meta-analysis. Adjusted statistical information was extracted where possible. The majority of studies were adjusted for age and gender (see table 2.1 for details of adjustments made for each study).

2.3.5. Quality assessment

The Strengthening the reporting of observational studies in Epidemiology (STROBE) checklist (see appendix 2B), which provides recommendations for reporting observational studies, was used to assess the quality of all eligible studies. The STROBE statement includes 22 checklist items. Each study was assigned either a low (>65%), medium (35-65%) or high (<35%) possibility of reporting bias.

2.3.6. Data synthesis

To investigate the association between ACEs and internalising psychopathology in adulthood, a meta-analysis was carried out on effects extracted from: 1) studies which focus on single types of family-related ACEs (those considered in this review); and 2) studies which provide a composite measure of multiple ACEs.

All analyses were conducted using the *metafor* package (Viechtbauer, 2010) for R version 3.2, 2015 (R Core Team, 2015). Odd ratios (ORs) and 95% confidence intervals (CIs) were chosen as the main effect size measure. Beta values and their affiliated 95% confidence intervals were converted to ORs using the antilogarithm (i.e. base e) of each value. As heterogeneity was expected both within and between studies, a random-effects multivariate model was carried out to combine effect sizes. This was executed using the rma.mv function in the *metafor* package. Specifically, this function uses a multilevel model structure whereby effect sizes are nested within papers. This approach allowed for all studies (i.e., papers reporting separate effects from the same sample of participants) to be included in the main analysis, without violating the assumption of independence. Heterogeneity was estimated using the Q_T and I^2 statistics to examine the percentage of variability in effect estimates that is accounted for by heterogeneity rather than sampling error.

Separate meta-analyses were conducted to explore the effect of ACEs on different internalising outcomes: depression, anxiety, and unspecified internalising symptoms. Separate random-effects meta-analyses were also conducted to investigate the size of the association between specific single and multiple types of ACEs and adulthood internalising psychopathology. Sub-analyses were conducted when there were three or more relevant eligible studies. In the case where there were overlapping studies (i.e. separate effect sizes from the same sample of participants), effect sizes

which reported on either / or anxiety or unspecified internalising symptoms were removed, due to these being the least reported outcomes. When there were less than three effect sizes available, a narrative synthesis of the results are given.

Moderation analyses in the total sample were conducted to test whether effects of ACEs on adulthood internalising outcomes differ significantly by outcome type and ACE type.

2.3.7. Publication bias

Indication of publication bias was assessed by degree of asymmetry in a funnel plot, with Egger's test (Egger, Smith, & Phillips, 1997). If any bias was found, the method of 'trim and fill' was also implemented to assess whether results differed substantially.

2.4. Results

2.4.1. Search results

The search of five databases generated 28,605 articles, of which 7772 duplicates were removed. In addition, a further 23 articles were found through searching the grey literature, leaving a total of 20,856 to be title screened. At phase 1 (title screening), 19,241 articles were excluded leaving 1642 articles to be screened at phase 2. At phase 2 (abstract screening), 1156 articles were excluded leaving 486 articles to be screened at phase 3. At phase 3 (full-text screening), 459 articles were excluded leaving a total of 27 articles to be coded. Among these 27 articles, 47 studies were coded for the systematic review. A breakdown of the search results and reasons for full text exclusion are presented in Figure 2.1.

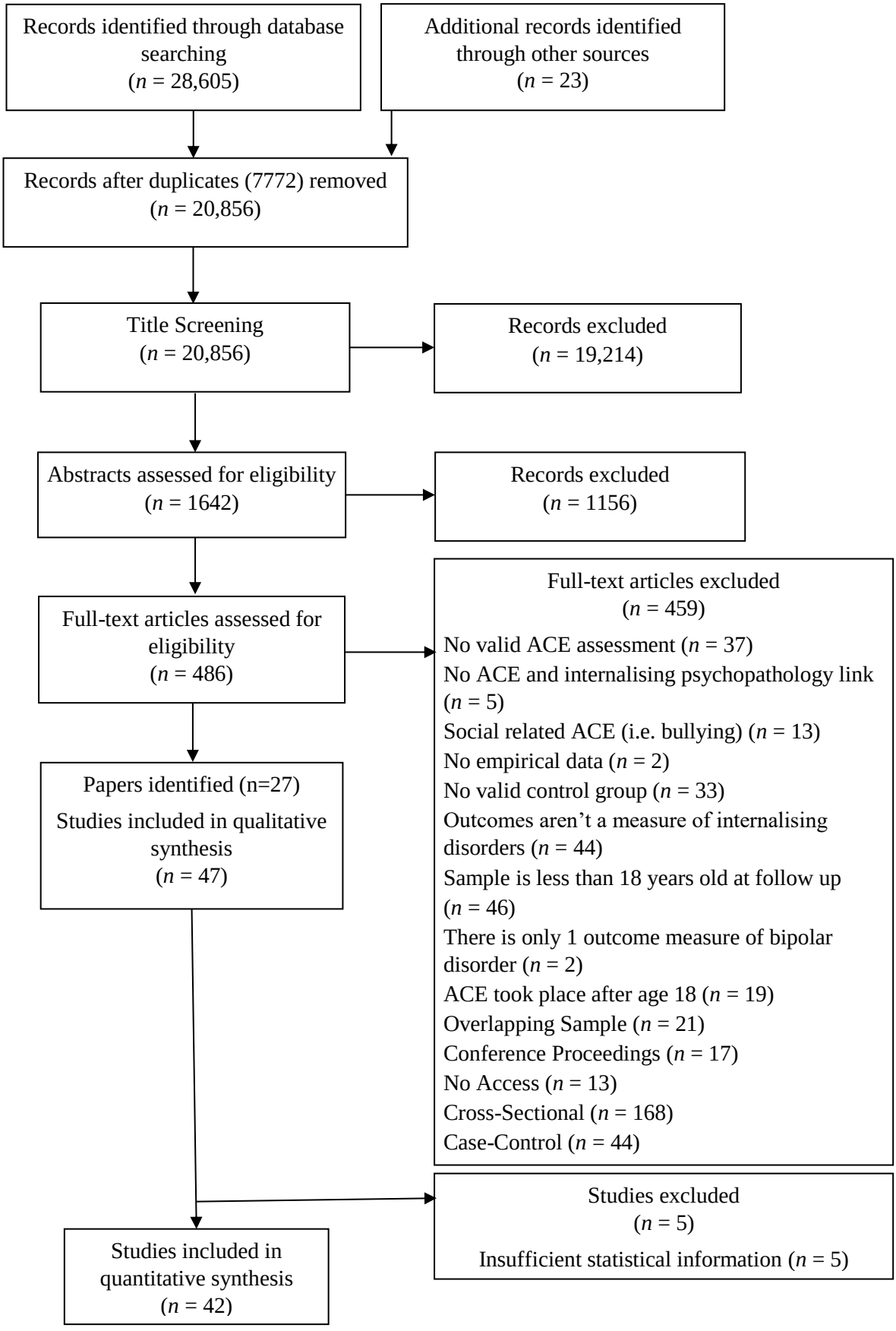


Figure 2.1. Flow diagram showing study selection procedure

Across all eligible 47 studies, in total there were 88,119 participants (54% females). The mean age at which ACEs were reported was 12 years (range: 2.5-18), and the mean age at which adult internalising psychopathology was measured was 29 years (range: 18.4-45). The mean follow up period was 17 years (range: 2-43).

In total, ten studies reported on the influence of multiple ACEs, and 37 studies reported on single types of adversity including: a) a composite measure of childhood maltreatment: emotional, physical and sexual, abuse and neglect, number of studies (*k*) = 7, sexual abuse (*k* = 5), emotional abuse (*k* = 1), physical abuse (*k* = 2); b) family conflict (*k* = 3; c) parental loss or death (*k* = 3); d) parental divorce and separation (*k* = 10); and e) parental psychopathology (*k* = 6) (see appendix 2M for all references). Depressive symptoms or depressive disorders were the most frequently reported outcomes, with 27 studies focusing on these. Ten studies reported anxiety symptoms or disorders as their main outcome, and ten studies reported on unspecified internalising symptomology. All studies scored above 65% on the STROBE checklist (range 65-100) indicating an appropriate amount of reporting quality in each article. (See table 2.1 for all study characteristics).

Table 2.1. Study Characteristics

First Author, Year (Country)	Project Name	Total Sample Size (% of females)	Follow up period (years)	Age ACE was reported	Mean age of follow up (years)	ACE Type (single / multiple)	Instrument (ACE measure)	Internalising disorder / symptoms type	Instrument	Factors adjusted for	Setting	Strobe score (%)	In M-A?
Coffino, 2009 (USA)	N.R.	147 (49)	20	6	26	PL/S (single)	Interview (teacher, parent and child)	Depression	YASR	Multiple factors	CBS	65	N
Cohen a, 2001 (USA)	CIC	614 (47)	4	18	22	CPA (single)	Self-report	Depression	DIS	Age, sex, SES, & race	CBS	79	Y
Cohen b, 2001 (USA)	CIC	610 (51)	4	18	22	CSA (single)	Self-report	Depression	DIS	Age, sex, SES, & race	CBS	79	Y
Cohen c, 2001 (USA)	CIC	610 (51)	4	18	22	CSA (single)	Self-report	Anxiety	DIS	Age, sex, SES, & race	CBS	79	Y
Daley, 2000 (USA)		128 (100)	5	18.29	22.29	PP (single)	RDC	Depression	DSM-M-R	Lifetime history of depression	CBS	68	Y
Fergusson a, 2013 (New Zealand)	CHDS	987 (51)	12	18	30	CSA (single)	Questionnaire	Depression	CIDI	Multiple (10) factors	CBS	88	Y
Fergusson b, 2013 (New Zealand)	CHDS	987 (51)	12	18	30	CSA (single)	Questionnaire	Anxiety	CIDI	Multiple (10) factors	CBS	88	Y
Ford a, 2011 (UK)	1958 NCDS	9377	33.7	11.3	45	ACEs (multiple)	Official records	Unspecified internalising symptoms	(CIS-R)	SES, gender and peer relationships	CBS	88	Y
Ford b, 2011 (UK)	1958 NCDS	9377	33.7	11.3	45	PD/S (single)	Official records	Unspecified internalising symptoms	(CIS-R)	SES, gender and peer relationships	CBS	88	Y

Ford c, 2011 (UK)	1958 NCDS	9377	33.7	11.3	45	Physical Abuse (single)	Official records	Unspecified internalising symptoms	(CIS-R)	SES, gender and peer relationships	CBS	88	Y
Ford d, 2011 (UK)	1958 NCDS	9377	33.7	11.3	45	Sexual abuse (single)	Official records	Unspecified internalising symptoms	(CIS-R)	SES, gender and peer relationships	CBS	88	Y
Franko, 2004 (USA)	NGHS	1361 (100)	5	16	21	PD/S (single)	Questionnaire (SRRS & SEI)	Depression	CES-D	School site, parental education, and depression status when ACE was measured	School Setting	76	Y
Gilman, 2003 (USA)	NCPP	1089 (47)	14	7	21	PD/S (single)	Parent report	Depression	DIS	Family history of mental illness, maternal age, age at interview, and study selection factors	CBS	79	Y
Gonzalez, 2012 (Canada)	OCHS	1475	17	15	21-35	PP (single)	Parent report	Depression	CIDI-SF	Completed years of education and household income	CBS	76	Y
Green a, 2013 (USA)	TWS	603 (0)	16	26.5	42.5	FC (single)	Self-report	Depression	CIDI	Unadjusted	CBS	81	Y
Green b, 2013 (USA)	TWS	625 (100)	16	26.5	42.5	FC (single)	Self-report	Depression	CIDI	Unadjusted	CBS	81	Y

Herrenkohl a, 2013 (USA)	LLS	355 (48)	33	3.75	36	CM (single)	Official records	Depression	BDI	Gender and SES	Sample from protective services	82	Y
Herrenkohl b, 2013 (USA)	LLS	355 (48)	33	3.75	36	CM (single)	Official records	Anxiety	GAD-7	Gender and SES	Sample from protective services	67	Y
Horan, 2014 (USA)	N.R.	896 (51)	33.3	6.2	39.5	ACEs (multiple)	Cumulative risk index of ACE	Unspecified internalising symptoms	BAI / CES-D	N.R.	CBS	79	Y
Lacey, 2014 (UK)	1970 British Birth Cohort	10,714 (51.1)	19.7	10.3	30	PD/S (single)	parent report	Unspecified internalising symptoms	Malaise Inventory	Fathers social class, mothers education, mothers age at birth of cohort child	CBS	87	Y
Liu, 2012 (USA)	CVA	299 (67)	2.5	18.8	21	CEA (Single)	LEQ	Depression	SADS-L	Cognitive risk status, past depressive episodes, current depressive symptoms	CBS	68	Y
Mersky, 2013 (USA)	CLS	1142 (54)	6	17	23	ACEs (multiple)	Official records	Depression	Own Survey	Multiple (8)		79	Y
Mersky, 2013 (USA)	CLS	1142 (54)	6	17	23	ACEs (multiple)	Official records	Anxiety	Own Survey	Multiple (8)		79	Y

Moffitt a, 2007 (New Zealand)	DMHDS	1037 (48)	21	7	32	CM (single)	Mixed Measures	Anxiety	DSM-IV	Gender	CBS	65	Y
Moffitt b, 2007 (New Zealand)	DMHDS	1037 (48)	21	7	32	CM (single)	Mixed Measures	Depression	DSM-IV	Gender	CBS	65	Y
Moffitt c, 2007 (New Zealand)	DMHDS	1037 (48)	21	7	32	PL/S (single)	Mixed Measures	Anxiety	DSM-IV	Gender	CBS	65	Y
Moffitt d, 2007 (New Zealand)	DMHDS	1037 (48)	21	7	32	PL/S (single)	Mixed Measures	Depression	DSM-IV	Gender	CBS	65	Y
Moretti, 2013 (Canada)	N.R.	179 (46)	4	15.34	19.93	CM (Single)	CTS	Depression	Adult version of the YSR	N.R.	Juvenile justice and clinical settings	67	N
Oldehinkel, 2014 (Netherlands)	DLPSA TRAILS	1584 (52)	5.5	13.6	19.1	ACEs (multiple)	Parent report	Depression	CIDI	Gender and comorbid anxiety	CBS	75	N
Oldehinkel, 2014 (Netherlands)	DLPSA TRAILS	1584 (52)	5.5	13.6	19.1	ACEs (multiple)	Parent report	Anxiety	CIDI	Gender and comorbid depression	CBS	75	N
Raposa, 2014 (Australia)	MUSP	705 (51)	20	2.5	22-25	ACEs (multiple)	Parent report	Depression	BDI-II	Gender	CBS	79	N
Richards a, 1997 (UK)	MRC NSHD	1054 (0)	43	7.5	43	PD/S (single)	Questionnaire	Unspecified internalising symptoms	PSF	SES, early vulnerability factors and current stressors	CBS	85	Y

Richards b, 1997 1 (UK)	MRC NSHD	1031 (100)	43	7.5	43	PD/S (single)	Questionnaire	Unspecified internalising symptoms	PSF	SES, early vulnerability factors and current stressors	CBS	85	Y
Schilling, 2008 (USA)		1093 (52)	2	17	18-20	ACEs (multiple)	Interview (NCS)	Depression	12-item version of the CES-D	Gender, race/ethnicity, parent's education, and dropout status	School Setting	79	Y
Shanahan a, 2011 (USA)	GSMS	1004 (43)	12	9	21	CM (single)	CAPA / YAPA	Depression	CAPA / YAPA	Unadjusted	CBS	70	Y
Shanahan b, 2011 (USA)	GSMS	1004 (43)	12	9	21	PP (single)	CAPA / YAPA	Depression	CAPA / YAPA	Unadjusted	CBS	70	Y
Shanahan c, 2011 (USA)	GSMS	1004 (43)	12	9	21	FC (single)	CAPA / YAPA	Depression	CAPA / YAPA	Unadjusted	CBS	70	Y
Sourander a, 2005 (Finland)	EMCPS	2712 (0)	15	8	23	PD/S (single)	Questionnaire	Anxiety	ICD-10	N.R.	CBS	76	Y
Sourander b, 2005 (Finland)	EMCPS	2712 (0)	15	8	23	PD/S (single)	Questionnaire	Depression	ICD-10	N.R.	CBS	76	Y
Storksen a, 2005 (Norway)	HUNT	1116 (0)	4	14.4	18.4	PD/S (single)	FCQ	Unspecified internalising symptoms	SCL	Age, parental education and Fathers absence	School Setting	70	Y
Storksen b, 2005 1 (Norway)	HUNT	1285 (100)	4	14.4	18.4	PD/S (single)	FCQ	Unspecified internalising symptoms	SCL	Age, parental education and Fathers absence	School Setting	70	Y
Thornberry, 2010 (USA)	RYDS	907 (27)	6.6	13.9	22.7	CM (Single)	Official records	Depression	CES-D	Multiple (6) factors	CBS	79	Y

Timko, 2008 (USA)	N.R.	320 (54)	23	11.3	34.3	PP (single)	RDC	Depression	Depressive Symptoms Severity Index	Gender and education	CBS	65	Y
van der Vegt a, 2009 (Netherlands)	N.R.	1364 (44)	14	12.4	26.3	ACEs (multiple)	Parent report	Anxiety	CIDI / DIS	Multiple (5) factors	International adoptees	65	Y
van der Vegt b, 2009 (Netherlands)	N.R.	1364 (44)	14	12.4	26.3	ACEs (multiple)	Parent report	Depression	CIDI / DIS	Multiple (5) factors	International adoptees	65	Y
Weissman (a), 2006 (USA)	N. R.	151 (58)	20	14.5	35	PP (single)	RDC	Depression	SADS-L	Age and gender	CBS	68	Y
Weissman (b), 2006 (USA)	N.R.	151 (58)	20	14.5	35	PP (single)	RDC	Anxiety	SADS-L	Age and gender	CBS	68	Y

Note: ACE, Adverse Childhood Experiences; BAI, The Beck Anxiety Inventory; BDI II, Beck Depression Inventory–II; BSI, Derogatis Brief Symptom Inventory; CAPA, Child and Adolescent Psychiatric Assessment; CBS, Community Based Sample; CEA, Childhood Emotional Abuse; CES-D, Centre for Epidemiologic Studies Depression Scale; CHDS, Christchurch Health and Development Study; CIC, Children in the Community; CIDI, Composite International Diagnostic Interview; CIDI-SF, Composite International Diagnostic Interview-Short Form; CIS-R, Revised Clinical Interview Schedule; CLS, Chicago Longitudinal Study; CM, Childhood Maltreatment; CPA, Childhood Physical Abuse; CSA, Childhood Sexual Abuse; CTS, Conflicts Tactics Scale; CVD, Temple-Wisconsin Cognitive Vulnerability to Depression Project; DIS, National Institute of Mental Health Diagnostic Interview Schedule; DLPSA, Dutch Longitudinal Population Survey of Adolescents DMHDS, Dunedin Multidisciplinary Health and Development Study; EMCPS, Epidemiological Multicentre Child Psychiatric Study; FC, Family Conflict; FCQ, Forced Choice Questionnaire; GAD-7, 7 Item Generalized Anxiety Disorder Questionnaire; GSMS, The Great Smoky Mountains Study; HUNT,

The Nord-Trøndelag Health study; ICD-10 classification system; Lung, and Blood Institute Growth and Health Study; LEQ, Lifetime Experience Questionnaire; LLS, Lehigh Longitudinal Study; M-A, Meta-Analysis; MRC NSHD, Medical Research Council National Survey of Health and Development; MUSP, Mater-University of Queensland Study of Pregnancy; N.R., Not Reported; NCDS, National Child Development Study; NCPP, National Collaborative Perinatal Project; NCS, National Comorbidity Survey; NGHS, National Growth and Health Study; NSFH, National Survey of Families and Households; OCHS, Ontario Child Health Study; PD/S, Parental Divorce / Separation; PL/S, Parental Loss / Separation; PP, Parental Psychopathology; PSF, Psychiatric Symptom Frequency scale; RDC, Research Diagnostic Criteria; RYDS, Rochester Youth Development Study; SADS-L, Schedule for Affective Disorders and Schizophrenia – Lifetime Version for adults; SCL, Symptom Check List; SEI, Social Environment Inventory; SES, Socioeconomic Status; SRRS, Social Readjustment Rating Scale; TRIALS, Tracking Adolescents' Individual Lives Survey; TWS, The Woodlawn Study; YAPA, Young Adult Psychiatric Assessment; YASR, Youth Adult Self Report Form; YSR, Achenbach Youth Self-report

2.4.2. Overall association between family-related ACEs and adult internalising psychopathology

All studies. The results for the overall association between family-related ACEs and internalising psychopathology are presented in Figure 2.2. The analysis included 42 studies, with a total of 83,920 individuals. Five studies, with a total of 4,199 individuals were excluded from the analysis due to insufficient statistical information. The synthesis of effect sizes was conducted using the log odds ratio (LOR) for each study. LORs were weighted according to the inverse of their variance. The weighted mean effect size averaged over all studies found that ACEs were significantly positively associated with internalising psychopathology, LOR = 0.61, 95% CI (0.45-0.76), SE = 0.08 $z = 7.56$, $p < .001$. The LOR was exponentiated for ease of interpretation of the odd ratio, OR = 1.83, 95% CI (1.57-2.15).

Heterogeneity analysis (Q and I^2 tests) indicated that effect sizes were heterogeneous, $Q_T = 291.37$, $p < .001$, compared with a critical value of $\chi^2 (41) = 58.12$ ($I^2 = 85.93\%$).

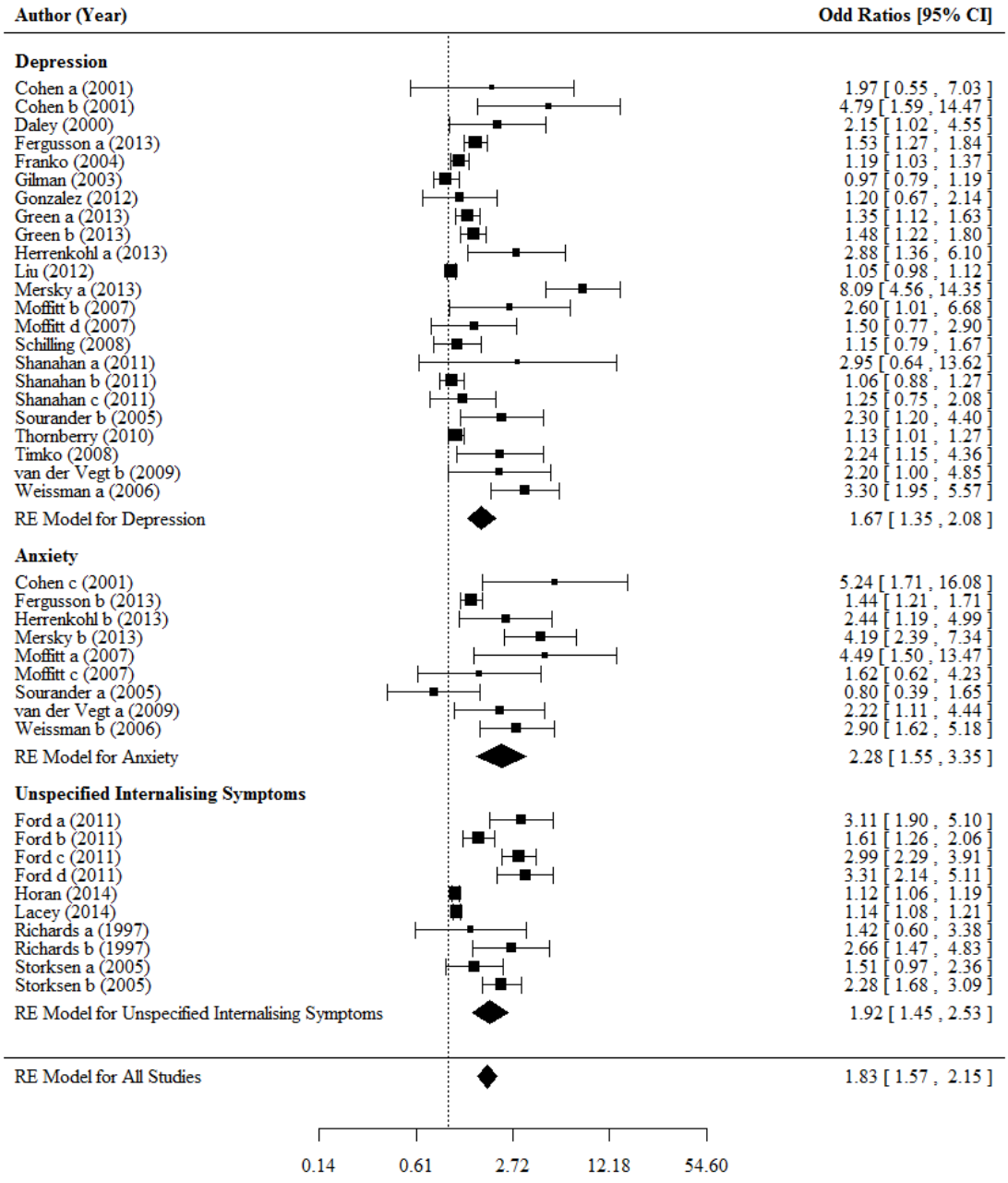


Figure. 2.2. Forest plot (stratified by outcome type) examining the overall association between family-related ACEs and internalising psychopathology in adulthood.

Funnel plot asymmetry (Figure 2.3) and Egger's test, $z = 5.32$, $p < .01$ indicated possible publication bias. The application of trim and fill method indicated 18 missing studies. However, when the estimated missing effects were included in the analysis, the association between ACEs and adulthood internalising psychopathology slightly reduced, but remained significant, OR = 1.27, 95% CI (1.06-1.52) (see appendices 2D and 2E).

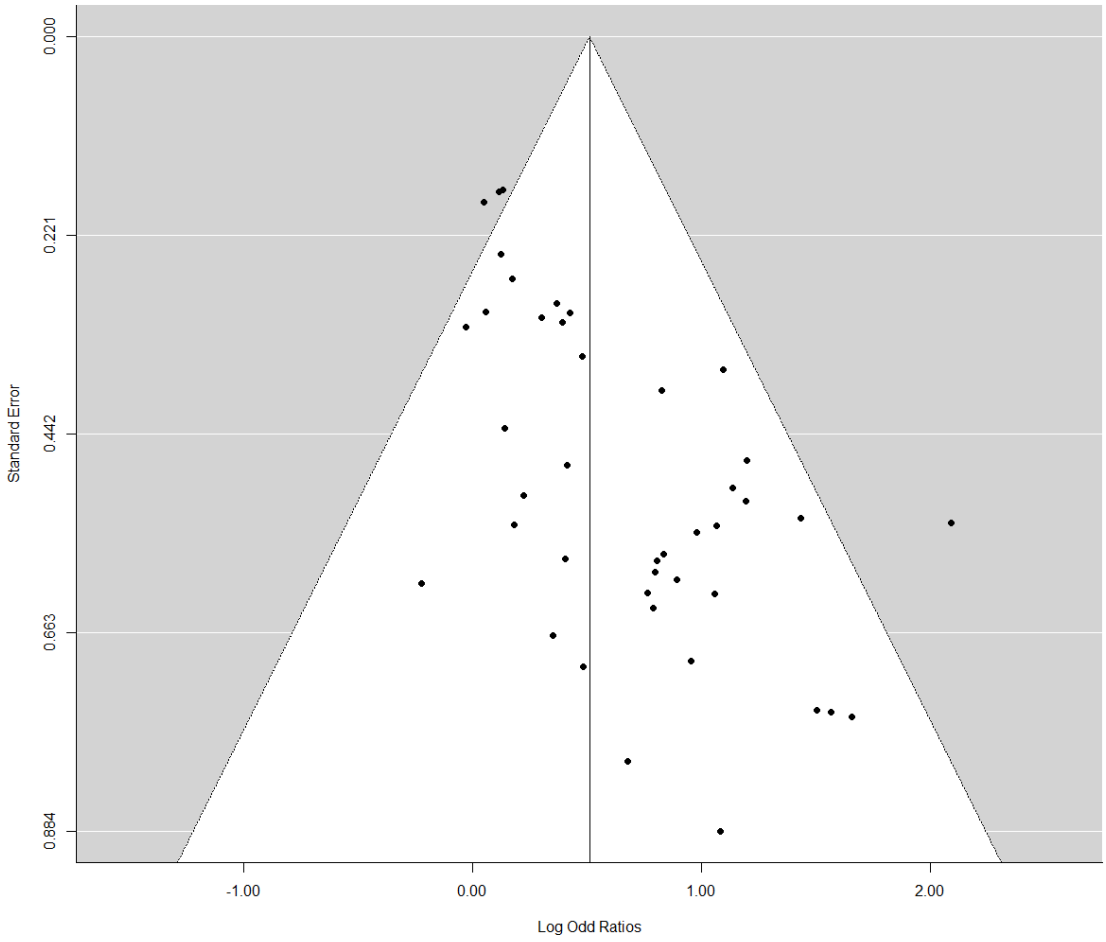


Figure 2.3. Funnel plot assessing publication bias among all included studies that investigated association between family-related ACEs and internalising psychopathology in adulthood

Depression studies. The analysis comprised 23 prospective studies with a total sample of 20,921 individuals. The weighted mean effect sizes averaged over depression studies found that ACEs were significantly associated with depression, LOR=0.52 (95% CI =0.30-0.73), SE=0.11, z = 4.70, p < .01. The LOR was exponentiated to allow interpretation of the odd ratio, OR = 1.67, 95% CI (1.35, 2.08). Heterogeneity analysis indicated that effect sizes were heterogeneous, Q_T = 119.37, p < .01, compared with a critical value of χ^2 (22) = 33.92 (I^2 = 81.57%). Funnel plot asymmetry (see appendix 2F) and Egger's test, z = 3.78, p < .01 indicate that possible selection biases may have taken place (e.g. publication bias). The application of trim and fill method indicated 9 missing studies. When the estimated missing effects were included in the analysis, association strengths between ACEs and depression were no longer significant, OR = 1.23, 95% CI (0.98, 1.55) (see appendix 2G and 2H).

Anxiety studies. The analysis comprised nine prospective studies with a total sample of 9,395 individuals. The weighted mean effect sizes averaged over studies found that ACEs were significantly associated with anxiety, LOR = 0.82, 95% CI (0.44, 1.12), SE = 0.20, z = 4.19, p < .001 (see Figure 2 for exponentiated LOR). Heterogeneity analysis indicated that effect sizes were heterogeneous, Q_T = 29.33, p < .01, compared with a critical value of χ^2 (8) = 15.51 (I^2 = 72.72%). Funnel plot symmetry (see appendix 2I) and Egger's test, z = 1.52, p = .13 did not suggest publication bias.

Studies of unspecified internalising symptoms. The analysis comprised of ten prospective longitudinal studies with a total sample of 53,604 individuals. The weighted mean effect sizes averaged over studies found that ACEs were significantly associated with unspecified internalising symptoms, LOR = 0.65, 95% CI (0.37, 0.93), SE = 0.14, z = 4.59, p < .001 (see table 2.3 for exponentiated LOR). Heterogeneity

analysis indicated that effect sizes were heterogeneous, Q_T = 118.75, p < .001, compared with a critical value of χ^2 (9) = 16.92 (I^2 = 92.42%). Funnel plot asymmetry (see appendix 2J) and Egger's test, z = 3.23, p < .01 indicated possible publication bias. The application of the trim and fill method indicated 5 missing studies. However, when the estimated missing effects were included in the analysis, association strengths between ACEs and unspecified internalising symptoms were no longer significant, OR = 1.24, 95% CI (0.86, 1.77) (see appendix 2K and 2L).

Although small differences in effect sizes were found for different internalising outcomes (i.e., depression, anxiety, unspecified internalising symptoms), moderation analysis revealed that these between group differences were not significant (Table 2.2).

Table 2.2. Results of meta-analysis using outcome type and ACEs amount as moderators

Variable	***k***	**QM**	**β (95%CI), *p* value**	***z***	***Q*E**
		X^2 (df)			X^2 (df)
Depression VS. anxiety	31	1.13 (1)	0.24 (-0.20, 0.69), $p = 0.29$	1.06	144.81 (29)***
Depression VS. unspecified internalising symptoms	34	1.01 (1)	0.18 (-0.17, 0.54), $p = 0.31$	1.01	244.74 (32)***
Anxiety VS. unspecified internalising symptoms	19	0.06 (1)	-0.06. (-0.53, 0.41), $p = 0.80$	-0.25	150.81 (17)***
Single VS. multiple ACEs	42	2.23 (1)	0.31 (-0.01, 0.72), $p = 0.13$	1.49	290.60 (40)***
Single VS. childhood maltreatment unspecified	42	0.57 (1)	0.20 (-0.31, 0.71), $p = 0.45$	0.75	291.37 (40)***

Single VS. Childhood Sexual abuse	42	1.12 (1)	0.27 (-0.23, 0.76) $p = 0.45$	1.06	267.14 (40)***
Single VS. childhood physical abuse	42	0.99 (1)	0.40 (-0.39, 1.17). $p = 0.32$	1.00	246.93 (40)***
Single VS. parental psychopathology	42	0.03 (1)	0.04 (-0.42, 0.50), $p = 0.87$	0.16	289.28 (40)***
Single VS. parental divorce / separation	42	2.93 (1)	-0.31 (-0.66, 0.04), $p = 0.09$.	-1.71	290.44 (40)***
Family conflict	42	1.31 (1)	-0.32 (-0.88, 0.23), $p = 0.25$	-1.14	286.42 (40)***
Parental loss	42	0.16 (1)	-0.17 (-1.03, 0.67), $p = 0.68$	-0.41	290.62 (40)***
Single VS. childhood maltreatment (all childhood maltreatment studies)	42	1.37 (1)	0.21 (-0.14, 0.55), $p = 0.24$	1.17	291.35 (40)***

Note: '***' $p < 0.001$.

2.4.3. Associations between specific single and multiple types of family-related ACEs and adult internalising psychopathology

Separate random-effects meta-analyses were conducted to investigate associations between specific single, such as childhood maltreatment, sexual abuse, parental psychopathology, parental divorce / separation, family conflict, and multiple types of ACEs, and adult internalising psychopathology. As outcome type (depression, anxiety and unspecified internalising symptoms) was not found to significantly moderate the size of effect for the overall association, these sub-analyses were not stratified by outcome type. As a smaller amount of studies were available for each sub-analyses, a multilevel approach could not be adopted for the synthesis of effect sizes. Due to this, in the case where there were overlapping samples (effect sizes extracted from the same population), those who reported on depressive symptoms were included and studies who reported on anxiety or unspecified internalising symptoms were excluded. If less than three studies were available for a sub-analysis, a narrative synthesis was carried out. This was done for: childhood physical abuse, childhood emotional abuse, and parental loss. The results presented below are organised by adversity type to highlight any differences in the size of the association between the sub-analyses. For each sub analysis where a random-effect meta-analysis was carried out, the exponentiated LOR and heterogeneity estimates are presented in table 2.3.

Childhood Maltreatment Unspecified. Four studies (n =3,303) were included in the sub-analysis of childhood maltreatment. Two studies (Herrenkohl, 2013; Moffitt et al., 2007), who reported on anxiety were not included due to overlapping samples. Childhood maltreatment was found to be significantly associated with internalising psychopathology in adulthood, LOR = 0.65, 95% CI (0.04, 1.25), p = 0.03.

Childhood Sexual Abuse. Three studies (*n* = 10,974) were included in the sub analysis of childhood sexual abuse. Two studies were not included (Cohen, Brown, & Smaile, 2001; Fergusson, McLeod, & Horwood, 2013) due to overlapping samples. Childhood sexual abuse was found to be significantly associated with internalising psycholpathology in adulthood, LOR = 0.94, 95% CI (0.27, 1.60), $p < 0.01$.

Parental Psychopathology. Five studies (*n* = 3,078) were included in the sub-analyses of parental psychopathology. All five studies included in this analysis reported on depression as an outcome. One study (Weissman et al., 2006) who reported on anxiety as an outcome was removed due to an overlapping sample. Parental psychopathology was significantly positively found to be associated with depression in adulthood, LOR = 0.56, 95% CI (0.10, 1.02), $p = 0.02$.

Parental Divorce / Separation. Nine studies (*n* = 29,739) were included in the random effects sub analysis of parental divorce / separation. One study (Sourander et al., 2005), who reported on anxiety as an outcome was removed due to an overlapping sample. Parental divorce / separation was found to be significantly positively associated with internalising psychopathology in adulthood, LOR = 0.40, 95% CI (0.17, 0.63), $p < 0.01$.

Family Conflict. Three studies (*n* = 2232) were included in the random effects sub-analysis of family conflict (Green et al., 2013; Shanahan, Copeland, Costello, & Angold, 2011). All three studies included in this sub-analysis reported on depression as an outcome. Family conflict was found to be significantly positively associated with depression in adulthood, LOR = 0.34, 95% CI (0.20, 0.47), $p < 0.01$.

Other ACEs. Two studies (*n* = 9,991) reported on the effects of *childhood physical abuse* on internalising symptoms in adulthood. (Cohen et al., 2001; Ford, Clark, & Stansfeld, 2011). Physical abuse was found to be a significant risk factor for adult

internalising symptoms: OR = 1.97, 95% CI (0.55, 7.0) (Cohen et al., 2001), and OR = 2.99, 95% CI (2.28, 3.90) (Ford et al., 2011).

One study (n = 299) reported on the effect of *childhood emotional abuse* and depression (Liu, Jager-Hyman, Wagner, Alloy, & Gibb, 2012). Emotional abuse was found to be a significant risk factor for depressive symptoms: OR = 1.05, 95% CI (0.99, 1.13), p = 0.06.

Two studies with an overlapping sample (n = 1037) reported on the effect of *parental loss* on internalising psychopathology in adulthood (Moffitt et al., 2007). Specifically, one study reported on depression as an outcome and the other reported on anxiety. Participants were 3, 5, 7, 9 and 11 years old when parental loss was reported (i.e. parental loss took place either at, or before, age 11), and 32 years old at follow up, spanning an average follow up period of 25 years. A positive association was found between early parental loss and depression, OR = 1.50, 95% CI (0.8, 3.0), and anxiety, OR = 1.62, 95% CI (0.6, 4.1), respectively, however neither of these associations were statistically significant.

Multiple ACEs. Five studies (n = 13,872) were included in the analysis of multiple (i.e., 3+) ACEs. Two studies (Mersky, Topitzes, & Reynolds, 2013; van der Vegt et al., 2009) who reported on anxiety as an outcome were not included due to overlapping samples. Multiple (i.e., 3+) ACEs were found to be significantly positively associated with internalising psychopathology in adulthood ACEs, LOR = 0.83, 95% CI (0.10, 1.55), p = 0.02.

Publication bias was assessed for each sub-analysis by assessing the degree of asymmetry using Eggers test (Egger et al., 1997). The method of trim and fill was implemented if any publication bias was indicated, and pooled effect sizes were recalculated (see table 2.3).

Although small differences in effects of specific ACEs on internalising psychopathology were found, moderation analysis indicated that these differences were not statistically significant (all *p*-values were non-significant) (Table 2.2). Due to the limited number of studies which reported separate effects for males and females, it was not possible to examine gender as a moderator. Moreover, as a large number of methods were used to assess ACE (e.g. parent report, teacher report, questionnaire, and mixed methods), it was also not possible to examine whether 'type of assessment' influenced the overall effect of ACE on internalising psychopathology.

Table 2.3. Results of sub analysis focusing of specific adverse childhood experience

	K $_{studies}$ ***(n*** $_{participants}$***)***	**OR (95%CI), *p* value**	***Q* test *p* value**	I^2 **(%)**	***z* score *p* value**	***n* missing studies identified**	**OR (95%CI), *p* value Inc. filled studies**
Childhood Maltreatment Unspecified	4 (3,303)	1.91 (1.04; 3.49), $p = 0.03$	10.03 $p = 0.02$	70.09	3.02 $p < 0.01$	1	1.78 (1.04, 3.03), $p = 0.03$
Sexual abuse	3 (10,974)	2.56 (1.32; 4.97), $p < 0.01$	13.43 $p < 0.01$	77.66	1.76 $p = 0.08$	0	-
Parental Psychopathology	5 (3,078)	1.75 (1.11; 2.76), $p = 0.02$	21.23 $p < 0.01$	81.16	1.30 $p = 0.19$	0	-
Parental Divorce / Separation	9 (29,739)	1.49 (1.18; 1.89), $p < 0.01$	41.60 $p < 0.01$	80.77	2.19 $p = 0.02$	2	1.37 (1.08, 1.73), $p < 0.01$
Family Conflict	3 (2232)	1.40 (1.23; 1.60), $p < 0.01$	0.63 $p = 0.7$	0%	1.30 $p = 0.19$	0	-
Multiple ACEs	5 (13,872)	2.28 (1.11; 4.72), $p = 0.02$	63.35	93.68	1.28 $p = 0.2$	0	-

2.5. Discussion

Historically the majority of research investigating associations between early life adversities and later life psychopathology has been cross-sectional. The aim of the present systematic review and meta-analysis was to appraise and synthesise the prospective evidence for the association between family-related single and multiple adverse childhood experiences (ACEs) and adult internalising psychopathology. Overall, 47 eligible studies (*n* = 88,119), from 27 articles were identified. All included studies were of reasonable good quality as indicated by the STROBE checklist. Notably, across all studies ACEs were reported at an average age of 12 years, and internalising psychopathology was followed up at an average age of 29 years.

The results suggest that family-related ACEs are a significant risk factor for the development of internalising psychopathology in adulthood. Specifically the present meta-analysis indicated individuals who have suffered family-related ACEs were 1.83 times more likely to develop internalising psychopathology in adulthood than those who have not experienced ACEs. Small non-significant differences were found between the different outcomes of internalising symptoms. Pooled estimates suggest that individuals are 1.67 times more likely to develop depression, 2.38 times more likely to develop anxiety and 1.92 times more likely to develop unspecified internalising symptoms.

Subgroup analyses revealed respective associations between specific single and multiple types of ACEs and adulthood internalising psychopathology (depression or unspecified internalising symptoms). All specific single and multiple ACEs were positively associated with adulthood outcomes, with pooled effect sizes ranging from small to medium. Notably, sexual abuse, closely followed by multiple ACEs (i.e., 3+), were the highest risk factors of internalising psychopathology. As with the different outcome types, effect size differences for ACE types were found to be not statistically

significant. Indication of publication bias was found, although when missing effects were included in the analysis, association strengths were attenuated but remained significant at the 5% level.

Results of the current meta-analysis are consistent with previous meta-analyses that focused on single types of ACEs, such as specific forms of childhood maltreatment (Lindert et al., 2014; Nanni et al., 2012). The current meta-analysis adds to the literature through the inclusion of a wide range of family-related ACEs, as well as multiple ACEs. Interestingly, multiple ACEs (3+), as well as sexual abuse, were associated with the highest risk (as compared to the other ACEs assessed) of developing internalising psychopathology. This is consistent with prior evidence which has found a dose-response relationship between the number of ACEs and health related outcomes, including internalising disorders (Horan & Widom, 2014a; Raposo, Mackenzie, Henriksen, & Afifi, 2013). This is also in line with prior evidence which suggests that some specific ACEs may pose a greater risk to the development of internalising symptoms than others (Kessler et al., 2010). It has been suggested that, as ACEs co-occur and accumulate over time (Dong et al., 2004), studies which focus on specific single and multiple types of adversities should ensure that statistical constrains are in place to control for the natural covariation of accompanying ACEs (Vachon et al., 2015). For example Vachon et al. (2015) found that 89% of cases involving childhood sexual abuse were accompanied by a non-sexual types of childhood maltreatment, whereas only 9% of non-sexual childhood maltreatment was accompanied by childhood sexual abuse. As such, the elevated odds associated with sexual abuse, as compared to other types of ACEs, could be the result of co-occurring ACEs (such as other types of maltreatment).

One possible explanation for the association between family-related ACEs and adult internalising psychopathology is that exposure to ACEs increases an individual's

vulnerability to the effects of later stressful life events. While different stressful experiences (e.g. divorce) during adulthood are associated with internalising disorders (Risch, Herrell, & Lehner, 2009; Richards, Hardy & Wadsworth, 1997; Brown & Harris, 1989), the associated risk significantly increases when ACEs have also been experienced by the individual (McLaughlin et al., 2011; Power et al., 2013). This observation supports the stress sensitization model. Another possible explanation is provided by the strength and vulnerability integration model (SAVI) (Charles, 2010). This model posits that aging is normally associated with improved emotion regulation abilities that boost mental health in adulthood. However, experiences which result in sustained stress are suggested to attenuate natural age-related improvements (Raposo et al., 2013). In line with these explanations, previous research has shown that ACEs, and chronic exposure to stress, can have lasting effects on the brain through repeated activation of the hypothalamic-pituitary-adrenal (HPA) axis and the release of glucocorticoids (Lupien, McEwen, Gunnar, & Heim, 2009). Prolonged exposure to glucocorticoids is suggested to lead to a decrease in resiliency of the HPA axis over time, resulting in an increased vulnerability to stress and elevated risk of internalising psychopathology.

The current systematic review and meta-analysis synthesises evidence from prospective longitudinal studies. Of note, studies included in this review were not representative of the world's population, with the majority of studies coming from the USA (23), the UK (7), and New Zealand (6). A majority of previous research which focuses on the association between ACEs and internalising outcomes relies on participant's retrospective recall of childhood events. As such, these studies cannot give rise to the temporal relationship between ACEs and the development of internalising psychopathology. Furthermore, the validity of retrospective, self-reported, recall is widely criticised, as depressed individuals are more likely to recall negative events

(Williams & Scott, 1988). As highlighted in the introduction, it has previously been proposed that the memory of an ACE, rather than the ACE itself, can be differentially associated with internalising symptoms in adulthood (Afifi et al., 2009). This meta-analysis synthesised evidence from studies which prospectively collected exposure to ACEs prior to the measurement of adulthood internalising psychopathology. All the included studies were of good quality as indicated by the STROBE checklist.

A number of possible limitations should be considered when interpreting the present findings. Substantial statistical heterogeneity was found in all analyses as studies varied considerably in terms of their approach to ACE measurement. A range of assessments and methods were used including self-report measures, questionnaires, and parent and / or teacher reports. Due to these substantial methodological differences, it was not possible to include all variables that could potentially moderate the outcome, for example gender and reporting method (e.g. parent reports vs. self-reports). Additional exploration of these factors would strengthen subsequent findings. Moreover, effect size differences, when comparing different types of ACEs and internalising outcomes, were found to be non-significant. However, as a limited number of papers were included in the analysis, these findings should be treated tentatively. Most included studies adjusted for confounding variables such as gender and socio-economic related factors. However, as it is not possible to adjust for all potential factors that might have confounded the association between ACEs and adult internalising psychopathology, some studies included may have overestimated the strength of associations. Furthermore, across all studies there was a relatively short follow up period of internalising psychopathology in adulthood. The average age at which ACEs were reported was 12 years, and the average age at which internalising symptoms were reported was 29 years, leaving a follow up

period of 17 years. Due to this, the association between ACEs and later life internalising psychopathology could not be observed.

In conclusion, the current findings indicate that individuals who experience family-related adversities are subject to a higher risk of developing internalising psychopathology in adulthood. Since the average age of participants was 29 years, findings from this review are mainly relevant to younger, as opposed to older adults. We suggest that future studies investigate the influence of ACEs on later life internalising psychopathology.

Chapter 3

Study 2: Cumulative adverse childhood experiences and adult affective symptoms: a critical review of the evidence

3.1. Abstract

Aim: This paper offers a narrative review of studies that focused on the association between cumulative ACEs and affective problems in adulthood, with a specific focus on methodological aspects of these studies and identifying directions for further research.

Method: An electronic database search was conducted using 'MEDLINE', 'Web of Science', 'EMBASE', 'psycARTICLES' and 'PsycINFO'.

Results: In total, 32 articles (k = 34) were identified as eligible for the current review. Twenty four eligible studies tested and found a linear association between cumulative ACEs and adult depression, eight studies tested and identified a linear association between the number of ACEs and adult anxiety, and three studies tested and identified a linear association between the number of ACEs and adult affective symptoms unspecified.

Conclusion: Findings revealed that the higher the number of ACEs the higher the odds of presenting with either adult depression, anxiety or affective symptoms unspecified. A number of methodological aspects, including the number of measures used to assess affective symptoms, have been identified as limitations of the existing research.

3.2. Introduction

Affective disorders are common worldwide, with the majority of these disorders having onset before age 24 (Whiteford et al., 2013). It is known that early onset affective problems are associated with a longer time-to-treatment, and, without intervention, are often characterised by greater severity and persistence into adulthood (Raven et al., 2016). Therefore, it is of critical importance to establish the role of the factors in early life that can have long-lasting effects on the risk of depression and anxiety. As explained in chapter 1, adverse childhood experiences (ACEs) are stressful experiences that occur during childhood and directly harm a child or affect the environment in which they live. ACEs are found to be extremely common in the general population (Kessler et al., 2010), with more than 8% of adults in England reporting experiencing 4 or more ACE (Bellis et al., 2014).

These high prevalence rates constitute a major public health problem as there is accumulating evidence for associations of various single types of ACEs with adult affective problems (see Chapter 2). However, investigating single types of risk is suggested to be problematic. For one, a majority of researchers do not account for the common co-occurrence of other risk factors (Dong et al., 2004), and therefore the impact of the risk factor under investigation is often overestimated (Evans et al., 2013). For example, individuals who grow up in single parent households, as a result of parental divorce, separation or death, are more likely to experience poverty and be subject to a parent with mental health problems (Evans et al., 2013).

Furthermore, mental disorders are multifactorial; there are multiple factors that contribute to the development of these disorders (Garber, 2006). Accordingly, it is now widely acknowledged that the accumulation of risk factors plays a much greater role in the development of psychopathology. This premise is grounded in the accumulation of

risk model (Rutter, 1979), which theorises that it is not just a single risk factor, but a number of risk factors, of which a child is exposed, that leads to maladaptive outcomes. To date, the accumulation of risk model has been supported by numerous findings within the child development literature (see Evans et al., 2013 for review). Moreover, a number of cross-sectional studies have found a dose-response relationship between the number of ACEs and a history of depressive disorders in adults (Chapman et al., 2004; Hammen, Henry, & Daley, 2000; Schilling, Aseltine, & Gore, 2008). For example, one study found that, compared to individuals who had not experienced ACEs, individuals who suffered four or more ACEs had a 4-12 fold increase in health risk behaviours and mental health outcomes, including depression (Felitti et al., 1998). Furthermore, consistent findings have been reported in more recent studies using a prospective design (Horan & Widom, 2014a).

However, the existing evidence may be methodologically limited as the majority of studies in this area rely on cross-sectional, retrospective reports of adversity, risking recall bias and are often limited to single time point outcomes in early life (see 1.2.3.). The aim of the present paper is to review recent advances on the association between cumulative ACEs and affective problems in adulthood. A specific focus on how ACEs were measured and modelled forms the focus of this review and future direction and implications of the literature are also discussed.

3.3. Method

3.3.1. Search strategy

A systematic search of studies investigating the association between family-related ACEs and adult affective symptoms was conducted using the Meta-analysis Of Observational Studies and Epidemiological guidelines (MOOSE) (Stroup et al., 2015) (see chapter 2 for a full break down of search strategy). Papers identified through this search were re-screened in order to select studies investigating associations between cumulative ACEs and adulthood affective symptoms (including depression, anxiety and affective problems not otherwise specified).

Five databases were searched, including 'MEDLINE' (National Library of Medicine), 'Web of Science' (Thomson Reuters), 'EMBASE' (Elsevier), 'psycARTICLES' and 'PsycINFO'. All databases were systematically searched from January 1980 up to, and including August 2016, using the following search terms: *early OR child* OR famil**, combined with: *advers* OR neglect* OR maltreat* OR "parental loss" OR separat* OR "parental ill*" OR "parental mental ill*"*, combined with: *anxi* OR depress* OR mood OR internalising*. The Boolean operator "AND" was used to combine search terms. Reference lists of previous reviews and eligible articles were screened to ensure that unidentified studies were considered (forward- and backward searching) (further detail on how search terms were generated is included in chapter 2.3.1).

3.3.2. Inclusion and exclusion criteria

Full detail of the inclusion and exclusion criteria are included in Chapter 2 (see 2.3.2). For this review papers were considered eligible if they reported the effects of three or more family-related ACEs that reflected the search terms specified. Studies were excluded if they solely reported on poverty, socio-economic status, substance misuse,

racial segregation, community violence, school violence, separation due to evacuation, or natural disaster.

Study design. Studies that used a cross-sectional, case-control or prospective design were included.

Cumulative ACEs. Papers were considered eligible if they reported the effects of three or more family-related ACEs that reflected the search terms specified. Studies were excluded if they solely reported on poverty, socio-economic status, substance misuse, racial segregation, community violence, school violence, separation due to evacuation, or natural disaster.

3.3.3. Screening procedure

All sources derived from the search were imported into EndNote, and duplicates were removed. Article screening was conducted in three separate phases: (1) title screening; (2) abstract screening; and (3) full text screening. Before phases 2 and 3 began, 10% of the abstracts and full-texts were selected at random using a random numbers generator, and were assessed independently by three researchers. Percent agreement was calculated to assess inter-rater agreement. In the abstract screening phase, if one or both of the coders deemed an abstract to be eligible for further screening, this was included for further examination. The percentage agreement between coders was 86% for the abstracts screened and 88% for the full-texts screened. Eligibility discrepancies were discussed during regular consensus meetings.

3.3.4. Data extraction

For all eligible papers the following informational was extracted from each study: basic data (first author, year, project name, country, setting, study design); demographics (total sample size, gender, age of participants); information regarding ACEs (number of ACEs, ACE types, ACE measure, cumulative measure); analysis information (analysis

type, model tested, covariates, reference category); statistical information (beta-values, standard errors and/or odds ratios, confidence intervals) and key findings (relationships).

3.3.5. Data synthesis

A narrative synthesis of eligible studied was conducted. To review studies investigating the association between cumulative ACEs and different types of affective symptom outcomes, studies were grouped using the outcome variable (i.e. depression, anxiety, and affective problems not otherwise specified (NOS)). Firstly, studies that assessed depression as their outcome were reviewed. Next studies that investigated anxiety as their outcome were reviewed, followed by studies that investigated affective problems (NOS). A breakdown of the search results and reasons for full text exclusion are presented in Figure 3.1.

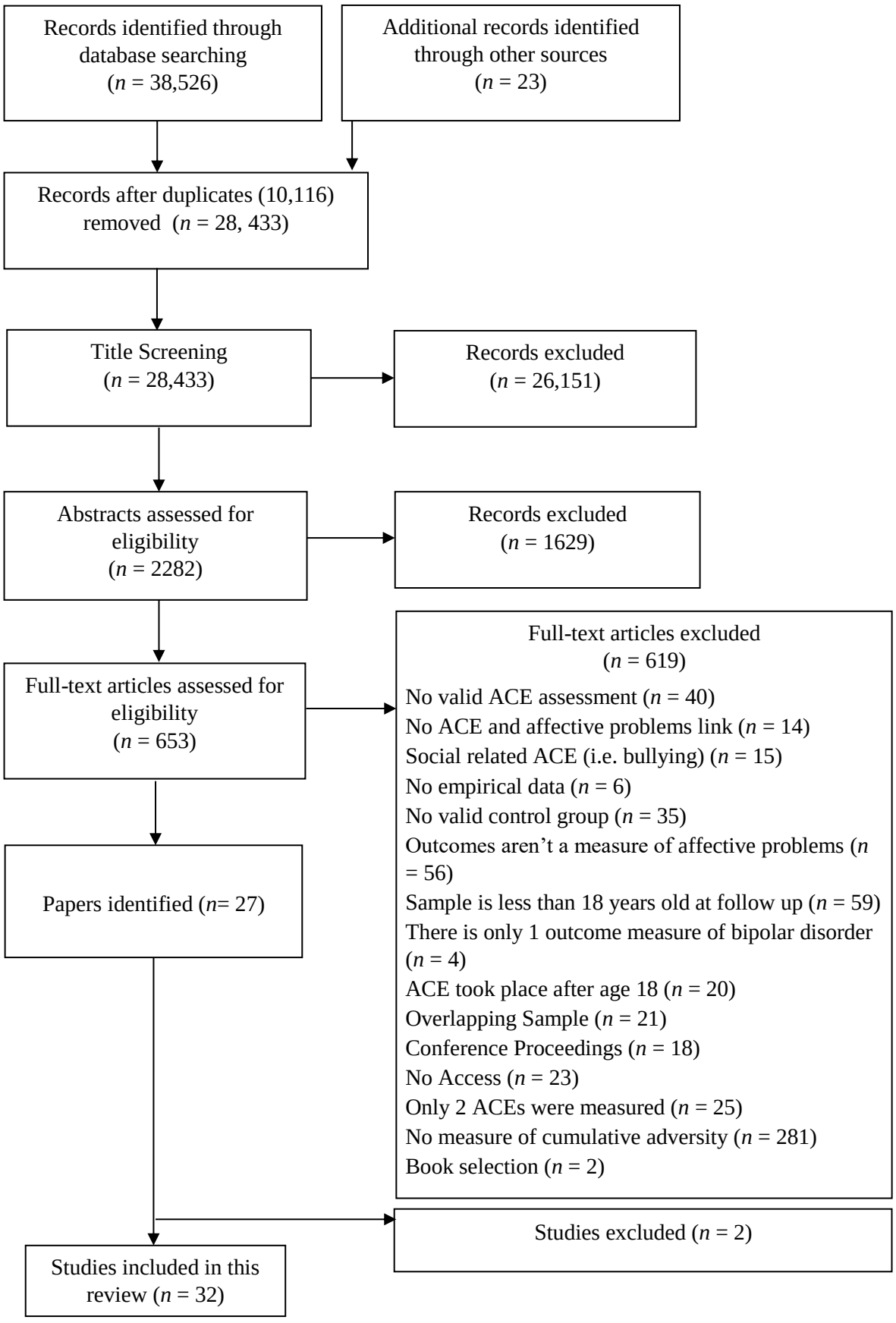


Figure 3.1. Complete flow diagram of studies included in this systematic review

3.4. Results

3.4.1. Summary of the eligible studies

The search of five databases generated 38,526 articles, of which 10,116 duplicates were removed. In addition, a further 23 articles were found through searching the grey literature, leaving a total of 28,466 to be title screened. At phase 1 (title screening), 26,151 articles were excluded leaving 2282 articles to be screened at phase 2. At phase 2 (abstract screening), 1629 articles were excluded leaving 653 articles to be screened at phase 3. At phase 3 (full-text screening), 619 articles were excluded.

A total of 32 articles that were eligible for the current review. Among these 32 articles, there were twenty-five cross-sectional studies and seven prospective studies investigating the association between cumulative ACEs and affective symptoms in adulthood. A breakdown of the search results and reasons for full text exclusion are presented in Figure 1. Across all studies there were 106,652 participants. A majority of the studies (15) included in this review were conducted in the United States, 3 studies were conducted in Canada, 7 studies were conducted in European countries (2 in the United Kingdom, 2 in the Netherlands, 2 in Finland and 1 in Norway), 1 study was conducted in Australia, 1 study was conducted in Japan, and 2 studies were conducted in South Korea (see table 3.1 for full details of the study characteristics).

Table 3.1. A summary of studies included in the cumulative systematic review

First Author, Year (Country)	Project name	Total sample size (% female)	Reported age of pps	ACE type (number of ACE's)	Instrument (ACE measure, cumulative measure)	Internalising problem type (instrument)	Factors adjusted for	Setting, Study design	Analysis type	Reference category, Model tested	Odds ratio (95% CIs) Regression coefficients (95% CIs and S.E)
Agorastos, 2014 (USA)	MRS	1254 (0)	*M* = 21.50	Multiple (5)	Questionnaire, ACE score	Depression (BDI)	Multiple (3)	Marines, C-S	Reg	1 ACE, Linear	Significant D-R relationship: the more ACEs, the higher depressive symptoms (b =.17). Risk for depressive symptoms similar for S and M ACE (S: OR=2.2, 1.3;3.8) (M: OR=2.1, 1.2;3.5)
Anda, 2002 (USA)	ACE study	9346 (54)	*M* = 56.60	Multiple (9)	Self-report, ACE score	Depression (DIS/CES-D)	Age, sex, education & race	Clinic, C-S	Reg	N.R. Linear	Significant D-R relationship between number of ACEs & depression
Arata, 2005 (USA)	N.R.	384 (69.5)	*M* = 20.40	Multiple (5)	Questionnaire, ACE score	Depression (CES-D)	N.R.	College C-S	Reg	0 ACEs, Linear	M ACE participants had significantly higher scores (mean= 12.12, SD=6.80) than those with 0 (mean=7.03, SD=5.48) or S (mean= 7.72, SD=6.87) (*F*= .27.15, $p < .0001$)

Arboleda-Florez, 2001 (Canada)	NPHS	16291 (51)	18+	Multiple (3)	Self-report, ACE score	Depression (CIDI-SF)	Multiple (6)	CBS, C-S	Reg	0 ACEs, Linear	Significant D-R relationship: exposure to each additional ACE increased prevalence of MDE (S: *b*= 0.78, SE=.1, O= 2.17, 1.65; 2.86; 3 ACEs: 1.55 (.15), OR= 4.69, 2.95; 7.46)
Bifulco, 2002 (UK)	N.R.	204 (100)	*M* = 35.00	Multiple (6)	Questionnaire, ACE score	Depression (PSE/ SCAN)	N.R.	CBS, C-S	Reg	0 ACEs, Linear	Strong D-R effect. 0 ACEs: 21% prevalence of depression; 1-2 ACEs: 40% ; 5-6 ACEs: 76%, $p <$ .0001
Bjorkenstam, 2015 (USA)	PSID	2128 (51)	N.R.	Multiple (7)	Questionnaire, ACE score	Any mood or anxiety disorder (K6 scale)	Sex, birth year, parental SEC, adolescent depressive symptoms	CBS, Pr	LR	0 ACEs, Linear	Compared to no CA's, multiple CA's were significantly associated with mood/anxiety disorders (AOR = 2.05, 0.94; 4.47)
Cabrera, 2007 (USA)	N.R.	6921 (0)	18+	Multiple (6)	Questionnaire, ACE score	Depression (PHQ)	Age, race /ethnicity	Soldiers, C-S	Reg	0 ACEs, Linear	Likelihood of screening positive for depression was sig higher for Ps with 2+ ACEs. 1 ACE: OR = 2.18 (1.54; 3.10); 4+ ACEs: 6.11 (4.10; 9.12)

Chapman, 2004 (USA)	ACE study	9460 (54)	*M* = 56.60	Multiple (8)	Self-report, ACE score	Depression (Own screening instrument)	N.R,	Clinic, C-S	Reg	0 ACEs, Linear	Compared to those reporting 0 ACEs, 5+ had a 3.7 increased risk for history of depressive disorders, $p < .0001$
Chung, 2008 (USA)	N.R.	1476 (100)	*M* = 24.00	Multiple (7)	Self-report, ACE score	Depression (CES-D)	Maternal age, race, marital status, education, income	Health centres, C-S	Reg	0 ACEs, Linear	D-R relationship: Increased numbers of ACEs sig associated with higher prevalence & rates of depressive symptoms. 1 ACE: OR=1.60 (1.10; 2.35); 5+ ACEs: OR = 5.35 (2.70; 10.61).
Dube, 2003 (USA)	ACE study	17337 (54)	*M* = 56.00	Multiple (8)	Questionnaire, ACE score	Depression (Self-report)	Age, sex, race & education	CBS, C-S	Reg	0 ACEs, Linear	For each unit increase in the ACE score, the ORs for depressed affect were increased. Strong, graded relationship. 1 ACE: OR = 1.3 (1; 1.8); 4+ ACEs: OR = 3.6 (2.; 5.0)
Felitti, 1998 (USA)	ACE study	9508 (53.7)	*M* = 56.10	Multiple (7)	Questionnaire, ACE score	Depression (NIMH)	Age, sex, race, education	Clinic, C-S	Reg	0 ACEs, Linear	Both prevalence & risk (OR) increased for depressed mood as number of ACEs increased. 1 ACE: OR = 1.5, 1.3; 1.7; 4+ ACEs: OR = 4.6, 3.8; 5.6

Fujiwara, 2010 (Japan)	WMH-J	1722 (49.4)	*M* = 50.8	Multiple (12)	Self-report, ACE score	Depression (CIDI), Anxiety (CIDI)	Multiple (5)	CBS, C-S	Reg	ACEs, Linear	There was no significant difference between the odds of presenting with depression when exposed to two ACEs (OR = 1.1, 95% CIs = 0.6; 2.2) and the odds when exposed to four ACEs (OR = 1.5, 95% CIs = 0.4; 6.7). Exposure to four ACEs = five times more likely to have an anxiety disorder (OR = 5.8, 1.0; 32.6).
Giovanelli, 2016 (USA)	CLS	1202 (50.3)	*M* = 23.00	Multiple (9)	Life-event checklist assessing, ACE score	Depressive symptoms (BSI)	N.R.	CBS, C-S	LR	0 ACEs, Linear	Compared to no CA's, multiple CA's were significantly associated with depressive symptoms (UOR = 3.87, 0.19; 0.40)
Green, 2010 (USA)	NCS	9282	18+	Multiple (12)	Questionnaire, ACE score	Anxiety (CIDI), Depression (CIDI)	Multiple (6)	CBS, C-S	Reg	0 ACEs, Linear	Increasing ORs with number of ACEs, from (OR = 1.3) for 1 ACE to highs of (OR = 3.4) for 6 CAs and (OR = 3.2) for 7 or more CAs.

Horan, 2014 (USA)	N.R.	896 (51)	*M* = 62.00	Multiple (12)	Multiple methods, cumulative risk index of ACE	Unspecified internalising symptoms (BAI/ CES-D)	N.R.	CBS, Pr	Reg	0 ACEs, Linear	Strong linear relationship was found, with exposure to a higher number of ACEs significantly related to more internalising symptoms (b = 0.11, SE = .03, p < .001).
Korkeila, 2010 (Finland)	HSSS	16877 (62)	20+	Multiple (6)	Questionnaire, ACE score	Depression (BDI/ prescriptions/ hospitalisations)	Gender, age	CBS, C-S	Reg	0 ACEs, Linear	Significant linear relationship between reporting childhood adversities and odds of depression (OR = 1.28) for 1-2 ACEs and (OR = 2.70) for 3-6 ACEs.
Lowe, 2015 (USA)	Grady Trauma Project	3192 (70.4)	*M* = 39.98	Multiple (5)	CTQ-SF, ACE score	MD symptoms (BDI), PTS symptoms (PSS-I)	Age, gender, non-Hispanic black race, comorbid symptoms	Hospital, C-S	Reg	0 ACEs, Linear	Higher CT predicts MD symptoms (b = 0.11, SE=.01, p < .001) and PTS symptoms (b = 0.13, SE= .01, p < .001)
McLaffert y, 2015 (UK)	WMHSI	1986 (52.2)	18+	Multiple (12)	CIDI, ACE score	Any mood or anxiety disorder (CIDI)	Multiple	Home setting, C-S	LR	'Low-risk', Linear	Poly-adversity class more likely to exhibit any AD (AOR= 5.25, 2.80; 9.83), p < .001 or any MoodD (AOR= 3.22, 2.12; 4.88), p < .001

Mersky, 2013 (USA)	CLS	1142 (54)	18-59	Multiple (8)	Official records, Cumulative ACE index	Depression (Own survey), Anxiety (Own survey)	Multiple (8)	CBS, Pr	LR	0 ACEs, Linear	Exposure to multiple ACEs was significantly associated with higher symptoms of anxiety in adults aged between 18 and 59 (r = 1.98, p < .001).
Park, 2014 (South Korea)	KECA	6027 (49.9)	18+	Multiple (10)	Questionnaire, ACE score	Anxiety (CIDI), Depression/ total adversity (CIDI)	Age, sex	CBS, C-S	LR	1 ACE, Linear	Multiple ACEs were significantly more likely to have anxiety disorders (OR = 2.14, 1.06; 4.33) and depression (OR = 2.34, 1.18; 4.64) compared to those exposed to single ACEs.
Park, 2015 (South Korea)	N.R.	137 (59.9)	50+	Multiple (10)	ACEQ, ACE score	Depressive symptoms (QIDS-SR)	Sex, age, educational years, marital and occupational status, APOE-4 carrier	Commun ity health centre, C-S	Reg	0 ACEs, Linear	Significant positive association between ACE scores and depressive symptoms (b = 0.60, 0.26; 0.93, p = .001) for a 1 score increase in ACE scores
Pirkola, 2005 (Finland)	Health 2000 study	4076	30+	Multiple (11)	Questionnaire, ACE score	Depression (CIDI) Anxiety (CIDI)	Age, sex, marital status, job status	Home setting, C-S	LR	N.R. Linear	Number of adversities as a continuous variable associated with depressive disorders (OR 1.30, 1.22; 1.39), anxiety disorders (OR 1.35, 1.25; 1.46)

Raposo, 2013 (Canada)	NESARC	7080	65+	Multiple (10)	Questionnaire, ACE score	Anxiety (Own interview), Depression (Own interview)	Gender, education, income, marital status, race, past MH	CBS, C-S	Reg	1 ACE, Linear	Children with exposure to multiple ACEs had an increased risk of having mood disorders when they were followed up in adulthood (OR = 2.20, 95% CIs = 1.00; 4.86) compared to those exposed to a single adversity (OR = 1.18, 95% CIs = 0.77; 1.82). Exception of those exposed to four or more ACEs, which was found to be non-significant (OR = 1.58, 95% CIs = 0.98; 2.56)
Reiser, 2014 (Canada)	N.R.	264 (81)	N.R.	Multiple (10)	ACEQ, ACE score	Anxiety (STAI-T, PANAS-NA, SHAI)	N.R.	University, C-S	BC	0 ACEs, Linear	Increased exposure to CA's associated with higher levels of anxiety as measured by SHAI scores; r (262) = 1.98, p = .001, PANAS-NA scores; r (262) = .34, $p < .001$ and STAI-T scores; r (262) = .29, $p < .001$

Remigio-Baker, 2013 (USA)	BRFSS	3437 (100)	18+	Multiple (9)	Self-report, ACE score	Depression (PHQ-8)	Smoking status & binge drinking, age, race/ethnicity, education, emotional support	NBS, C-S	LR	0 ACEs, Linear	OR of reporting symptoms increased with each additional ACE. (1 ACE: OR = 2.11, CI = 1.16–3.81; 2 ACEs: OR = 2.90, CI = 1.51–5.58; 3 or 4 ACEs: OR = 3.94, CI = 2.13–7.32; 5+ ACEs: OR = 4.04, CI = 2.26–7.22)
Rudenstine, 2015 (USA)	OhArNG MHI	991 (8.8)	25-44	Multiple (3)	CAES, ACE score	Depression (PHQ-9), PTSD (PCL-C)	Age, gender, recent combat related deploy	Military, Pr	Reg	0 ACEs, Linear	Compared to no CA, 2+ types of CA associated with depression (AOR= 2.5, 1.3; 4.9) and PTSD (AOR= 2.0, 0.9; 4.5)
Schilling, 2008 (USA)	N.R.	1093 (52)	17+	Multiple (3)	Self-report, ACE score	Depression (12 item version of the CES-D)	Gender, race/ ethnicity, parent's education, and dropout status	School setting, Pr	Reg	N.R, Linear & quadratic	Significant relationship between total cumulative childhood adversity and depressive symptoms in adults, this relationship was curvilinear (b = 0.14, SE = 0.19, p < .001). Further analyses, weight (severe events) accounted for relationship, rather

											than cumulative adversity.
Thoreson, 2015 (Norway)	N.R.	4527 (45)	*M* = 43.90	Multiple (3)	Telephone interview, ACE score	Anxiety (HSCL), Depression (HSCL)	Adult violence, gender, age	Home setting, C-S	Reg	0 ACEs, Linear	Higher number of childhood violence categories significantly predicts anxiety/depression scores (b = 0.64, 0.55; 0.72, $p \leq 0.007$)
Turner, 2003 (USA)	N.R.	649 (59)	19+	Multiple (32)	Self-report, ACE score & category	Depression (CES-D)	Gender, age, minority status, parental education	College setting, C-S	Reg	0-2 ACEs, Linear	Significant association between cumulative ACEs and depression (OR = 1.19) for increase of 1 event in cumulative adversity.
van Delft, 2016 (Netherlands)	N.R.	124 (100)	*M* = 32.77	Multiple (5)	Treatment files, ACE score	Depression (CES-D)	Depressive mood time 1, SES	Juvenile institution, Pr	Reg	0 ACEs, Linear	Significant association between CCM and depression (b = 0.12, SE= .07, p < .05) for a 1 unit increase in CCM
Van der Vegt, 2009 (Netherlands)	N.R.	1364 (44)	'Adulthood'	Multiple (3)	Parent report, ACE score	Anxiety (CIDI/ DIS), Depression (CIDI/ DIS)	Age, age of placement, gender, country of origin, parent SES	International adoptees, Pr	Reg	0 ACE's, Linear	Those with experience of multiple adversities had an increased risk of having anxiety disorders (OR = 2.22, 1.11; 4.45) and depressive disorders (OR = 2.20, 1.00; 4.86)
Zheng, 2016 (Australia)	B&ETDS	3567 (12.5)	*M* = 41.00	Multiple (16)	Questionnaire, ACE score	PTSD (PCL-C)	Age, sex service,	Military, C-S	Reg	0-2 ACEs, Linear & quadratic	Compared to no/low CA's, high (5+) CA's were significantly

								service status, rank	associated with PTSD symptoms (AOR = 2.06, 1.67; 2.55)

Note: ACE, Adverse Childhood Experience; ACEQ, Adverse Childhood Experience Questionnaire; AD, Anxiety Disorder; AOR, Adjusted Odds Ratio; BAI, The Beck Anxiety Inventory; BDI, Becks Depression Inventory; B&ETDS, Bougainville & East Timor Deployment Studies; BRFSS, Behavioural Risk Factor Surveillance System Survey; BSI, Brief Symptom Inventory; CA, Childhood Adversities; CAES, Childhood Adverse Events Survey; CBS, Community Based Sample; CCM, Cumulative Childhood Maltreatment; CES-D, Centre for Epidemiological Studies scale for Depression; CIDI, Composite International Diagnostic Interview; CIDI-SF, Composite International Diagnostic Interview-Short Form; CLS, Chicago Longitudinal Study; C-S, Cross-Sectional; CT, Childhood Trauma; CTQ-SF, Childhood Trauma Questionnaire – Short Form; DIS, National Institute of Mental Health Diagnostic Interview Schedule; D-R, Dose-Response; HSCL, Hopkins Symptom Checklist; HSSS, Health and Social Support Study; KECA, Korean Epidemiologic Catchment Area Study; LR, Logistic Regression; M, Multiple; MD, Major Depression; MDD, Major Depressive Disorder; MoodD, Mood Disorder; MRS, Marine Resilience Study; N.A., Not Applicable; NESARC, National Epidemiologic Survey on Alcohol and Related Conditions; NIMH, Diagnostic Interview Schedule of the National Institute of Mental Health; NPHS, National Population Health survey; N.R., Not Reported; OhArNG MHI, Ohio Army National Guard Mental Health Initiative; PANAS-NA, The Positive And Negative Affect Schedule – Negative Affect subscale; PCL-C, PTSD Checklist Civilian; PHQ-9, Patient Health Questionnaire-9; Pr, Prospective; PSE, Present State Examination; PSID, Panel Study of Income Dynamics; PSS-I, Posttraumatic Symptom Scale – Interview version; PTS, Posttraumatic Stress; PTSD, Post Traumatic Stress Disorder; QIDS-SR, Quick Inventory of Depressive Symptomology; S, single; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; SEC, Social Economic Class; SES, Socioeconomic Status; SHAI, Short Health Anxiety Index; STAI-T, Trait form of the State –Trait Anxiety Inventory for adults; UOR, Unadjusted Odds Ratio; WMH-J, World Mental Health Japan Survey; WMHSI, World Mental Health Survey Initiative

3.4.2. Methodological aspects of eligible studies

3.4.2.1. Definition and measures of affective symptoms

Depression. Depression was assessed using either a diagnostic (e.g. Composite International Diagnostic Interview [CIDI]) or dimensional (e.g. Becks Depression Inventory [BDI]) assessment tool. The most common tool for assessing depression was the CIDI with 6 studies using the full length version of the scale and 1 study using the short-form version of the CIDI. Following this, 5 studies used the Centre for Epidemiological Studies scale for Depression (CES-D), 3 studies used the BDI, 3 studies used the patient heath questionnaire, 2 studies used the diagnostic interview schedule for the National Institute of Mental Health (NIMH/DIS), 1 study used the Present State Examination (PSE), 1 study used the Brief Symptom Inventory (BSI), 1 study used the quick inventory of depressive symptoms –short form (QIDS-SF), 1 study used the Hopkins Symptom Checklist (HSCL), 2 studies used their own screening instrument, one study used a self-report measure, and 1 study conducted their own interview.

Anxiety. The most common tool for assessing anxiety was also the CIDI with 5 studies using the full length version. Following this 1 study used the Posttraumatic Symptom Scale – Interview version (PSS-I), 1 study used the HSCL, 1 study used multiple measures to assess anxiety (including the Trait form of the State –Trait Anxiety Inventory for adults [STAI-T], The Positive And Negative Affect Schedule – Negative Affect subscale [PANAS-NA], and the Short Health Anxiety Index [SHAI]), 1 study used their own survey and 1 study used their own interview.

Affective symptoms unspecified. To assess affective symptoms unspecified, 1 study used the CIDI, 1 study used the K6-Scale, and 1 study used The Beck Anxiety Inventory (BAI) and the CES-D.

3.4.2.2. Definitions and measures of ACEs

A variety of different types of ACEs were measured across all studies. These included different forms of childhood maltreatment: sexual abuse, physical abuse, emotional abuse and neglect, parental separation or divorce, and parental death. Most studies assessed 6-12 ACEs, with an average of 8.41 (range = 3-32). ACEs were assessed through a variety of different methods with thirteen studies using a questionnaire, eight studies using self-report, one study using a life event checklist, one study using multiple methods, one study using the Childhood Trauma Questionnaire – Short Form (CTQ-SF), one study using the Composite International Diagnostic Interview (CIDI), one study using official records, two studies using the Adverse Childhood Experience Questionnaire (ACEQ), one study using the Childhood Adverse Events Survey (CAES), one study using a telephone interview, one study using treatment records, and one study using parent report. All studies measure cumulative ACEs through deriving a cumulative summary score of number of ACEs experiences. Using this cumulative risk index, categorical variables tended to be created which grouped studies into 0, 1, 2, 3 and 4+ ACEs.

3.4.3. The association between cumulative ACEs and adult depression

Most of the studies identified as eligible used a cross-sectional design and measured depression as their main outcome. Across all studies, twenty-seven investigated the effect between cumulative ACEs and depression. Of these studies, 22 used a cross-sectional design and 5 used a prospective design. Across all studies that measured depression as an outcome, 24 identified a linear relationship between cumulative adversities and the likelihood of developing depression in adulthood (i.e. the higher the number of ACEs the higher the odds of presenting with depressive symptoms) (Agorastos et al., 2014; Anda et al., 2002; Arata et al., 2005; Arboleda-

Florez & Wade, 2001; Bifulco, Moran, Baines, Bunn, & Stanford, 2002; Cabrera, Hoge, Bliese, Castro, & Messer, 2007; Chapman et al., 2004; Chung, Mathew, Elo, Coyne, & Culhane, 2008; Dube, Felitti, Dong, Giles, & Anda, 2003; Felitti et al., 1998; Giovanelli, Reynolds, Mondi, & Ou, 2016; Green, 2010; Korkeila et al., 2010; Lowe, Quinn, Richards, Rundle, & Galea, 2017; Mersky et al., 2013; Park, Nam, Sim, & Hong, 2015; Park, Hong, et al., 2014; Pirkola et al., 2005; Raposo, Mackenzie, Henriksen, & Afifi, 2014; Remigio-Baker, Hayes, & Reyes-Salvail, 2014; Rudenstine et al., 2017; Schilling et al., 2008; Turner & Butler, 2003; van der Vegt et al., 2009).

Three studies did not identify a linear relationship between the number of ACEs and the likelihood of developing depression in adulthood. One study reported a quadratic relationship between cumulative ACEs and depressive symptoms in adulthood ($b = 0.14$, $SE = 0.19$, $p < .001$) (Schilling et al., 2008). However, of note, the authors report that the association between cumulative ACEs and depressive symptoms in adulthood was lost when accounting for adversity severity. A study by Agorastos et al. (2014) also did further analyses to test the relationship between ACEs and depression. Initially the study reported a significant dose-response relationship between the two variables, yet further analyses showed that risk for depressive symptoms were similar for those with single (OR = 2.2, 95% CIs = 1.3; 3.8) and multiple adversities (OR = 2.1, 95% CIs = 1.2; 3.5). Finally, one study by Fujwara and Kawakami (2011) found no association between the number of ACEs and depressive disorders. There was no significant difference between the odds of presenting with depression when exposed to two ACEs (OR = 1.1, 95% CIs = 0.6; 2.2) and the odds when exposed to four ACEs (OR = 1.5, 95% CIs = 0.4; 6.7).

3.4.4. The association between cumulative ACEs and adult anxiety

Across all papers, nine studies investigated the association between cumulative ACEs and anxiety in adulthood. Of these studies, seven used a cross-sectional design and two used a prospective design. Eight studies reported a significant linear association between cumulative ACEs and anxiety in adulthood (Fujiwara & Kawakami, 2011; Green, 2010; Mersky et al., 2013; Park, Hong, et al., 2014; Pirkola et al., 2005; Raposo et al., 2013; Reiser et al., 2014; Thoresen et al., 2015; van der Vegt et al., 2009). One study found that the association between cumulative ACEs and adult anxiety was lost when assessing those exposed to 4 or more ACEs (OR = 1.58, 95% CIs = 0.98; 2.56) (Raposo et al., 2013).

3.4.5. The association between cumulative ACEs and adult affective symptoms unspecified

Three eligible studies identified through the systematic search measured affective symptoms (i.e. depression and / or anxiety) not otherwise specified. One of these studies used a cross-sectional design and two studies used a prospective design. One study found a strong linear relationship, with exposure to a higher number of ACEs significantly related to more affective symptoms (b = 0.11, SE = .03, p < .001) (Horan & Widom, 2014b). Another study found that those who experienced a higher number of adversities were more likely to exhibit any anxiety disorder (OR = 5.25, 95% CIs = 2.80; 9.83, p < .001) or any mood disorder (OR = 3.22, 95% CIs = 2.12; 4.88, p < .001) (McLafferty, 2015). A prospective study also found that compared to those who experienced no ACEs, those who experienced multiple ACEs were two times more likely to present with a mood/anxiety disorder in adulthood (OR = 2.05, 95% CIs = 0.94; 4.47) (Bjorkenstam, 2015).

3.5. Discussion

The majority of studies identified through this review tested and found a linear association between cumulative ACEs and affective symptoms in adulthood. Of the 32 studies identified, 24 studies tested and identified a linear association between the numbers of ACEs adult symptoms of depression, eight studies tested and identified a linear association between the number of ACEs and adult symptoms of anxiety, and three studies tested and identified a linear association between the number of ACEs and adult affective symptoms unspecified. Findings revealed that the higher the number of ACEs the higher the odds of presenting with either depression, anxiety or affective symptoms unspecified in adulthood. These findings support theories which propose a linear association between cumulative risk and maladaptive outcomes (Sameroff, Arnold, Seifer, Baldwin, & Baldwin, 1993).

Among studies identified through this review a range of measures were used to assess affective symptoms. The most common measure used to assess affective symptoms was the Composite International Diagnostic Interview (CIDI). All of the assessment tools used in the identified studies were validated measures. However, a number of studies also used their own screening instruments to assess affective symptoms. This is suggested to be problematic when attempting to synthesise findings as there are often item differences between measures, which creates heterogeneous outcomes (Fried, 2017). In future, studies should attempt to use consistent and validated measures of affective symptoms in an attempt to make outcomes more homogeneous.

All studies included in this review assessed cumulative risk though summing the number of ACEs each participant was exposed to. This approach to aggregating risk has been previously criticised as information on risk factor intensity is lost. For example, those who experience parental divorce, childhood poverty and maternal depression,

would be given a score of three and those who experience a childhood chronic illness, parental death and an overcrowded household, would also be given a score of three. This acknowledged variation in intensity has led to the consideration of weighting methods to incorporate severity into aggregate measures of cumulative ACEs. For example, a summed score based on pre-determined effect sizes has been found to greatly improve the prediction of pathology compared to a simple sum (Ross & Mirowsky, 1979).

Among studies included, only a small number of studies used a prospective design to test the association between cumulative ACEs and affective symptoms in adults (also see Chapter 2). The majority of studies used cross-sectional, retrospective reports of cumulative ACEs. This is problematic as prior evidence has shown only a modest agreement between prospective and retrospective measures of ACEs (Reuben et al., 2016). What is more, retrospective ACEs measures, in comparison to prospective measures have been found to more strongly predict adult outcomes, when the outcomes were measured through self-report (Reuben et al., 2016). It is suggested that observed differences between retrospective and prospective reports of ACEs are due to potential bias from those with affective symptoms when reporting ACEs (Bernet & Stein, 1999; Hardt & Rutter, 2004).

A number of potential mechanisms have been hypothesised to explain the associations between cumulative ACEs and affective symptoms in adulthood. Historically, the allostatic load hypothesis was proposed as the neurobiological model to explain the effect of stress on maladaptive outcomes (McEwen, 2000). This theory provided a framework for explaining the neurobiological mechanisms linking a variety of ACEs to health. Accordingly, it has been demonstrated that ACEs are associated with enduring changes in brain structure and function, including the amygdala and

hippocampus (Rao et al., 2010),which can lead to changes in mood and behaviour (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). ACEs are also associated with changes in other biological systems such as the metabolic physiology endocrine, and immune system (Berens, Jensen, & Iii, 2017). These changes are suggested to lead to allostatic overload, resulting in adverse health outcomes, including affective disorders (Danese & McEwen, 2012a). Exposure to stress in early life, as a result of growing up in a dysfunctional household, may lead to lower self-esteem and lower self-worth, which could increase the risk for affective disorders in later life. For example, researchers have shown that abuse and neglect in childhood are associated with poor self-esteem and severe life events in adulthood (Bifulco, Brown, Moran, Ball, & Campbell, 1998). Moreover, the stress sensitisation model suggests that early life stress lowers the threshold for reactivity to later stress and thus increases risk for the onset of disorder when presented with stress later on in life. For example, growing up in an adverse family environment may lead to elevated stress reactivity that in turn may increase the risk for affective disorders in later life (McLaughlin, Conron, Koenen, & Gilman, 2010).

A separate line of inquiry posits the view that due to genetic vulnerability (e.g. a short allele of the serotonin transporter gene polymorphism 5HTTLPR), some individuals are more prone to be affected by environmental stressors such as ACEs (Caspi et al., 2003). For example, prior research has shown that children who carry 'vulnerability' genetic variants are more likely to develop maladaptive outcomes, such as psychopathological outcomes (e.g. depression), when exposed to a stressor (e.g. childhood maltreatment). This model has been referred to as the diathesis-stress model and it specifically proposes that stressful life experiences precipitate the onset of psychopathology in the presence of certain genetic risk factors (Kim-Cohen et al., 2006;

Moffitt, Caspi, & Rutter, 2005), however empirical evidence for the role of specific genetic variants in modifying effects of environmental exposures is inconsistent (Karg, Burmeister, Shedden, & Sen, 2011; Risch, Herrell, Lehner, et al., 2009). As such it is suggested that improving environmental measures (i.e. ACE measures) could reduce heterogeneity between studies (Thompson, Kazantseva, & Gaysina, 2017)

The present study supports the association between cumulative ACEs and affective symptoms in adulthood through reviewing and synthesising the existing literature. However, the existing studies could be methodologically limited due to the risk in bias of retrospectively reporting ACEs and affective symptoms measured at one time point. Therefore, longitudinal cohort studies with prospectively collected measures of ACEs and multiple measures of affective symptoms across the life course (from childhood through late adulthood) could be particularly valuable in addressing these limitations and advancing the research field.

Chapter 4

Study 3: The impact of cumulative adverse childhood experiences on life course affective symptoms: Evidence from a birth cohort with a 70 year follow up

4.1. Abstract

Background: Cumulative adverse childhood experiences (ACEs) are a known risk factor for affective disorders. However, the existing evidence tends to focus on outcomes at a single time point (often in young adulthood), without consideration for severity of affective symptoms across the life course.

Aim: To investigate associations between a cumulative ACE score and affective symptom severity at ages 13, 15, 36, 43, 53, 60-64 and 69 years.

Method: Data were drawn from the MRC National Survey of Health and Development (NSHD), an ongoing longitudinal study of 5362 individuals born in England, Scotland and Wales during the week of March 1946. In total, 24 measures of ACEs from different domains including family instability, socio-economic status, child rearing and parenting, parental health, and childhood health, were summed up to create a cumulative ACEs score. Associations between a cumulative ACE score and severity of affective symptoms (no symptoms, mild, moderate or severe symptoms) at seven time points (ages 13, 15, 36, 43, 53, 60-64 and 69) were assessed using multinomial logistic regression.

Results: Findings revealed that higher cumulative ACE score was associated with increased risk of severe affective symptoms at ages 60-64 and 69 years, but not at earlier ages. Furthermore, there was a positive linear relationship between cumulative ACEs and affective symptom severity at ages 60-64 and 69, but not at earlier ages.

Conclusions: Findings suggest that experiencing higher exposures to adversities during childhood poses risk of more severe affective symptoms in late adulthood.

4.2. Introduction

Exploring associations between adverse childhood experiences (ACEs) and the development and persistence of affective disorders is important as it enables preventative measures to be implemented and allows practitioners to assess the risk of symptoms developing. The long-term influence of ACEs on affective disorders across the life course is historically rooted in theories on the aetiology of affective psychopathology (see 1.1.4).

The existing evidence from both cross-sectional and prospective studies suggests that single types of ACEs, such as parental death, childhood maltreatment, or poverty (Kessler et al., 2010; Sands et al., 2017; Secinti, Thompson, Richards, & Gaysina, 2017; Shanahan et al., 2011), as well as accumulation of different types of ACEs (see Chapters 2 and 3), are significantly associated with a greater vulnerability for affective disorders in adulthood.

The majority of studies investigating associations between cumulative ACEs and adult affective disorders have operationalised cumulative risk through the creation of a risk index. This index represents the sum of multiple risk factors either across a period of time (e.g. from age 5 to 18), or at a specific time point (e.g. at age 10). Using this approach several cross-sectional studies have identified a dose-response relationship between the number of ACEs and a history of depressive disorders in adults (Chapman et al., 2004; Hammen et al., 2000; Schilling et al., 2008). One study found that, compared to individuals who had not experienced ACEs, those who suffered four or more ACEs had a 4-12 fold increase in health risk behaviours and mental health outcomes, including depression in adulthood (Felitti et al., 1998). Furthermore, using a prospective design, a recent study showed that a greater number of ACEs was linearly associated with an increase in anxiety and depression symptomology in adulthood

(Horan & Widom, 2014a). Furthermore, a recent meta-analysis of prospective studies (see chapter 2) and a narrative review of studies using different designs (see chapter 3) provides evidence for the association between cumulative ACEs and affective symptoms in adulthood.

One of the key limitations of the existing studies focusing on the accumulation of ACEs and the effect on adult affective disorders is that they only consider these effects at a single time point, often measuring affective disorders in young adulthood. However, as highlighted earlier (see 1.1.4), prospective birth cohort studies offer the unique opportunity to prospectively investigate the effects of early life experiences on mental health outcomes across the life course. For example, a study using data from the British 1958 birth cohort found associations between childhood maltreatment (neglect and abuse) and poor mental health from childhood and adolescence (age 7, 11 and 16) through adulthood (age 50) (Geoffroy, Pereira, Li, & Power, 2016).

The present study aims to investigate whether multiple ACEs summed up in a cumulative ACE score are associated with affective symptoms across the life course (i.e., at ages 13, 15, 36, 43, 53, 60-64 and 69 years), using data from the British 1946 birth cohort. Specifically, the study aims to investigate the linear and quadratic relationship between cumulative ACEs and affective symptom severity at each time point using multinomial logistic regression.

4.3. Methods

4.3.1. Sample

The MRC National Survey of Health and Development (NSHD) is an ongoing longitudinal study of an original sample of 5362 individuals born in England, Scotland and Wales during one week of March 1946. Participants were strategically sampled from 1 in 4 single births within marriage to wives of manual workers, and all single births to wives of non-manual and agricultural workers. This study was first initiated to explore changes in fertility rates in Britain since the mid-19th century, and to investigate the extent to which the use of midwifery and obstetric services prevented premature infant death, and promoted the health of mothers and infants (Wadsworth, Kuh, Richards, & Hardy, 2006). The NSHD members have been prospectively studied 24 times, from birth up to 69 years of age. Follow ups occurred every 2 years during childhood and main data collections in adulthood took place at ages 26, 36, 43, 53, 60-64 and 69. The present study uses the data across seven decades of life: from birth up to age 69.

The MRC NSHD is the longest running British cohort, with cohort members reaching age 70 in 2016. This longitudinal survey offers a major resource for testing life course hypotheses on the development of health and disease, and their lifetime determinants and consequences. As one of the aims of the NSHD is to maintain a representative population of individuals born in post-war Britain, specific attention is paid to the predictors of drop out.

At age 69, 2546 (47%) were contacted for follow up (Kuh et al., 2016; Stafford et al., 2013). Attrition by age 69 was due to death (n = 957), emigration (n = 574), prior refusal (n = 620), and those untraceable for more than 5 years (n = 395). Of note, complete representativeness of an aged matched national population cannot

be established because the selection of the survey member predated major immigration flows and, as noted, births outside of wedlock and multiple births (Wadsworth et al., 2003).

4.3.2. Measures

4.3.2.1. Affective symptoms

Affective symptoms (anxiety and depression) were assessed at ages 13, 15, 36, 43, 53, 60-64 and 69 years. At age 13 and 15 affective symptomology was assessed using a forerunner of the Rutter Behaviour Questionnaire for teachers (Rutter, 1967). The teachers' questionnaire, or Child Scale B, (Rutter, 1967b) consisted of 26 descriptions of behaviour against which the teacher was asked to describe aspects of the children's personality, behaviour and attitudes on a 3 point scale (more, the same, or less than class mates). The test had both a good inter-rater reliability (r = 0.72) and retest reliability (r = 0.89) (Rutter, 1967). Questionnaires have previously been subjected to classical linear factor analysis, with one factor comprising 11 items being identified as anxiety/ depression and affective symptoms and behaviours (Colman, Wadsworth, et al., 2007; Jones, Murray, Jones, Rodgers, & Marmot, 1994). The items that loaded onto the affective symptoms factor were "timid child," "rather frightened of rough games," "extremely fearful," "always tired and washed out," "usually gloomy and sad," "avoids attention," "very anxious," "unable to make friends," "diffident about competing," "frequently day dreams in class," and "becomes unduly miserable or worried in response to criticism".

Anxiety and depressive symptoms were measured again at age 36 using a short version of the Present State Examination (PSE) (Wing et al., 1974, 2011). This is a clinical interview, administered by trained nurses, which aims to assess the frequency and severity of affective symptoms over the previous month. The short

version of the PSE assessed 40 items, each of which were scored on a 3-point or 4-point scale.

Symptoms were further assessed at age 43 using the Psychiatric Symptom Frequency (PSF) scale (Lindelow, Hardy, & Rodgers, 1997). The PSF is an 18-item scale used to measure symptoms of anxiety and depression which have occurred over the previous 12 months. Questions on this scale are phrased as 'have you…?' (E.g. 'have you felt on edge or keyed up or mentally tense?'), and responses to each question were coded as 0 = 'not in the last year', 1 = 'occasionally', 2 = 'sometimes', 3 = 'quite often', 4 = 'very often', and 5 = 'everyday'. From these codes a total score ranging from 0 to 90 could be calculated. A previous investigation of the PSF found that a cut off score of 22 adequately identified those with evidence of anxiety and depressive symptoms (Lindelow et al., 1997). The PSF has been previously found to higher internal consistency ($\alpha = .88$) (Lindelow et al., 1997).

Anxiety and depression were reported at 53, 60-64 and 69 years using the 28-item version of the General Health Questionnaire (GHQ-28) (Goldberg & Hillier, 1979). This is a scaled questionnaire used to detect common mental health problems in the general population. Items on this questionnaire asked participants about specific complaints over the past few weeks. Examples included 'have you recently been getting scared or panicky for no good reason?' and, 'have you recently been thinking of yourself as a worthless person?' Each of these questions are accompanied by four responses, typically being, 'not at all', 'no more than usual', 'rather more than usual' and 'much more than usual', scoring from 0 to 3, respectively. Thus a total score on the GHQ can range from 0-84, allowing means and distributions to be calculated.

In line with previous approaches to improve precision of measurement of affective symptoms (Colman et al., 2007), item response models (i.e. confirmatory factor analysis for categorical data) were applied to derive latent factor scores, which were treated as continuous measures of anxiety and depression at each time point. Appendix 4D provides stability correlations for the derived factor scores. In addition, these latent factor scores were grouped in order to create four-category ordinal variables to make these categories comparable across the seven time points (see Chapter 5). Group one indicated those with a lack of symptoms (1^{st} to 50^{th} percentile on the estimated factor score), group two indicated those with occasional symptoms (50.1 to 75^{th} percentile), group 3 indicated those with moderate symptoms (75.1^{th} to 90^{th} percentile) and the fourth group indicated those with severe symptoms (90.1 to 100^{th} percentile).

4.3.2.2. Adverse childhood experiences

In total, 24 measures of ACEs (from birth through age 15 years) representing six domains: 'family stability', 'family socio-economic status, 'parental age', 'childrearing environment and parenting', 'parental health' and 'child's health'. Early life predictors were measured at three distinct time-points. Seven predictors, including birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, and father's occupational status, were measured at the birth of the survey member (1946); six predictors, including, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair, were measured when the survey member was age 4 years (1950); and nine predictors including, parental divorce by age 15, death of any parent by age 15, number of residential moves, lack of home amenities, family size, parents interest in primary and secondary education, husbands perceived health, mothers

perceived health and maternal neuroticism, were measured by age 15 years. All predictors were selected a priori and were based on previously reported indicators of the early life circumstances (Rodgers, 1990; Stafford et al., 2015). This information was collected prospectively through a variety of sources, including health visitor reports, parent report and self-report. For this study, using the imputed variables (see below), binary variables were derived for each early life predictor as outlined below. A cumulative risk index of early adverse experiences was calculated through summing binary predictors.

Family Stability: Parental divorce was prospectively collected between the ages of 5 and 15 years. As only a small number of survey members experienced parental divorce, data for this variable was dichotomised at age 15 years. Parental death and age at separation from mother between birth and 15 years were dichotomised. Number of residential moves between these ages ranged from 0 to 8, and was categorised in to 3+ moves, and 0-2 moves.

Family socioeconomic circumstances: Father's and mother's education was classified as primary level only, or beyond this. The number of amenities lacking from the family home was recorded between the ages of 2 and 15 years. This ranged from 0 (n = 1394) to 8 (n = 1), and was recoded to lacking 4 or more, 2 or 3 vs. 1 or less amenities. The number of family members per bedroom in each household was recoded when survey members were 4 years of age. This ranged from 1 (n = 88) to 8 (n = 56), and was recoded to 3 or more, vs. less than 3 family members per bedroom. Number of children in family was recorded when study members were 15 years old. This ranged from 1 (n = 572) to 16 (n = 1), and was recoded to 4 or more children vs. 1-3 children.

Parental age: Age of father and mother was coded at the birth of the survey member. The mean age of fathers was 32 years (SD = 6.51). The mean age of mothers at birth of survey member was 29 years (SD = 5.70). Binary variables were created to indicate teenage fathers and mothers (age 19 years or younger vs older than this), and older fathers and mothers (41 years or older vs. younger than this).

Childrearing and parenting: Breastfeeding was dichotomised into breastfed vs never breastfed. Information on mother's management and understanding of the child compared with others was collected by health visitors when the survey member were 4 years old, this was rated during the home based interview by a health visitor, and scored as among the best, average, or among the worst. Because only four mothers fell into the worst category in the sample selected for analysis, these were combined with those rated as average and compared to those who were among the best.

Parental interest in the study member's primary and secondary education was classified as high interest in either secondary or primary education vs. average interest, and low interest in either secondary or primary education.

Cleanliness of child and cleanliness of house were classified as average or among the least clean vs. among the most clean. State of repair of clothes and shoes were classified as "unsatisfactory" vs. "satisfactory".

Parental health: Fathers and mothers perceived health was recorded by the mother when survey members were 15 years of age. Fathers and mothers perceived health was classified as excellent, vs. average/ poor. Maternal neuroticism was also recoded when the survey members were 15 years old using the six item neuroticism scale of the Maudsley Personality Inventory (Jensen, 1958). Maternal neuroticism

was classified though grouping those that scored 6 on the scale as presenting neurotic symptoms vs those that scored below 6.

Child health: Mean birth weight was 3376.52 grams (SD = 541.36), and was classified as 2500 to 4000 grams vs. below or 2500 grams, and above 4000 grams. Chronic childhood illness before the age of 15 years was coded as yes vs. no. Chronic childhood illness was defined as "a physical, usually non-fatal condition which lasted longer than three months in a given year or necessitated a continuous period in hospital of more than one month".

4.3.3. Analytical procedure

4.3.3.1. Missing data and multiple imputation

Listwise deletion and mean substitution methods for addressing missing data patterns are thought to be highly problematic as they can lead to bias and reduced power (Enders, 2010). When using these traditional missing data approaches, statistical analysis were conducted under the assumptions that all absent data are missing completely at random (MCAR). The MCAR assumption is rarely met with observational studies as environments are uncontrolled.

Alternative methods for addressing missing data include multiple imputation (MI), which substitutes a set of plausible values for each missing value; and full information maximum likelihood (FIML), which produces parameter estimates that are maximally likely given all the observed data (Enders, 2010). These techniques account for missing data in a variety of conditions while increasing the effective sample size, reducing the standard errors and minimizing bias (Enders, 2010). Moreover, these two methods are more appealing as they require weaker assumptions about the cause of missing data, and allow valid inferences to be made

when the study design includes careful consideration of the reasons why data might be missing (Little, Jorgensen, Lang, & Moore, 2014).

When using these methods analyses are conducted under the assumption that missingness is 'missing at random' (MAR). MAR is when the distribution of missingness is unrelated to the missing values themselves, after accounting for the observed variables in the model. Specifically, if missingness is related to observed variables in the data, and the variables that predict missingness are included in the analysis or imputation model, then modern treatment methods will result in unbiased parameter estimates (Enders, 2010).

Multiple imputation technique using the MICE package for R (Buuren & Groothuis-oudshoorn, 2011) version 3.2, 2015 (R Core Team, 2015) was implemented to impute missing data for each predictor variable in this study. Five multiply-imputed data sets were created and pooled

Predictors of dropout have been previously identified including low education attainment, mild cognitive impairment and socioeconomic disadvantage (Kuh et al., 2016; Stafford et al., 2013). As predictor variables were collected at three distinct time points (i.e. at birth, at age 4 and by age 15), three steps were carried out in order to impute missing data. Firstly, multiple imputation (MI) was used to impute missing data for variables collected at the birth of the survey member (i.e. in 1946). Missing data for 7 predictors were imputed: birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, and father's occupational status. Second, MI was used to impute missing data for variables collected in 1950 (i.e. at age 4). Missing data for 6 predictors were imputed: crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Variables collected at birth were used as auxiliary variables

when running MI for these variables. Third, MI was used to impute missing data for variables collected in 1961 (i.e. age 15). Missing data for 9 predictors were imputed: parental divorce by age 15, death of any parent by age 15, number of residential moves, lack of home amenities, family size, parents interest in primary and secondary education, husbands perceived health, mothers perceived health and maternal neuroticism. Missing data for 2 predictors measured by age 15 (age at break with mother and childhood chronic illness) were not imputed as there was little or no missing data on these variables (appendix 4B for n of missingness on each variable). Auxiliary variables included all those predictors before age 15 (i.e. those recorded in 1946 and 1950) and cognitive ability, recorded in 1954 (age 8 years) and 1957 (age 11 years).

4.3.3.2. Regression analyses

Multinomial logistic regression models were fitted to test associations between a cumulative ACE score and affective symptoms using categorical variables: no symptoms (reference group), mild, moderate or severe symptoms, at ages 13, 15, 36, 43, 53, 60-64 and 69 years. For these analyses, first the cumulative ACE score was entered into the model (model 1). To investigate whether the associations between a cumulative ACE score and affective symptoms differed between men and women, interactions between sex and ACEs were also tested. There were no significant ACEs by sex interactions on affective symptoms at any time point (all *p*-values > .05), therefore sex was used as a covariate in the regression models (model 2). Third, additional adjustments were made for cognitive ability at age 8, educational attainment by age 26, and socio-economic position at age 53 (model 3). These covariates were selected because of the previous studies reporting

their associations with both ACEs and affective symptoms (Hatch et al., 2007; Porche, Costello, & Rosen-Reynoso, 2016).

Linear regression models were used to test for linear trend for associations between a cumulative ACE score and affective symptoms scores at each age derived through the confirmatory factor analyses. As a sensitivity analysis, regression analyses (model 3) were further run on the sample who had information on affective symptoms at all seven time-points.

4.4. Results

4.4.1. Attrition and multiple imputation

Missingness for the ACE variables ranged from 0% (childhood chronic illness) to 41% (parents interest in primary and secondary education). Multiple imputation technique was used to impute missing values for each ACE predictor with missing data. Appendix 4A summarises the count and percentage for each original and imputed binary variable of ACEs.

A cumulative ACE score was created for both the original and imputed binary ACE variables by summing the number of dichotomised childhood adversities experienced by each survey member. Table 4.1 summarises descriptive information (means and standard deviation) of the original and imputed cumulative ACE score. The average original cumulative ACE score: 4.99 (*SD* = 3.06) was significantly lower than the imputed cumulative ACE score: 5.82 (*SD* = 2.92), t (5361) = 127.39, p <.001.

Table 4.1. Mean and standard deviation of original and imputed cumulative ACE score

Sample	Count	Cumulative ACE score, mean (SD)
Complete case	1830	4.99 (3.06)
Originally missing	3532	5.52 (3.09)
All imputed	5362	5.82 (2.92)

Table 4.2. A cumulative ACE score (mean and standard deviation) across affective symptom severity groups at different ages

Age	**ACE score: mean (SD)**			
	No symptoms	**Mild Symptoms**	**Moderate symptoms**	**Severe symptoms**
13	5.39 (3.10)	5.40 (3.08)	5.37 (3.11)	5.41 (3.01)
N (%)	1858 (50.4)	910 (24.7)	551 (14.9)	367 (10)
15	5.43 (3.09)	5.23 (2.99)	5.45 (3.20)	5.30 (3.00)
N (%)	2086 (55.6)	731 (19.5)	566 (15.1)	371 (9.9)
36	5.30 (3.02)	5.38 (3.08)	5.37 (2.99)	5.21 (3.15)
N (%)	1682 (50.6)	813 (24.5)	495 (14.9)	332 (10)
43	5.35 (3.00)	5.36 (3.08)	5.38 (3.14)	5.40 (3.13)
N (%)	1623 (50)	811 (25)	488 (15)	323 (10)
53	5.33 (3.06)	5.50 (3.03)	5.47 (3.10)	5.23 (3.12)
N (%)	1518 (51.8)	684 (23.3)	440 (15)	290 (9.9)
60-64	4.71 (2.94)	5.15 (3.03)	4.75 (3.01)	5.30 (3.23)
N (%)	1092 (50.3)	539 (24.8)	326 (15)	215 (9.9)

69	4.74 (2.94)	4.91 (3.02)	4.68 (3.04)	5.57 (3.36)
N (%)	1287 (60.4)	316 (14.8)	316 (14.8)	211 (9.9)

4.4.2. Association between cumulative ACEs and life course affective symptoms

Means and standard deviations of a cumulative ACE score across different affective symptom severity groups (i.e. no symptoms, mild symptoms, moderate symptoms and severe symptoms) at each age are presented in Table 4.2. Multinomial regression models were fitted to test for the associations between a cumulative ACE score and affective symptom severity at each age. First, unadjusted models were run (Table 4.3). No significant associations were found in the unadjusted models for affective symptoms at ages 13, 15, 36, 43 and 53. At age 60-64, there were significant associations between a cumulative ACE score and mild affective symptoms (OR = 1.05, b =.05, Wald χ^2 = 7.46, p = .006) and severe affective symptoms (OR = 1.07, b =.06, Wald χ^2 = 6.81, p = .009). At age 69 years, there was a significant association between a cumulative ACE score and severe affective symptoms (OR = 1.09, b =.09, Wald χ^2 = 13.41, p <.001). There were no significant associations between a cumulative ACE score and affective symptoms at earlier ages (13, 15, 36, 43, and 53).

Linear regression models were run in order to investigate the linear trend between a cumulative ACE score and CFA scores of affective symptoms at ages 13, 15, 36, 43, 53, 60-64 and 69. These results (Table 4.3, last column) indicated a linear trend for association between a cumulative ACE score and affective symptom score at ages 60-64 (b =.007, p =.017) and 69 (b =.008, p =.03), but not at earlier ages.

When multinomial regression models and linear regression models were adjusted for sex (model 2), the associations remained statistically significant for ages 60-64 and 69 (Table 4.4).

Table 4.3. Associations between a cumulative ACE score and affective symptoms at different ages: Model 1 (unadjusted)

Age	Affective symptom severity groups OR (95% CI)				Affective symptoms score b (SE)
	No symptoms (reference)	**Mild symptoms**	**Moderate symptoms**	**Severe symptoms**	
13		1.00 (.98; 1.03)	1.00 (.97; 1.03)	1.00 (.97; 1.04)	.002 (.003)
N (%)	1858 (50.4)	910 (24.7)	551 (14.9)	367 (10)	
15		.98 (.95; 1.01)	1.00 (.97; 1.03)	.99 (.95; 1.02)	.000 (.003)
N (%)	2086 (55.6)	731 (19.5)	566 (15.1)	371 (9.9)	
36		1.01 (.98; 1.04)	1.01 (.97; 1.04).	.99 (.95; 1.03)	-.001 (.005)
N (%)	1682 (50.6)	813 (24.5)	495 (14.9)	332 (10)	
43		1.00 (.97; 1.03)	1.00 (.97; 1.04)	1.00 (.97; 1.04)	.002 (.004)
N (%)	1623 (50)	811 (25)	488 (15)	323 (10)	
53		1.02 (.99; 1.05)	1.01 (.98; 1.05)	.99 (.95; 1.03)	.001 (.003)
N (%)	1518 (51.8)	684 (23.3)	440 (15)	290 (9.9)	
60-64		**1.05 (1.01; 1.08)****	1.00 (.96; 1.05)	**1.07 (1.02; 1.12)****	**.007 (.003)***
N (%)	1092 (50.3)	539 (24.8)	326 (15)	215 (9.9)	
69		1.02 (.98; 1.06)	.99 (.95; 1.03)	**1.09 (1.04; 1.14)*****	**.008 (.003)****
N (%)	1287 (60.4)	316 (14.8)	316 (14.8)	211 (9.9)	

Note: *** $p < .001$; ** $p < .01$; * $p < .05$

Table 4.4. Associations between a cumulative ACE score and affective symptoms at different ages: Model 2 (adjusted for sex)

Age	Affective symptom severity groups OR (95% CI)				Affective symptoms score b (SE)
	No symptoms (reference)	**Mild symptoms**	**Moderate symptoms**	**Severe symptoms**	
13		1.00 (.98; 1.03)	1.00 (.97; 1.03)	1.00 (.97; 1.04)	.002 (.003)
N (%)	1858 (50.4)	910 (24.7)	551 (14.9)	367 (10)	
15		.98 (.95; 1.01)	1.00 (.97; 1.03)	.99 (.95; 1.02)	.000 (.003)
N (%)	2086(55.6)	731 (19.5)	566 (15.1)	371 (9.9)	
36		1.01 (.98; 1.04)	1.01 (.97; 1.04).	.99 (.95; 1.03)	-.001 (.005)
N (%)	1682 (50.6)	813 (24.5)	495 (14.9)	332 (10)	
43		1.00 (.97; 1.03)	1.00 (.97; 1.04)	1.00 (.97; 1.04)	.002 (.004)
N (%)	1623 (50)	811 (25)	488 (15)	323 (10)	
53		1.02 (.99; 1.05)	1.01 (.98; 1.05)	.99 (.95; 1.03)	.001 (.003)
N (%)	1518 (51.8)	684 (23.3)	440 (15)	290 (9.9)	
60-64		**1.05 (1.01; 1.08)****	1.00 (.96; 1.05)	**1.07 (1.02; 1.12)****	**.008 (.003)****
N (%)	1092 (50.3)	539 (24.8)	326 (15)	215 (9.9)	
69		1.02 (.98; 1.06)	.99 (.95; 1.03)	**1.09 (1.04; 1.14)*****	**.008 (.003)****
N (%)	1287 (60.4)	316 (14.8)	316 (14.8)	211 (9.9)	

Note: *** $p < .001$; ** $p < .01$

Finally, fully adjusted regression models (including sex, childhood cognitive ability, educational attainment, and adult socio-economic position) were fitted for affective symptoms at all ages (Model 3, Table 4.5). Consistently, no significant associations between the cumulative ACE score and affective symptom severity or affective symptoms score were found at ages 13, 15, 36, 43 and 53, whereas the associations found at ages 60-64 and 69 were mainly unchanged. Specifically, at age 60-64, there were significant associations between the cumulative ACE score and mild affective symptoms (OR = 1.06, b =.06, Wald χ^2 = 7.46, p = .005) and severe affective symptoms (OR = 1.07, b =.06, Wald χ^2 = 6.81, p = .009). With every 1 unit increase in the cumulative ACE score, the odds of mild and severe affective symptoms at this age increase by 6% and 7% respectively. At age 69 years, there was a significant association between the cumulative ACE score and severe affective symptoms (OR = 1.09, b =.09, Wald χ^2 =14.10, p <.001). With every 1 unit increase in a cumulative ACE score, the odds of severe affective symptoms at this age increase by 9%. The associations shown in linear regression models were attenuated but remained significant at age 60-64 (b =.01, p =.011), but not at age 69 (b =.005, p =.212).

As sensitivity analyses, we re-ran the fully adjusted regression models for the sub-sample with the complete information on affective symptoms at all time-points. Appendix 4E presents the results of the complete case analyses using fully adjusted models. No significant associations were found using this sub-sample for affective symptoms at any age (all p values >.05).

Table 4.5. Associations between a cumulative ACE score and affective symptoms at different ages: Model 3 (fully adjusted)

Age	Affective symptom severity groups OR (95% CI)				Affective symptoms score b (SE)
	No symptoms (reference)	**Mild symptoms**	**Moderate symptoms**	**Severe symptoms**	
13		1.03 (.99; 1.07)	.99 (.95; 1.03)	.99 (.94; 1.04)	.001 (.004)
N (%)	1858 (50.4)	910 (24.7)	551 (14.9)	367 (10)	
15		.95 (.92; .99)	1.02 (.98; 1.06)	.98 (.93; 1.03)	.000 (.004)
N (%)	2086(55.6)	731 (19.5)	566 (15.1)	371 (9.9)	
36		1.01 (.97; 1.05)	1.02 (.97; 1.07)	.97 (.92; 1.03)	-.003 (.007)
N (%)	1682 (50.6)	813 (24.5)	495 (14.9)	332 (10)	
43		1.01 (.97; 1.05)	.99 (.95; 1.04)	1.04 (.99; 1.10)	.006 (.005)
N (%)	1623 (50)	811 (25)	488 (15)	323 (10)	
53		1.03 (.97; 1.05)	1.03 (.98; 1.08)	.97 (.92; 1.03)	.001 (.004)
N (%)	1518 (51.8)	684 (23.3)	440 (15)	290 (9.9)	
60-64	-	**1.06 (1.01; 1.10)****	1.02 (.97; 1.08)	**1.08 (1.02; 1.12)****	**.010 (.004)****
N (%)	1092 (50.3)	539 (24.8)	326 (15)	215 (9.9)	
69	-	1.00 (.95; 1.05)	.98 (.94; 1.03)	**1.07 (1.01; 1.13)*****	.005 (.004)
N (%)	1287 (60.4)	316 (14.8)	316 (14.8)	211 (9.9)	

Note: *** $p < .001$; ** $p < .01$

4.5. Discussion

The aim of the present study was to examine associations between a cumulative ACE score and affective symptoms at different time points across the life course. In total, 24 prospectively collected measures ACEs were summed to create a cumulative ACE score; and associations between this score and affective symptoms score and severity (i.e. no symptoms, mild symptoms, moderate symptoms, and severe symptoms) at ages 13, 15, 36, 43, 53, 60-64 and 69 were tested. A cumulative ACE score was associated with affective symptoms scores at ages 60-64 years and 69 years, but not at ages 13, 15, 36, 43, or 53 years. Also, a higher cumulative ACE score was associated with an increased odds of mild and severe affective symptoms at age 60-64 and with severe affective symptoms at age 69 years.

These results indicate that accumulation of ACEs may have a stronger effect on affective symptoms in later life (i.e. between ages 60-69) than in adolescence or young and middle adulthood. However, it is worth noting that present findings are inconsistent with previous evidence indicating a dose-response relationship between ACEs and affective disorders in earlier periods of the life course (Evans, Li, & Whipple, 2013; Raposo, Mackenzie, Henriksen, & Afifi, 2013).

The present findings need to be interpreted with caution, taking into account several important limitations. First, the measures of childhood maltreatment were not available for the NSHD cohort members. As childhood maltreatment is a well-known risk factor for adult affective symptoms (Li et al., 2016), a cumulative ACE score used in this study may not capture the breath of childhood adversity experienced by NSHD survey members. Therefore, the observed effects of accumulation of ACEs on affective symptoms across the life course may have been underestimated.

Second, only one approach to derive a cumulative ACE score was used in this study by summing 24 different types of ACEs. This approach assumes children who experienced childhood chronic illness, parental death and an overcrowded house would have a risk score of 3, and children who experienced parental divorce, low socio-economic status and maternal neuroticism would also have a risk score of 3. As such, cumulative risk focused specifically on the number of ACEs experienced rather than the severity or type of experience. Notably, this approach fails to distinguish between distinct types of environmental experiences, implicitly assuming that different experiences influence development through the same underlying mechanisms. Previous shortcomings of this approach have been noted including the loss of information on risk intensity for each ACE (Evans et al., 2013). Notably, a recent study has shown difference in effect sizes between acute (parental divorce, separation from parents) and chronic stressors (socio-economic status) (Colman et al., 2014). As the cumulative risk score used in this study included both acute (i.e., parental death) and chronic (i.e., childhood chronic illness) ACEs, findings should be taken tentatively as the respective impact of specific ACEs on the outcome could have been under or overestimated. In future, it's suggested that weighting each ACE based on pre-determined effect sizes could improve the accuracy of results (Roy & Raver, 2014).

Third, when computing a cumulative ACE score, survey members with missing data on any predictor variables had to be excluded from the analysis, leading to a loss of power. To deal with this limitation, multiple imputation technique (MICE) was used in order to impute missing data on each predictor before computing a cumulative ACE score. Multiple imputation is a data driven method which used the distribution of data, as well as information from other included

variables in the data set (auxiliary variables) to impute missing data. Of note, there was a significant difference between the mean number of ACEs for non-imputed variable (M = 4.99, SD = 3.06), and the mean number of ACEs for the imputed variable (M = 5.82; SD = 2.92) suggesting that those with missing data were more likely to experience multiple ACEs. Furthermore, when analyses were run on participants with complete information on affective symptoms at all time-points, no significant associations were found between the cumulative ACE score and affective symptoms. However, as a result of this stratification method, the sample sizes for these analyses were small. Thus results should be taken with caution due the loss of power.

The main strength of the present study is that prospective longitudinal studies such as NSHD offer an advantage over official records and cross-sectional surveys as they capture individuals who may experience affective symptoms in various times across the life course but do not use mental health services (Moffitt et al., 2010). Another strength of the current study is the availability of prospectively collected data on a wide range of ACEs.

With these strengths and limitations in mind, mechanisms of action, which attempt to explain why the association between cumulative ACEs and affective symptoms emerged only in late midlife, are considered. It is known that older adults face many stressful life events and substantial changes in life circumstances (Gerstorf et al., 2010) that can lead to an increased risk for affective disorders. For example, death of a spouse (Domingue, Liu, Okbay, & Belsky, 2017; Schoevers et al., 2000), and loneliness (Adams, Sanders, & Auth, 2004; Cornwell & Waite, 2009) are shown to be associated with an increased risk for later life depression. As such, one theory termed the ‘kindling’ effect (and sometimes referred to as stress sensitisation and

stress amplification theories) posits that those with previous multiple exposures to adversities (e.g., accumulation of ACEs) may have a particularly high vulnerability for mental health problems if they experience adversities later in life (Rudolph & Flynn, 2011; Rutter, Kim-Cohen, & Maughan, 2006).

In conclusion, the present study suggests that people who experience higher number of ACEs are at an increased risk of affective symptoms later in life, beyond adolescence and young adulthood. These findings have the implications for older adults as this group may be particularly vulnerable and may benefit from preventive interventions.

Chapter 5

Study 4: Life course profiles of affective symptoms and their early life risk factors

5.1. Abstract

Background: Previous evidence indicates that trajectories of affective symptoms (symptoms of depression and anxiety) are heterogeneous over the life course. However, few studies have investigated profiles of affective symptoms from childhood through to later life and explored the role of early life risk factors in the development of these profiles.

Aim: The present study aimed to: 1) derive latent trajectories of affective symptoms over a period of more than 50 years (from age 13 through age 69), and 2) examine a wide range of early life risk factors (from birth through age 15) for associations with specific life course trajectories of affective symptoms.

Method: Data from the MRC National Survey of Health and Development (NSHD) (n = 5362) were used. Symptoms of anxiety and depression were measured prospectively at ages 13, 15, 36, 43, 53, 60-64 and 69. A latent variable modelling approach was applied to improve the precision of measurement, and latent profile analysis was used to model longitudinal profiles of affective symptoms. Twenty-four prospectively measured early life factors across six domains: family stability, family socio-economic status, parental age, childrearing and parenting, parental health, and childhood health, were tested for associations with different symptom profiles using multinomial logistic regression.

Results: Four life course profiles of affective symptoms were identified: 1) absence of symptoms (66.6% of the sample); 2) adolescent symptoms with good adult outcome (15.2%); 3) adult symptoms only (with no symptoms in adolescence and late life) (12.9%); 4) symptoms in adolescence and mid adulthood (5.2%). Notably, all of the affective symptom trajectories converge to low symptom level at ages 64 and 69 years. Among the early life factors tested, only four were significantly

associated with affective symptom trajectories, with small effect sizes observed: childhood chronic illness was associated with adult symptoms only; whereas growing up in an overcrowded house and parental poor perceived health were associated with symptoms in adolescence and adulthood. However, no associations were found for twenty of the early life predictors.

Conclusion: These findings demonstrate that people differ in terms of their life course symptoms of anxiety and depression, and that these differences are not largely influenced by early life factors.

5.2. Introduction

Lifetime prevalence and lifetime morbid risk of affective disorders are very high, with estimates showing that 1 in 4 people worldwide suffer from one or more episodes of affective disorder during the life course (Kessler et al., 2012; S. Stansfeld et al., 2014). The majority of affective problems have early onset, with 50% of individuals presenting symptoms by the age of 14 years, and 75% by the age of 24 years (Kessler, Amminger, et al., 2007). Early onset affective problems are associated with a longer time-to-treatment, and, without intervention, are often characterised by greater severity and persistence into adulthood (Raven et al., 2016). However, notably, some individuals with early onset affective disorders do not develop recurrent problems, whereas others have repeated affective episodes across the life course. Evidence from studies of children followed into early adulthood, as well as of adult samples with follow-up of more than ten years, suggests that long-term trajectories of affective disorders are heterogeneous, with trajectories varying in terms of severity (low, medium and high) and stability (stable, increasing, decreasing) (Musliner, Munk-Olsen, Eaton, & Zandi, 2016; Paksarian et al., 2016). This evidence highlights the importance of assessing affective disorders longitudinally as opposed to using measures at a single time point in life. Moreover, identifying groups of people who differ in the age of onset and recurrence of affective symptoms across the life course is an important step for studying the aetiology and development of affective disorders, and allows more personalised and effective prevention and treatment strategies to be developed.

Birth cohort studies with multiple measures of affective symptoms combined with advances in person-centred approaches to longitudinal data provide a unique opportunity to model individual life course trajectories of symptoms (Colman,

Ploubidis, et al., 2007). Moreover, birth cohorts using prospectively collected rather than retrospectively reported data provide an opportunity to illuminate the role of early life influences on life course mental health (Power, Kuh & Morton, 2014).

So far, a few studies have estimated trajectories from childhood or adolescence through young or middle adulthood (Colman et al, 2007; Gibbs, Fergusson & Horwood, 2010; Olino et al, 2010). In one of these studies, Colman et al. (2007) applied latent variable mixture modelling to identify longitudinal profiles of depressive and anxious symptoms from childhood through to mid-adulthood (from age 13 through age 53) using data from the MRC National Survey of Health and Development (NSHD): a nationally representative British birth cohort with multiple measures of affective symptoms. In this study, six distinct profiles of affective symptoms were identified: absence of symptoms (44.7%); repeated moderate symptoms (33.6%); adult-onset moderate symptoms (11.3%); adolescent symptoms with good adult outcomes (5.8%); adult-onset severe symptoms (2.9%); and repeated severe symptoms (1.7%).

Moreover, studies using birth cohort data have provided evidence for the role of early life factors in life course mental health, suggesting that the effects of specific adverse childhood experiences, including both socio-economic and psychosocial adversities, as well as their accumulation, have a long-term impact on mental health and well-being (Evans et al., 2003; Secinti et al., 2017; Mai Stafford et al., 2015). However, there is a gap in our knowledge of whether these early life experiences may have different impact on life course trajectories of affective disorders.

Therefore the present study aims to extend the previous research by: 1) deriving trajectories of affective symptoms over a longer period of 56 years, from childhood (age 13) through late life (age 69); and 2) examining a wide range of early

life risk factors (from birth through age 15) for associations with specific life course trajectories of affective symptoms.

5.3. Method

5.3.1. Sample

The MRC National Survey of Health and Development (NSHD) is an ongoing longitudinal study with the original sample of 5362 individuals born in England, Scotland and Wales during one week in March 1946. Participants were randomly sampled from 1 in 4 single births within marriage to wives of manual workers, and all single births to wives of non-manual and agricultural workers. This study was first initiated to explore changes in fertility rates in Britain since the mid-19th century, and to investigate the extent to which the use of midwifery and obstetric services prevented premature infant death, and promoted the health of mothers and infants (Wadsworth, Kuh, Richards, & Hardy, 2006). The NSHD cohort members have been prospectively studied 24 times, from birth up to 69 years of age. Follow ups occurred every 2 years during childhood and main data collections in adulthood took place at ages 26, 36, 43, 53, 60-64 and 69. The present study uses the data across seven decades of life: from birth up to age 69.

5.3.2. Measures

5.3.2.1. Affective symptoms

Affective symptoms (anxiety and depression) were assessed at ages 13, 15, 36, 43, 53, 60-64 and 69 years. At age 13 and 15 affective symptomology was assessed using a forerunner of the Rutter Behaviour Questionnaire for teachers (Rutter, 1967). The teachers' questionnaire, or Child Scale B, (Rutter, 1967b) consisted of 26 descriptions of behaviour against which the teacher was asked to describe aspects of the children's personality, behaviour and attitudes on a 3 point scale (more, the same, or less than class mates). The test had both a good inter-rater reliability (r = 0.72) and retest reliability (r = 0.89) (Rutter, 1967). Questionnaires have previously been

subjected to classical linear factor analysis, with one factor comprising 11 items being identified as anxiety/ depression and affective symptoms and behaviours (Colman, Wadsworth, et al., 2007; Jones, Murray, Jones, Rodgers, & Marmot, 1994). The items that loaded onto the affective symptoms factor were "timid child," "rather frightened of rough games," "extremely fearful," "always tired and washed out," "usually gloomy and sad," "avoids attention," "very anxious," "unable to make friends," "diffident about competing," "frequently day dreams in class," and "becomes unduly miserable or worried in response to criticism".

Anxiety and depressive symptoms were measured again at age 36 using a short version of the Present State Examination (PSE) (Wing et al., 1974, 2011). This is a clinical interview, administered by trained nurses, which aims to assess the frequency and severity of affective symptoms over the previous month. The short version of the PSE assessed 40 items, each of which were scored on a 3-point or 4-point scale.

Symptoms were further assessed at age 43 using the Psychiatric Symptom Frequency (PSF) scale (Lindelow, Hardy, & Rodgers, 1997). The PSF is an 18-item scale used to measure symptoms of anxiety and depression which have occurred over the previous 12 months. Questions on this scale are phrased as 'have you…?' (E.g. 'have you felt on edge or keyed up or mentally tense?'), and responses to each question were coded as 0 = 'not in the last year', 1 = 'occasionally', 2 = 'sometimes', 3 = 'quite often', 4 = 'very often', and 5 = 'everyday'. From these codes a total score ranging from 0 to 90 could be calculated. A previous investigation of the PSF found that a cut off score of 22 adequately identified those with evidence of anxiety and depressive symptoms (Lindelow et al., 1997). The PSF has been previously found to higher internal consistency ($\alpha = .88$) (Lindelow et al., 1997).

Anxiety and depression were reported at 53, 60-64 and 69 years using the 28-item version of the General Health Questionnaire (GHQ-28) (Goldberg & Hillier, 1979). This is a scaled questionnaire used to detect common mental health problems in the general population. Items on this questionnaire asked participants about specific complaints over the past few weeks. Examples included 'have you recently been getting scared or panicky for no good reason?' and, 'have you recently been thinking of yourself as a worthless person?' Each of these questions are accompanied by four responses, typically being, 'not at all', 'no more than usual', 'rather more than usual' and 'much more than usual', scoring from 0 to 3, respectively. Thus a total score on the GHQ can range from 0-84, allowing means and distributions to be calculated.

5.3.2.2. Early life risk factors

In total, 24 measures of early life risk factors (from birth through age 15 years) representing six domains: family instability, family socio-economic status, parental age, childrearing environment and parenting, parental health and 'child's health, were included in the present study. All early life predictors were selected a priori, and the selection was based on previous reports using data from the MRC NSHD (Rodgers, 1990; Stafford et al., 2015). The information on early life risk factors was collected prospectively through a variety of sources, including health visitor reports, parent report, and teacher reports. For this study, a binary or categorical variable was created for each early life predictor (Table 5.3 provides a list of all early life variables). The sample size of each analysis varied depending on whether the participants' information was available for each early life predictor (see Table 5.3).

Family Stability. Parental divorce was prospectively collected between the ages of 5 and 15 years. As only a small number of survey members experienced parental divorce, data for this variable was dichotomised at age 8 years. Parental death between the ages of 0 and 15 years was also dichotomised. Age at break with mother between birth and 15 years was dichotomised into those who were and were not separated from their mother before 15 years. Number of residential moves was obtained between the ages of 0 and 15 years, ranging from 0 to 8, and was categorised into: 4 or more moves, 1-3 moves, or no moves.

Family socioeconomic circumstances. Father's and mother's education was classified as primary level only, or beyond this. The number of amenities lacking from the family home was recorded between the ages of 2 and 15 years. This ranged from 0 (n = 1394) to 8 (n = 1), and was recoded into: lacking 4 or more, lacking of 2-3, or lacking 0-1 amenities. The number of family members per bedroom in each household was recoded when survey members were 4 years of age. This ranged from 1 (n = 88) to 8 (n =56), and was recoded into: 3 or more, 1 ½ - 2 ½, or 1 or less family members per bedroom. Number of children in family was recorded when study members were 15 years old. This ranged from 1 (n = 572) to 16 (n = 1), and was recoded into: 4 or more children, or 1-3 children.

Parental age. Age of father and mother was recorded at the birth of the survey member. The mean age of fathers was 32 years (SD = 6.51). The mean age of mothers at birth of survey member was 29 years (SD = 5.70). Binary variables were created to indicate teenage fathers and mothers (age 19 years or younger, or older than this), and older fathers and mothers (41 years or older, or younger than this). Two early life predictors (teenage mother and teenage father) were omitted from the

analysis due to low sample sizes (see Table 3 for the percentage of teenage mothers and teenage fathers by each affective symptom profile).

Childrearing and parenting. Breastfeeding was classified as breastfed for 5 or more months, 1-4 months, or never breastfed. Information on mother's management and understanding of the child compared with others was collected by health visitors when the survey members were 4 years old, this was rated during the home based interview by a health visitor, and scored as among the best, average, or among the worst. Because only four mothers fell into the worst category in the sample selected for analysis, these were combined with those rated as average and compared to those who were among the best.

Parental interest in the study member's primary and secondary education was classified as high interest in either secondary or primary education, or average and low interest in either secondary or primary education.

Cleanliness of child and cleanliness of house was also reported, and those who were described as average or among the least clean were compared with those among the most clean. State of repair of clothes and shoes was classified as "unsatisfactory" or "satisfactory".

Parental health. Fathers and mothers perceived health was recorded by the mother when survey members were 15 years of age. Fathers and mothers perceived health was classified as excellent, average, or poor. Maternal neuroticism was also recoded when the survey members were 15 years old using the six item neuroticism scale of the Maudsley Personality Inventory (Jensen, 1958). Maternal neuroticism was classified though grouping those that scored 6 on the scale as presenting neurotic symptoms and those who scored below 6.

Child health. Birth weight was recorded in grams. Mean birth weight was 3376.52 grams (SD = 541.36), and was classified as 2500-4000 grams (normal birth weight), below 2500 grams (low birth weight), and above 4000 grams (high birth weight). Chronic childhood illness before the age of 15 years was coded as yes or no. Chronic childhood illness was defined as "a physical, usually non-fatal condition which lasted longer than three months in a given year or necessitated a continuous period in hospital of more than one month. In addition, conditions were included only if they were of sufficient severity to interfere with the child's activities in some degree." In addition, conditions were included only if they were of sufficient severity to interfere with the child's activities in some degree.

Accumulation of adverse childhood experiences. Using the imputed data for early life predictors, binary variables were derived for each early life risk factor, and a cumulative ACE score was calculated using a summing approach (see Chapter 4).

5.3.3. Analytical procedure

In line with previous approaches to improve precision of measurement of affective symptoms (Colman et al., 2007), a latent variable modelling framework was applied to affective symptoms measures at ages 13, 15, 36, 43, 53, 60-64 and 69. Confirmatory factor analysis for categorical data was applied to derive latent factor scores, which were treated as continuous measures of anxiety and depression at each time point (appendix 4D provides stability correlations for the derived factor scores).

Next, these latent factor scores were grouped in order to create four-category ordinal variables at each of the seven time-points. Group 1 indicated those with a lack of symptoms (1st to 50th percentile on the estimated factor score), group 2 indicated those with occasional symptoms (50.1 to 75th percentile), group 3 indicated those with moderate symptoms (75.1 to 90th percentile) and group 4

indicated those with severe symptoms (90.1 to 100th percentile). Using the derived ordinal measures of symptoms of anxiety and depression, latent class mixture modelling was applied to identify groups of individuals with differing longitudinal experiences of depression and anxiety symptoms (as explained in the next section). This analysis included all individuals who had at least one of the seven assessments of affective symptoms (n = 4974, 92.8%). Among those, individuals who had all seven assessments (n = 574), individuals who had six assessments (n = 563), had five (n = 1351), had four (n = 900), had three (n = 549), had two (n = 806), and had one (n = 231), were included in the analysis. A sub-sample of 388 (7%) survey members who did not undergo any of these assessments was excluded from the analyses. The models were run using Mplus version 6 (Muthén & Muthén, 2010).

5.3.3.1. Latent profile analyses

Latent profile analysis (LPA) is a statistical method designed to identify patterns of trajectories for different sub groups within a population. It assumes that unobserved variables (i.e. latent classes or profiles) offer a more valid explanation for the relationships among observed variables, than the characteristics of the observed variables alone. Specifically, correlations between observed variables are used to model unobserved (i.e. latent) variables, such as membership of an unobserved class or profile. Dissimilar to conventional growth modelling approaches, such as latent growth curve models, which model a single average growth parameter, latent profile analysis assumes that a subset of heterogeneous growth trajectories exist, which are significantly different from the overall estimate (Jung & Wickrama, 2008). Subsequently, these methods are often applied when researchers are aiming to identify groups following distinct trajectories over time and estimate trajectory parameters separately for each group. As previous findings have

indicated heterogeneous growth trajectories of anxiety and depression symptoms using measures at ages 13, 15, 36, 43, and 53 (Colman, Ploubidis, et al., 2007), we employed LPA, with ordinal indicators being entered as continuous variables in the model to derive growth trajectories between ages 13 and 69. When applying this method, as the number of suitable latent profiles is initially unknown, model fit indices are compared and the substantive coherence of the class solution selected is considered (Bauer & Curran, 2004). For this analysis, a series of models were fitted estimating three to seven class solutions. In order to identify the most parsimonious description of early to later life trajectories of affective symptoms, model fit indices were compared using Likelihood ratio bootstrap *p* value, Bayesian Information Criteria (BIC), Akaike's Information Criteria (AIC). Lo-Mendell-Rubin bootstrap *p* value of likelihood ratio test, and entropy. All models were run with random starting values, using maximum likelihood estimation with robust standard errors.

5.3.3.2. Sensitivity analyses

A series of sensitivity analyses were also run for the LPA. As numerous studies show a higher prevalence of depression in women than men, sex-specific differences of the profiles were investigated through running the LPA separately for men and women. As LPA draws on all of the data points available in the data set (i.e. it included all individuals who has at least one of the seven assessments of affective symptoms – $n = 4974$) missing data points are included in the analysis using full information maximum likelihood (FIML) when estimating the posterior probabilities of class membership. As a wealth of evidence has shown that affective symptoms are associated with an increase in risk of mortality across the life course (Cuijpers et al., 2014; Cuijpers & Smit, 2002; Henderson, Hotopf, Shah, Hayes, & Kuh, 2011) this is problematic as survey members data that was available at early waves, but who died

in later waves may generate bias in these estimates. Due to this, the LCA models were re-run using only those who were still alive by age 69 years.

5.3.3.3. Multinomial logistic regression analyses

A series of multinomial logistic regression analyses were conducted to investigate whether each early life predictor and the accumulation of early life predictors was associated with our four identified life course profiles of affective symptoms. For each analysis, the no affective symptoms profile was used as the comparison group. For a cumulative ACE score, a one-way ANOVA was used to determine whether there was a significant difference between the number of early life events experienced for each affective symptom profile.

5.4. Results

5.4.1. Life course profiles of affective symptoms

Latent factor scores were derived for each affective symptom measure at ages 13, 15, 36, 43, 53, 60-64 and 69, using confirmatory factor analysis appropriate for categorical data. These latent factor scores were saved and an ordinal variable containing four levels of affect (no symptoms, mild symptoms, moderate symptoms, and severe symptoms) was derived for each of the seven time points. Table 5.1 shows the number and percentage of survey members in each category, at each time point (for the total sample; and men and women, separately). The distribution of latent factor scores of affective symptom measures at each time point are presented in appendix 5 (A-G).

Fit indices for each class solution are displayed in Table 5.2. The four-class solution was selected as the best fitting model as this was the most parsimonious model with the highest entropy value. The four longitudinal profiles of affective symptoms as defined by LCA are shown in Figure 5.1. The first group indicated those who had no affective symptoms (n = 3315; 66.6%). The second group indicated those who had affective symptoms in adolescence only (n = 757; 15.2%). The third group consisted of those who had affective symptoms in adulthood only (n = 643; 12.9%). The fourth group consisted of participants who had affective symptoms in adolescence and mid adulthood (n = 259; 5.2%). Figure 5.1 displays the posterior probability for each longitudinal latent profile at each of the seven-time points and includes those who took part in at least one of the seven measurements (n = 4974). The second-best fitting model was the six-class solution (Table 5.2).

Table 5.1. Number of participants (%) with information on affective symptoms at each time point

Age, years	Ordinal affect symptom levels	Men *N* = 2815	Women *N* = 2547	Total *N* = 5362
13	No symptoms	981 (34.8)	877 (34.4)	1858 (34.7)
	Mild symptoms	465 (16.5)	445 (17.5)	910 (17)
	Moderate symptoms	292 (10.4)	259 (10.2)	551 (10.3)
	Severe symptoms	195 (6.9)	172 (6.8)	367 (6.8)
	Total Valid	1933 (68.7)	1753 (68.8)	3686 (68.7)
	Total Missing	882 (31.1)	794 (31.2)	1678 (31.3)
15	No symptoms	1073 (38.1)	1013 (39.8)	2086 (38.9)
	Mild symptoms	389 (13.8)	342 (13.4)	731 (13.6)
	Moderate symptoms	300 (10.7)	266 (10.4)	566 (10.6)
	Severe symptoms	197 (7)	174 (6.8)	371 (6.9)
	Total Valid	1959 (69.6)	1795 (70.5)	3754 (70)
	Total Missing	856 (30.4)	752 (29.5)	1608 (30)

36	No symptoms	898 (31.9)	784 (30.8)	1682 (31.4)
	Mild symptoms	414 (14.7)	399 (15.7)	813 (15.2)
	Moderate symptoms	261(9.3)	234 (9.2)	495 (9.2)
	Severe symptoms	180 (6.4)	152 (6)	332 (6.2)
	Total Valid	1753 (62.3)	1569 (61.6)	3322 (62)
	Total Missing	1062 (37.7)	978 (38.4)	2040 (38)
43	No symptoms	857 (30.4)	766 (30.1)	1623 (30.3)
	Mild symptoms	414 (14.7)	397 (15.6)	811 (15.1)
	Moderate symptoms	262 (9.3)	226 (8.9)	488 (9.1)
	Severe symptoms	187 (6.6)	136 (5.3)	323 (6)
	Total Valid	1720 (61.1)	1525 (59.9)	3245 (60.5)
	Total Missing	1095 (38.9)	1022 (40.1)	2117 (39.5)
53	No symptoms	798 (28.3)	720 (28.3)	1518 (28.3)
	Mild symptoms	365 (13)	319 (12.5)	684 (12.8)
	Moderate symptoms	237 (8.4)	203 (8)	440 (8.2)

	Severe symptoms	157 (5.6)	133 (5.2)	290 (5.4)
	Total Valid	1557 (55.3)	1375 (54)	2932 (54.7)
	Total Missing	1258 (44.7)	1172 (46)	2430 (45.3)
60-64	No symptoms	577 (20.5)	515 (20.2)	1092 (20.4)
	Mild symptoms	249 (8.8)	290 (11.4)	539 (10.1)
	Moderate symptoms	156 (5.5)	170 (6.7)	326 (6.1)
	Severe symptoms	61 (2.2)	154 (6)	215 (4)
	Total Valid	1043 (37.1)	1129 (44.3)	2172 (40.5)
	Total Missing	1772 (62.9)	1418 (55.7)	3190 (59.5)
69	No symptoms	684 (24.3)	603 (23.7)	1287 (24)
	Mild symptoms	144 (5.1)	172 (6.8)	316 (5.9)
	Moderate symptoms	142 (5)	174 (6.8)	316 (5.9)
	Severe symptoms	70 (2.5)	141 (5.5)	211 (3.9)
	Total Valid	1040 (36.9)	1090 (42.8)	2130 (39.7)
	Total Missing	1775 (63.1)	1457 (57.2)	3232 (60.3)

Table 5.2. Indices for a model fit for a latent profile analyses with five different solutions

	3 classes	**4 classes**	**5 classes**	**6 classes**	**7 classes**
Likelihood ratio bootstrap *p* value[a]	<.001	**<.001**	<.001	<.001	<.001
Bayesian Information Criteria[b]	57258.00	**57258.00**	56297.79	56338.93	55889.51
Akaike's Information Criteria[c]	58010.65	**57010.55**	56597.34	55987.29	55485.77
Lo-Mendell-Rubin bootstrap *p* value of likelihood ratio test comparing current model to previous model[d]	<.001	**<.001**	.115	.095	.041
Entropy[e]	.69	**.74**	.65	.66	.68

N = 4974. [a]*p*>.01 indicates good fit; [b]lowest value indicates better fit; [c]lowest value indicates better fit; [d]indicates addition of this class significantly improves fit; [e]value closest to 1 indicates high certainty in classification.

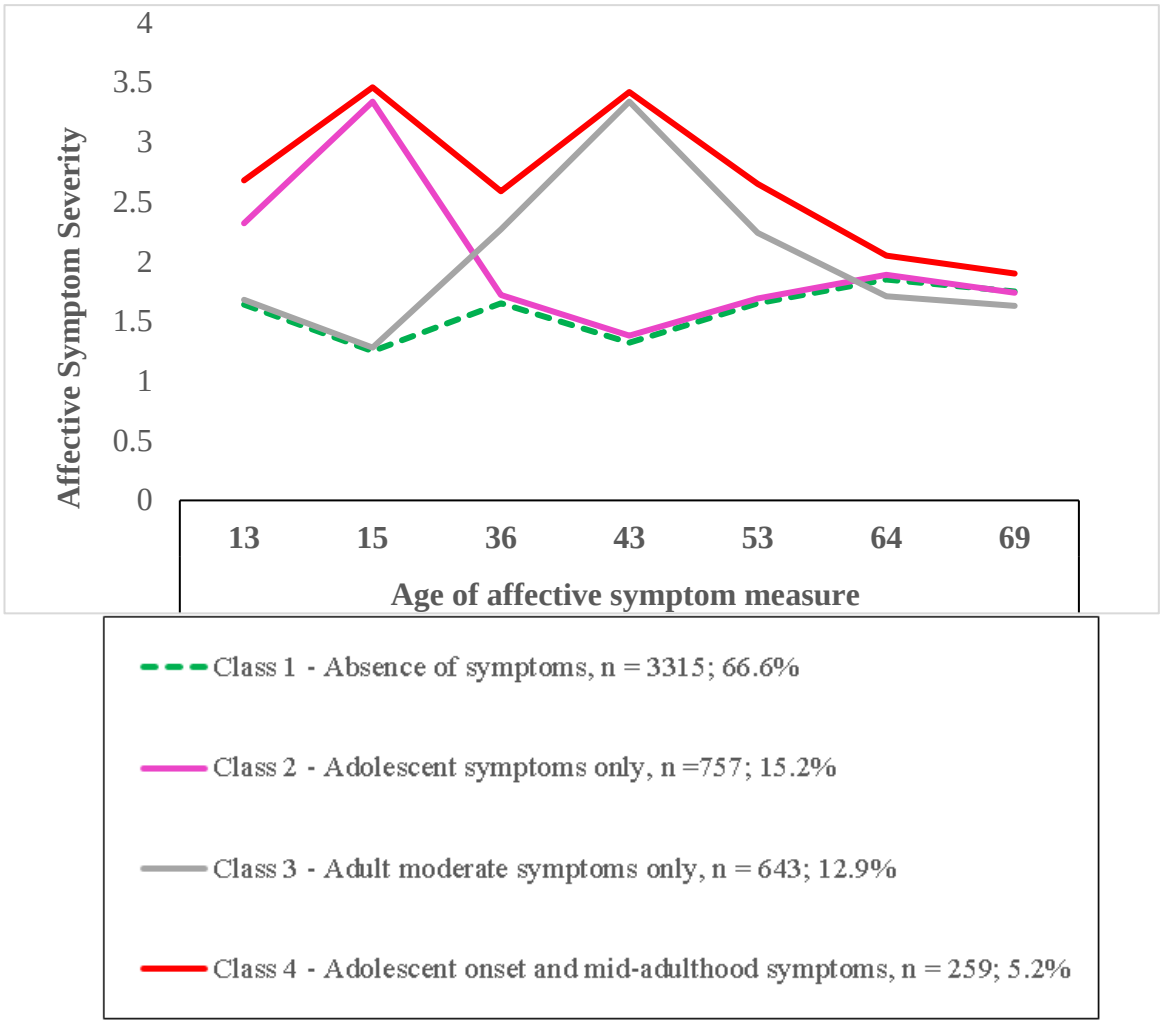


Figure 5.1. Four life course profiles of affective symptoms from ages 13 to 69 years

In addition, in order to investigate whether the trajectories differed between sexes, models were investigated separately for men and women (Appendix 5L & 5M). Although the three-class model had a slightly higher entropy value, the four-class solution was shown to be the best fitting model for both males and females (i.e. based on the BIC and AIC fit criteria; Appendix 5K).

As affective symptoms are shown to be associated with mortality (Cuijpers et al., 2014; Cuijpers & Smit, 2002; Henderson et al., 2011; Mykletun et al., 2009), additional analysis was conducted in order to examine whether the affective symptom profiles differed when excluding all participants who died before age 69 (*n* = 672). Those who were alive at age 69 and had information on at least one time point on affective symptoms were included (*n* = 4302). Model fit criteria were assessed when running the LCA on those who survived by age 69 (Appendix 5N). The four-class solution was deemed to be the best fitting model based on the observed fit statistics (i.e., the highest entropy value). Of note, the four profiles identified when excluding individuals who died included similar symptom trajectories. The first group indicated those who no symptoms (*n* = 2307; 57.2%). The second group indicated those who had symptoms in adolescence only (*n* = 718; 17.8%). The third group had symptoms in adulthood only (*n* = 643; 12.9%). And the fourth group had symptoms in adolescence and mid adulthood (*n* = 296; 7.3%) (Appendix 5O).

5.4.2. Early life risk factors for life course profiles of affective symptoms

A total of 4974 participants were included in the association analyses testing for the effects of individual early life predictors on life course profiles of affective symptoms (Table 5.4). Two early life predictors (teenage mother and teenage father)

were omitted from the analysis due to low sample sizes. Table 5.3 presents counts and percentages for early life factors across four affective symptom profiles.

For the profile of symptoms in adolescence only, no early life predictors were found to be significant predictors. For the profile of symptoms in adulthood only, one early life predictor – childhood chronic physical illness – was identified: those who experienced childhood chronic illness were 1.36 times more likely to develop adolescent symptoms only compared to those who did not experience childhood chronic illness (b =.31, Wald χ^2 = 8.98, p = .003). For the profile of symptoms in adolescence and mid adulthood, three early life predictors were identified: those who lived in a house with 3 or more people per room were 1.9 times more likely to develop these symptoms compared to those who lived in a house with 1-2 persons per room (b =.64, Wald χ^2 = 1.24, p = .031); those whose fathers had average health were 1.44 times more likely to develop symptoms in adolescence and adulthood than those whose fathers perceived their health as excellent (b =.37, Wald χ^2 =6.40, p = .01); those whose mothers reported their health to be poor were 1.44 times more likely to have symptoms in adolescence and mid adulthood than those whose mothers perceived health was excellent (b =.36, Wald χ^2 = 5.13, p = .02) (see Table 5.4).

Table 5.3. Contingency table for imputed early life risk factors across four life course profiles of affective symptoms

Adversity Category	Adversity Type	Comparison groups (0, 1, 2)	Absence of symptoms *N* (%)	Adolescent symptoms only *N* (%)	Adult symptoms only *N* (%)	Adolescent onset and mid adulthood symptoms *N* (%)	Total *N* (%)
Family Instability	Parental Divorce (by age 15)	no divorce	2882(86.9)	666(93.4)	560(92.4)	229(93.8)	4337(87.2)
		divorce	433(13.1)	91(6.6)	83(7.2)	30(6.2)	637(12.8)
	Death of any parent (by age 15)	no death	3065(92.5)	708(93.5)	600(93.3)	241(93.1)	4614(92.8)
		death	250(7.5)	49(6.5)	43(6.7)	18(6.9)	360(7.2)
	Break with Mother (before 15 years)	no	2730(94.6)	635(94.6)	543(94.4)	163(93.7)	4702(94.5)
		yes	157(5.4)	36(5.4)	32(5.6)	11(6.3)	272(5.5)
	Residential Moves	0 (ref)	870(26.2)	208(27.5)	176(27.4)	63(24.3)	1317(26.5)
		1 – 3 moves	2260(68.2)	507(67)	424(65.9)	184(71)	3375(67.9)
		4+ moves	185(5.6)	42(5.5)	43(6.7)	12(4.6)	282(5.7)
Family Socio-economic circumstances	Fathers Education	> primary	1435(43.3)	303(40)	283(44)	103(39.8)	989(24.8)
		primary only	1880(56.7)	454(60)	360(56)	156(60.2)	2850(57.3)
	Mothers Education	> primary	1260(38)	263(34.7)	228(35.5)	95 (36.7)	1846(37.1)
		primary only	2005(62)	494(65.3)	415 (64.5)	164(63.3)	3128(62.9)
	Lack of home amenities	Lacks 0 or 1(ref)	1288(38.9)	285(37.6)	230(35.8)	107(41.3)	1910(38.4)
		Lacks 2 or 3	1544(46.6)	353(46.6)	306(47.6)	126(48.6)	2329(46.8)

		Lacks 4+	483 (14.6)	119(15.7)	107(16.6)	26(10)	735 (14.8)
	Crowding	½ - 1 person per room (ref)	1848(55.7)	432(57.1)	377(58.6)	132(51)	2789(56.1)
		1 ½ – 2 ½ people per room	1364(41.1)	297(39.2)	241(37.5)	113(43.6)	2015(40.5)
		3+ people per room	103(3.1)	28(3.7)	25(3.9)	14(5.4)	170(3.4)
	Father's occupational status	non-manual	1393(42)	300(39.6)	251(39)	103(39.8)	2047(41.2)
		Manual	1922(58)	457(60.4)	392(61)	156(60.2)	2927 (58.8)
	Family size	0-3 children	1591(71.1)	372(69.3)	316(71)	107(69.9)	2786(70.8)
		4+ children	646(28.9)	165(30.7)	129(29)	46(30.1)	1147(29.2)
Parental age	Teen Father	20+ years	3278(98.9)	751(99.2)	635(98.8)	258(99.6)	4922 (99)
		<20 years	37 (0.7)	6(0.8)	8(1.2)	1(0.4)	52(1)
	Teen Mother	20+ years	3226(97.3)	740(97.8)	627(97.5)	252 (97.3)	4845(97.4)
		<20 years	89(2.7)	17(2.2)	16(2.5)	7(2.7)	129(2.6)
	Mid aged father	40 years or less	2962(88.3)	658(86.9)	576(89.6)	224(86.5)	4384(88.1)
		>40 year	389 (11.7)	99 (13.1)	67 (10.4)	35 (13.5)	590 (11.9)
	Mid aged mother	40 years or less	3169(95.6)	732(96.7)	626(97.4)	250(96.5)	4777(96)
		>40 year	146(4.4)	25(3.3)	17(2.6)	9(3.5)	197(4)
Childrearing environment and parenting	Breastfeeding	Breastfed for 5+ months (ref)	1398(42.2)	312(41.2)	248(38.6)	113(43.6)	2071(41.6)
		Breastfed for 1-4 months	1169(35.3)	256(33.8)	229(35.6)	87(33.6)	1741(35)
		Never breastfed	748(22.6)	189(25)	166(25.8)	59(22.8)	1162(23.5)
		Among the best	1608(48.5)	378(49.9)	306(47.6)	119(45.9)	2411(48.5)

	Mothers management and understanding	Average / Among the worse	1707(51.5)	379(50.1)	337(52.4)	140(54.1)	2563(51.5)
	Parents interest in child education	High interest in primary or secondary education (ref)	1377(41.5)	334(44.1)	277(43.1)	104(40.2)	2092(42.1)
		Average interest in primary or secondary education	1262(38.1)	260(34.3)	249(38.7)	88(34)	1859(37.4)
		Low interest in primary or secondary education	676(20.4)	163(21.5)	171(18.2)	67(25.9)	1023(20.6)
	Cleanliness of child (1950)	Among the most clean	2037(61.4)	468(61.8)	390(60.7)	160(61.8)	3055(61.4)
		Average/Among the least clean	1278(38.6)	289(38.2)	253(39.3)	99(38.2)	1919(38.6)
	Cleanliness of house (1950)	Among the most clean	1945(58.7)	445(58.8)	362(56.3)	151(58.3)	2903(58.4)
		Average / Among the least clean	1370(42.3)	312(41.2)	281(43.7)	108(41.7)	2071(41.6)
	Clothes repair (1950)	Satisfactory state of repair	3250(98)	747(98.7)	629(97.8)	255(98.5)	4881(98.1)
		Unsatisfactory state of repair	65(2)	10(1.3)	14(2.2)	4(1.5)	93(1.9)
	Shoes repair (1950)	Satisfactory size and type	3229(97.4)	737(97.4)	624(97)	253(97.7)	4843(97.4)
		Unsatisfactory size and type	86(2.6)	20(2.6)	19(3)	6(2.3)	131(2.6)
Parents Health	Fathers perceived health	Excellent	1608(48.5)	356(47)	323(50.2)	108(41.7)	2395(48.2)
		Average	1033(31.2)	244(32.2)	211(32.8)	100(38.6)	1588(31.9)
		Poor	674(20.3)	157(20.7)	109(17)	51(19.7)	991(19.9)

	Mother perceived health	Excellent	1370(41.3)	297(39.2)	281(43.7)	95(36.7)	2043(41.4)
		Average	1183(35.7)	280(37)	221(34.4)	88(34)	1772(35.6)
		Poor	762(23)	180(23.8)	141(21.9)	76(29.3)	1159(23.3)
	Maternal neuroticism	no	3227(97.3)	740(97.8)	631(98.1)	250(96.5)	4848(97.5)
		yes	88(2.7)	17(2.2)	12(1.9)	9(3.5)	126(2.5)
Childhood Health	Birth Weight	2500 – 4000 grams	2753(83)	634(83.8)	531(82.6)	215(83)	4133(83.1)
		>4000 grams	361(10.9)	83(11)	70(10.9)	24(9.3)	538(10.8)
		2500 or less grams	201(6.1)	40(5.3)	42(6.5)	20(7.7)	303(6.1)
	Chronic Illness (before age 15)	no (or after 15 years)	2715(81.9)	606(80.1)	494(76.8)	210(81.1)	4025(80.9)
		yes	600(18.1)	151(19.9)	149(23.2)	49(18.9)	949(19.1)

Table 5.4. Associations between different types of early life factors and life course profiles of affective symptoms (profile with no affective symptoms is the reference group)

			Life course profiles of affective symptoms OR (95% CI)		
			Adolescent symptoms only	Adult symptoms only	Adolescent onset and mid adulthood symptoms
Family Instability	Parental Divorce		1.10 (.86;1.40)	1.01 (.79; 1.30).	1.15 (.77;1.70)
	Death of any parent		1.18 (.86; 1.62)	1.14 (.81; 1.59)	1.09 (.67;1.79)
	Break with Mother		.95 (.67; 1.35)	.84 (.59; 1.20)	.98 (.56; 1.72)
	Residential Moves	1 – 3 moves	.94 (.78;1.12)	1.10 (.87; 1.39)	1.18 (.80; 1.75)
		4+ moves	1.15 (.79; 1.66)	1.15 (.79; 1.66)	.90 (.47; 1.69)
Family Socioeconomic circumstances	Fathers Education		1.18 (.94; 1.48)	.84 (.67; 1.05)	.92 (.63; 1.34)
	Mothers Education		1.08 (.86; 1.37)	1.03 (.79; 1.32)	1.26 (.85; 1.87)
	Lack of home amenities	Lacks 2 or 3	1.11 (.88; 1.40)	1.23 (.96; 1.59)	.98 (.75; 1.28)

		Lacks 4+	1.11 (.88;1.41)	1.24 (.96; 1.60).	.65 (.42; 1.01).
	Crowding	1 – 2 ½ people per room	1.01 (.84; 1.22)	.97 (.79; 1.18)	1.00 (.72; 1.39)
		3+ people per room	1.14 (.71; 1.84)	.90 (.51; 1.60)	**1.90 (1.06; 3.42)***
	Father's occupational status		1.00 (.83; 1.20)	1.04 (.86; 1.27)	1.05 (.76; 1.46)
	Family Size		1.10 (.90; 1.35)	1.00 (.80; 1.26)	1.06 (.74; 1.51)
Parents age	Older aged father		1.17 (.86; 1.59)	1.07 (.76; 1.50)	1.13 (.66; 1.94)
	Older aged mother		.86 (.47; 1.57)	1.54 (.92; 2.60)	.94 (.34; 2.62)
Childrearing and Parenting	Breastfeeding	Breastfed for 1-4 months	1.05 (.85; 1.28)	1.19 (.96; 1.49)	.96 (.67; 1.36)
		Never breastfed	1.16 (.93; 1.45)	1.32 (1.04; 1.68)	.83 (.55; 1.26)
	Mothers management and understanding		.91 (.75; 1.09)	.94 (.77; 1.14)	.99 (.71; 1.37)
	Paternal neglect (PBI)		.82 (.63; 1.06)	1.04 (.80; 1.35)	.66 (.43; 1.00)
	Maternal neglect (PBI)		1.04 (.81; 1.34)	1.20 (.93; 1.55)	.97 (.66; 1.43)

	Parent's interest in child education	Average interest in education	.86 (.64; 1.14)	1.18 (.89; 1.56)	.89 (.54; 1.48)
		Low interest in education	1.32 (1.02; 1.72)	1.02 (.77; 1.36)	1.50 (.96; 2.34).
	Cleanliness of child (1950)		.98 (.81; 1.18)	.91 (.74; 1.11)	.98 (.71; 1.37)
	Cleanliness of house (1950)		.97 (.80; 1.17)	.90 (.73; 1.10)	1.13 (.82; 1.56)
	Clothes repair (1950)		.61 (.27; 1.35)	1.16 (.60; 2.24)	.31 (.04; 2.25)
	Shoes repair (1950)		1.28 (.69; 2.38)	.90 (.50; 1.62)	.69 (.30; 1.63)
Parental Health	Fathers perceived health	Average	1.07 (.89; 1.28)	1.02 (.84; 1.23)	**1.44 (1.09; 1.91)***
		Poor	1.05 (.85; 1.30)	.82 (.64; 1.38)	1.13 (.80; 1.59)
	Mother perceived health	Average	1.09 (.91; 1.31)	1.29 (1.02; 1.63)	1.07 (.79; 1.45)

		Poor	1.09 (.89; 1.34)	.90 (.72; 1.12)	**1.44 (1.05;1.97)***
	Maternal neuroticism		.86 (.46; 1.61)	1.07 (.57; 1.10)	1.54 (.65; 3.63)
Childhood Health	Birth Weight	>4000 grams	1.00 (.77; 1.29)	1.01 (.77; 1.32)	1.10 (.68;1.79)
		2500 or less grams	.86 (.61; 1.22)	1.08 (.77;1.53)	1.40 (.79; 2.47)
	Chronic Illness		1.03 (.92; 1.38)	**1.36 (1.11; 1.67)****	1.06 (.76; 1.46)

N = 4974. *** $p < .001$; ** $p < .01$; * $p < .05$

For the accumulation of early life risk factors (ACEs), the one-way ANOVA did not reveal a significant difference between the number of cumulative early life events across the four affective symptom profiles, $F(3) = .413$, $p = .743$; Table 5.5)

In addition, the association analyses were run using a sub-sample ($n = 4302$) excluding those who died by age 69 ($n = 672$) (see supplementary Table 5.5). Results revealed that for the profile of symptoms in adolescence only, no early life predictors were identified. For the profile of symptoms in adulthood only, two early life predictors –family size and childhood chronic physical illness– were identified. Those who grew up in a family with 4 or more children were 1.33 times more likely to develop adult symptoms only compared to those who grew up in a family with 3 or fewer children ($b = .28$, Wald $\chi^2 = 6.26$, $p = .012$); and those who experienced childhood chronic illness were 1.36 times more likely to develop adolescent symptoms only compared to those who did not experience childhood chronic illness ($b = .31$, Wald $\chi^2 = 6.19$, $p = .013$). For the profile of symptoms in adolescence and adulthood, no early life predictors were identified.

Table 5.5. A cumulative ACE score across four life course profiles of affective symptoms: means and standard deviations (SD)

	Absence of symptoms	**Adolescent symptoms only**	**Adult symptoms only**	**Adolescent onset and mid adulthood symptoms**	**Total**
N	3315	259	757	643	4974
Mean (SD)	5.78 (2.92)	5.86 (2.95)	5.76 (2.97)	5.95 (2.30)	5.79 (2.93)

5.5. Discussion

The present study derived latent profiles of affective symptoms from adolescence (age 13) through to older adulthood (age 69) using assessments at seven time points (i.e., at ages 13, 15, 36, 43, 53, 60-64 and 69). Four distinct trajectories of affective symptoms were identified. The first and largest group indicated those who had no symptoms across the life course. The second group indicated those who had symptoms in adolescence only. The third group consisted of those who had symptoms in adulthood only. The fourth group consisted of those who had symptoms in both adolescence and mid adulthood. Notably, affective symptoms declined markedly after age 64, with almost all participants converge to low level of affective symptoms in late adulthood.

These findings are consistent with prior evidence that found that affective symptoms are heterogeneous over the life course. For example, Musliner, Munk-Olsen, Eaton and Zandi (2016) conducted a systematic review of studies investigating longitudinal trajectories of depressive symptoms. In line with the present study, most studies included in the review (k = 25) identified either three or four distinct trajectories that varied in terms of severity and stability across of maximum period of 23 years (Musliner et al., 2016). The present study adds to the existing research by identifying four different trajectories of affective symptoms from early period of life (age 13) through late adulthood (age 69), with the longest period of follow-up (>50 years) to date.

Interestingly, our findings differ from the previous study using NSHD data (Colman et al. 2007) that also utilised latent class analysis approach to affective symptoms measured at five time-points (at ages 13, 15, 36, 43, and 53). In this study, a six-class solution, rather than a four-class solution, was the best fit for the data.

Interestingly, Colman et al. (2007) identified a profile with repeated moderate symptoms across the life course (33.6% of participants). Of note, in the present study, we did not identify a profile with repeated affective symptoms across all seven time points. On the contrary, we showed that symptoms decrease for all the participants after age 60-64. Similarly to our finding, another study that focused on adult affective symptoms from age 19-20 across three decades of life (Paksarian et al., 2016) demonstrated that persistent affective symptoms across the life course are not common.

Nevertheless, some consistencies were observed between the patterns of symptom profiles identified in the present study based on seven time points (across the period from age 13 through 69) and in the previous study by Colman et al. (2007) based on measures at five time-points (from age 13 through age 53). First, both studies showed that the profile with no affective symptoms had the largest number of people. Second, both studies identified the profile with adolescent symptoms only and the profile with adult symptoms only. Third, although a profile with repeated symptoms (across all seven time-points) was not revealed in the present study, a profile with persistent symptoms from adolescence through to mid adulthood was found which is consistent with the findings by Colman et al. (2007). These differences between the two studies are largely due to the observed decline of affective symptoms after age 60-64. The convergence of most participants of NSHD to low levels of affective symptomatology resulted in less life course heterogeneity for the surviving sample at age 69 compared to the heterogeneity at age 53 which was reflected in the fewer - compared to the study by Colman et al. (2007) - latent groups that were needed to fully captured heterogeneity up to age 69. Considering that we were able the replicate the findings of Colman et al. (2007) up to age 53

(results available from corresponding author upon request), the discrepancy in the number of profiles between the two studies implies that life course stage specific longitudinal typologies are needed to appropriately capture heterogeneity in affective symptomatology over time.

The present study extended the previous work by exploring a wide range of early life risk factors, across six different domains, and the accumulation of these factors, for associations with identified life course profiles of affective symptoms. These domains were family instability, family socio-economic status, parental age, childrearing environment and parenting, parental health and child's health. Across these domains, twenty-four early life predictors were investigated in total. No associations between cumulative early life factors and life course profiles of affective symptoms were found. Moreover, only four early life risk factors: childhood chronic illness, residential overcrowding, and mothers and father perceived ill health, were associated with different life course profiles of affective symptoms. These findings are consistent with previous evidence that shows childhood chronic illness, residential overcrowding and parental ill health to be associated with poor mental health and wellbeing outcomes (Evans et al., 2003; Secinti et al., 2017; Stafford et al., 2015). Of note, the effect sizes for early life predictors identified as significant in the present study were relatively small. However, as anxiety and depression have high population prevalence, we argue that these results have high public health importance. Moreover, drawing on previous literature, we acknowledge that a number of previously identified early life risk factors for anxiety and depression (Clark et al., 2010) were not significantly associated with life course profiles of affective symptoms in the present study. Specifically, early life risk factors, such as parental divorce (Sands et al., 2017), parental loss (Otowa et al., 2014; Tyrka et al.,

2008) and parental psychopathology (Wickramaratne & Weissman, 1998), have been extensively examined in this context. However, the majority of these studies rely on retrospective reports of early life events, which may be subject to recall bias. As such, not many studies have investigated associations between prospectively collected early life predictors and life course profiles of affective symptoms. Moreover, the majority of these studies investigated mental health outcomes at a single time point, and therefore the results may not be comparable when considering life course trajectories of affective symptoms.

The present study has a number of strengths and limitations. First, prospectively collected data on affective symptoms at seven time points from a nationally representative sample of British population born in 1946 were utilized in the present study. Another notable strength of the study was the length of follow (>50 years) up to age 69 years. These two unique attributes of the study allowed for the first time to model life course trajectories of affective symptoms from adolescence through late adulthood. Another strength of the present study was a wide range of prospectively measured early life risk factors used to predict different symptom trajectories.

In order to identify homogeneous sub-populations with varying trajectory parameters, a group-based trajectory modelling was employed. As this method of analysis predicts posterior probability of being assigned to a certain 'class', all the data available at each time point was included in the analysis. This approach minimised the amount of missing data when estimating the latent classes. However, one limitation of latent class analysis is that the outcomes (i.e. the latent classes) are approximations of symptom patterns, and do not represent actual data points. However, the classes derived can be viewed as evidence based approximations which

can be used to infer a valid representation symptom patterns in the population. Due to the different measures used at each time point, the trajectories could not be compared with repeated measures modelling of the data.

In conclusion, this study identified four life course profiles of affective symptoms: 1) absence of symptoms (66.6% of the sample); 2) adolescent symptoms with good adult outcome (15.2%); 3) adult symptoms only (with no symptoms in adolescence and late life) (12.9%); 4) symptoms in adolescence and mid adulthood (5.2%). Of note, the life course profiles indicate that affective symptom trajectories converge to low symptom levels at ages 64 and 69 years. Among the 24 early life risk factors tested, only four were significantly associated with affective symptoms profiles: childhood chronic illness was associated with adult symptoms only; whereas growing up in an overcrowded house and parental poor perceived health were associated with symptoms in adolescence and adulthood. However, no associations were found for twenty of the early life predictors. These findings demonstrate that people differ in terms of their life course symptoms of anxiety and depression, and that these differences are not largely influenced by early life risk factors. Understanding the role of risk factors that influence the development of heterogeneous affective symptom trajectories may help professionals to establish appropriate times for intervention and builds upon our knowledge of why symptoms develop, persist or diminish over time.

Chapter 6

General discussion

Affective disorders are highly prevalent over the life course and can impact cognitive and physical health, social functioning and personal relationships. It has been recognised that affective disorders are heterogeneous and change over time (Mars et al., 2015; Musliner et al., 2016; Paksarian et al., 2016). A growing body of evidence suggests that specific adverse childhood experiences (ACEs), including both socio-economic and psychosocial adversities, as well as their accumulation, have a long-term impact on affective symptoms (Evans et al., 2003; Secinti et al., 2017; Stafford et al., 2015). The overarching aim of this thesis was to examine effects of a wide range of single ACEs and their accumulation on affective symptoms across the life course. The thesis consists of four studies which together address this overarching aim. The main objective of this chapter is to synthesise and summarise the evidence from each study, discuss their key findings and implications, before acknowledging the strengths and limitations of the research area in general, along with providing some suggestions for future research.

6.1. Summary of findings

In Study 1, a systematic literature review and meta-analysis of prospective studies that investigate associations between single family-related ACEs: parental divorce, parental psychopathology, childhood maltreatment, sexual abuse and family conflict, and cumulative family-related ACEs, and adult affective symptoms was conducted. Through synthesising effect sizes from 42 eligible studies using a multilevel meta-analysis, it was revealed that all single types of ACEs were associated with an increased risk of affective symptoms in adulthood. Notably, the strengths of association were observed to vary across different types of ACEs, however differences between effect sizes were not statistically significant. These findings demonstrate that ACEs pose risk for affective symptoms beyond childhood

and adolescence, and that this risk may vary depending on the type and number of ACEs. The findings of the systematic review and meta-analysis also highlight key gaps in the current literature. Firstly, most of the prospective studies identified focus on the association between single types of ACEs and affective symptoms in adulthood. Only five prospective studies investigated the effects of cumulative ACEs, and through synthesising the effect sizes from these studies, it was demonstrated that accumulation of ACEs was one of the strongest predictors of adult affective symptoms.

In order to illuminate these findings further, in Study 2, a review of recent advances of cross-sectional, case-control and prospective studies investigating the association between cumulative ACEs and affective disorders in adulthood was conducted. Across 32 eligible studies identified, 24 studies found a linear association between the number of ACEs and adult depression, eight studies identified a linear association between the number of ACEs and adult anxiety, and three studies tested and identified a linear association between the number of ACEs and adult unspecified affective symptoms. This shows strong evidence for a linear association between cumulative ACEs and affective disorders in adulthood. However, it was noted that a range of different assessments of ACEs and adult affective symptoms were used in past studies, with the majority of these studies focusing on a single time point in adulthood (predominantly in young adulthood), therefore it remained unclear whether the associations between cumulative ACEs and affective disorders may differ across the life course, particularly whether the association weakens or strengthens with age.

Study 3 addressed this gap by investigating the effects of cumulative ACEs on affective symptoms across the life course using data from the British 1946 birth

cohort. In total, 24 family-related ACEs across six domains: family instability, family socio-economic status, parental age, childrearing environment and parenting, parental health and child's health) were summed to create a cumulative ACE score. Associations between a cumulative ACE score and an affective symptoms score, and severity: no symptoms, mild symptoms, moderate symptoms, and severe symptoms, were investigated from childhood through late adulthood (i.e., at ages 13, 15, 36, 43, 53, 60-64 and 69). Findings showed that a higher cumulative ACE score was associated with a higher score of affective symptoms and the risk of severe affective symptoms in late adulthood (ages 60-64 and 69), but not at earlier ages. These findings indicate that the risk of affective symptoms in those who experienced multiple ACEs persists beyond childhood and adolescence, and may be more pronounced in late adulthood. In line with the previous research, the observed associations in late adulthood were linear indicating that as ACEs accumulate the level of affective symptoms increases.

Study 4 applied a life course approach to affective symptoms in order to capture how symptoms changed over time and whether early life risk factors influenced these changes. This study utilised the wealth of data on affective symptoms available at the British 1946 birth cohort in order to model life course profiles of affective symptoms (from age 13 through age 69) and to investigate their associations with 24 ACEs and a cumulative ACE score. Four life course profiles of affective symptoms were identified with latent class analysis: no symptoms, adolescent symptoms only, adult symptoms only, and adolescent and adult symptoms. Association analyses revealed only four associations with identified life course profiles of affective symptoms. Specifically, the presence of chronic childhood illness was associated with the profile with adult symptoms only; whereas parental poor

perceived health and living in an overcrowded house were associated with the profile with both adolescent and adult symptoms. Sex differences were not found to significantly moderate any of the associations. This finding is consistent with previous studies, using the NSHD that did not find sex differences when testing associations between ACEs and life course affective symptoms (Caleyachetty et al., 2017; Colman, Ploubidis, et al., 2007). No associations between a cumulative ACE score and life course profiles of affective symptoms were found. These findings demonstrate that affective symptoms are heterogeneous across the lifespan, and that differences in life course trajectories of affective symptoms are unlikely to be explained by early life factors.

6.2. Strengths and limitations

A key strength of the present thesis is the prospective longitudinal nature of the data reviewed (Studies 1 and 2) and utilised (Studies 3 and 4). As revealed by Studies 1 and 2, very few previous studies have used longitudinal data in order to investigate the effects of cumulative ACEs on affective symptoms in adulthood, with the majority of studies relying on retrospective recall of ACEs (Chapman et al., 2004; Felitti et al., 1998; Green, 2010; Kessler et al., 2010). One important limitation of cross-sectional studies is that these studies cannot give rise to the temporal relationship between ACEs and affective symptoms, thus limiting potential inferences about causality. Moreover, the validity of retrospective self-reported recall has been widely criticised, as individuals with affective symptoms may be more, or less, likely to report previous adverse events (Williams & Scott, 2009). This is problematic as it has previously been found that the memory of an ACE, rather than the ACE itself, can be differentially associated with affective symptoms in adulthood (Afifi et al., 2009; Reuben et al., 2016). For example, significant associations

between ACEs and adult outcomes have been found to be stronger when retrospective measures, compared to prospective measures, were used (Reuben et al., 2016). It is suggested that observed differences between retrospective and prospective reports of ACEs can be due to potential bias from those with affective symptoms when reporting ACEs (Bernet & Stein, 1999; Hardt & Rutter, 2004).

Another strength of the present thesis is the focus on the role of multiple ACEs and their accumulation on affective symptoms over the life course. Previous strengths of this approach have been outlined in the Introduction (Horan & Widom, 2014a). Briefly, examining cumulative risk through summing the number of ACEs acknowledges that childhood adversities tend to accumulate and increases statistical power where some ACEs are rarely reported or experienced. Furthermore, formulating a composite metric of cumulative ACEs may also reduce measurement error (Evans, 2003; Flouri et al., 2010).

Moffitt et al. (2010) outlies two ways in which prospective longitudinal data on mental health offer an advantage over official records and cross-sectional survey data. Firstly, birth cohort population based data capture individuals who are experiencing mental health symptoms but are not using mental health services; secondly, prospectively collected data does not rely on prevalence rates using retrospective reports. As discussed in detail in the Introduction and Chapter 5, birth cohort data are also particularly valuable as they can be utilized to investigate the life course profiles of affective disorders that differ in the onset, severity and persistence of the symptoms.

Another specific strength of this thesis is the exceptional length of the follow-up period: data on affective symptoms utilised in Studies 3 and 4 were available from adolescence (age 13) through late adulthood (age 69). These data and the advanced

group-based latent variable modelling used (i.e. latent class analysis) allowed the identification of homogeneous sub-groups with varying trajectories of life course affective symptoms. Latent class analysis predicts posterior probability of being assigned to a certain 'class', allowing all the data, available at each time point, to be included in the analysis. This approach to modelling symptom trajectories can be particularly beneficial when using birth cohort data as it minimises the amount of missing data when estimating the latent classes.

However, there are a number of limitations of the present research that need to be acknowledged. First, a cumulative ACE score that has been widely used in previous research reviewed in Study 2, as well as in Studies 3 and 4, of the present thesis is based on the number of ACEs experienced rather than the severity or type of ACEs. Notably, this approach fails to distinguish between distinct types of adverse experiences, implicitly assuming that different ACEs influence development of affective disorders through the same underlying mechanisms. Previous shortcomings of this approach have been noted including the loss of information on risk intensity for each ACE (Evans et al., 2013). Moreover, a recent study has shown differences in effect sizes between acute (e.g., parental divorce, separation from parents) and chronic stressors (e.g., socio-economic adversity) (Colman et al., 2014). As the cumulative ACE score used in this thesis included both acute (i.e., parental death) and chronic (i.e., childhood chronic illness) ACEs, findings should be taken tentatively as the respective impact of specific ACEs on the outcome could have been under or overestimated. In future, it is suggested that weighting each ACE based on pre-determined effect sizes could improve the accuracy of results (Roy & Raver, 2014).

Moreover, as shown in Study 1, childhood abuse was the strongest risk factor for adult affective disorders. However, child abuse was not measured in the British 1946 birth cohort, and therefore was not included as an early life risk factor in Studies 3 and 4. Therefore, it is suggested that the cumulative ACE score derived in the thesis might not capture the breath of childhood adversity experienced, and thus associations between ACEs and subsequent affective symptoms may have been underestimated.

Furthermore some of the early life factors or predictors available in the NSHD and utilised for studies 3 and 4 differed from those identified during the screening process for studies 1 and 2. For example, in studies 1 and 2 specific types of adverse childhood experiences, such as childhood maltreatment and parental death, were considered. Whereas in studies 3 and 4, less extreme types of early life experiences were investigated, including indicators of family socio-economic position (e.g. fathers' social class; lack of home amenities) and indicators of childhood rearing and parenting environment (e.g.. mothers management and understanding; parents interest in child's education). As a result of this discrepancy between early life factors or predictors presented in these chapters, different terms are used: early life factors or predictors are referred to as adverse childhood experiences in studies 1 and 2.

Another important limitation that is unavoidable for the long-running studies such as British 1946 birth cohort is missing data. In order to deal with missing data in this thesis, a multiple imputation technique was used to impute missing data on each ACEs before computing the cumulative ACE score. However, multiple imputation is a data driven method which used the distribution of data, as well as information from other included variables in the data set (auxiliary variables) to impute missing data.

A notable strength of using multiple imputation is that missing values are dealt with prior to the analysis (Schafer & Graham, 2002). This was beneficial as it allowed additional data (e.g., cognitive ability and education attainment) that were not used for the analysis, be included as auxiliary variables when imputing the missing values.

Finally, potential limitations of the latent variable modelling used need also be acknowledged. First, the derived latent classes are approximations of symptom patterns, and do not represent actual data points. However, the classes derived can be viewed as evidence based approximations which can be used to infer a valid representation of symptom patterns in the population. Second, due to the different measures of affective symptoms collected at each time point in the NSHD, the trajectories could not be compared with repeated measures modelling of the data.

The current thesis builds upon the evidence from existing prospective longitudinal studies. Through reviewing and synthesising effect sizes from these studies, single and cumulative ACEs were found to significantly predict affective symptoms in adulthood (see chapter 2). However, publication bias was identified when synthesising effects and results were no longer found to be significant when 'missing' effect sizes were included in the analyses. Consequently, findings from Chapter 2 should be taken tentatively (as no effect may exist within the population). Moreover, this highlights the importance of using platforms such as the Open Science Framework (OSF) to encourage and increase the publication and dissemination of null findings.

The majority of existing studies originated in developed countries such as the USA, the UK, and New Zealand. Of note, the patterns of associations may be different in developing countries. Moreover, the NSHD is representative of the

British population born in 1946, and the results may not be generalised to the contemporary British population of the same age.

6.3. Plausible mechanisms

This thesis adds to the growing body of evidence on the long term association between single and cumulative ACEs on affective problems across the life course. This research is extremely useful in identifying individuals who may have an increased vulnerability to developing maladaptive outcomes and generating preventative methods. However, one important acknowledgment is that the findings of this thesis do not imply causality. One reason for this is that most studies have not rigorously ruled out plausible confounding factors which could be completing explanations for the statistical associations found (D'Onofrio et al., 2014; Lahey, D'Onofrio, & Waldman, 2009). For example, epidemiological studies may overestimate the magnitude of the effect because genetic factors may account for part of the association. In order to combat this, some researchers suggest that quazi-experimental designs should be used as they rely on design features rather than relying on statistical controls (D'Onofrio et al., 2014). Secondly, association studies do not explain the underlying mechanisms through which risk factors influence the likelihood of an outcome. Respectively, researchers who are interested in these processes tend to investigate risk mechanisms, which describe the intervening paths that link the risk factor to the outcome of interest.

Mechanisms of action that may mediate the impact of ACEs on the presence, severity and chronicity of affective disorders need to be addressed.

Multiple plausible mechanisms underlying the link between ACEs and affective symptoms have been proposed. A recent review of the studies in this field suggests that exposure to ACEs leads to changes in development of nervous,

endocrine, and immune systems, resulting in impaired cognitive, social, and emotional functioning and increased allostatic load (Danese & McEwen, 2012b).

Previously, the concept of allostatic load has been introduced as a comprehensive neurobiological model of the effects of stress (McEwen, 2000). Allostatic load is based on the idea of allostasis, the viewpoint that multiple physiological regulatory systems are constantly adjusting to the demands of the environment in order to activate specific adaptive responses. Over time, the process of ongoing adaptation can lead to alterations in physiological systems (namely the nervous, the endocrine, and the immune systems), which may cause them to lose their ability to function efficiently and effectively in the face of persistent needs to adapt. The concept of allostatic load refers to physiological dysregulation in multiple biological systems, as the cumulative toll that the body pays for adaptation efforts. Thus, allostatic load represents a higher order construct of collected dysregulations across the major biological regulatory systems (Taylor, Way, & Seeman, 2011; Lupien et al., 2006) that have been found to lead to the development of affective disorders (Danese & McEwen, 2012b; Evans, 2003).

One of the important direct mechanisms that can contribute to allostatic load and the development of affective disorders is dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Specifically, the HPA axis mediates changes in hippocampal architecture, neuroendocrine-induced alterations in lipid metabolism, hemodynamics, and translocation of immune cells are among the hypothesised underlying mechanisms causing such shifts in bodily efficiency for coping with stressors (McEwen, 2000). More recently, evidence has shown that ACEs are linked to differences in biological risk profiles (Koss & Gunnar, 2017). For example, there is evidence that offspring of depressed mothers are at risk of heightened activity of

the HPA axis (Lupien, King, Meaney, & Mcewen, 2000). Moreover, there is evidence that children as young as 10–13 years show increased activation of major stress response systems in response to chronic stress in childhood (Evans & English, 2002).

These recent findings are consistent with the earlier theories which attempted to explain how risk factors can lead to an increase in vulnerability to affective disorders. Diathesis-stress theory (Monroe & Simons, 1991) posits that not all individuals are equally susceptible to negative influences of environmental stressors. Specifically, it suggests that genetic factors serve as vulnerability factors through predisposing individuals who are experiencing one or more stressful life events (e.g., financial difficulties, family crises), to be more susceptible to the development of affective problems (Hammen et al., 2000; Hazel, Hammen, Brennan, & Najman, 2008). For example, genetic variants implicated in regulating the HPA axis have been found to increase risk for psychopathology in the context of environmental risk (Velders et al., 2012).

Another mechanism of action that attempts to explain the association between ACEs and later life affective problems is termed the ‘kindling’ effects (and sometimes referred to as stress sensitisation and stress amplification theories). This theory posits that ACEs increase vulnerability to the influence of stressors which occur later in the life course (Rudolph & Flynn, 2011; Rutter, Kim-Cohen, & Maughan, 2006). Evidence for this theory is demonstrated through findings which show that the effect of ACEs are mediated by stressful life events throughout adulthood.

However, it should be noted that not everyone who faces early adversity will experience mental health problems later in life. This phenomenon is known as

resilience (Rutter, 2003, 2007). The concepts of vulnerability and resilience are interrelated, and it has been a focus of recent research to identify some protective factors and mechanisms that can improve the outcomes for those children and adolescents who are at particular high risk for persistent negative outcomes. For example, a number of factors that can protect versus negative effects of maternal depression in adolescents have been identified, including perceived parental care, adolescent peer relationships (Collishaw et al, 2017). This line of research can be expanded in future to identify protective factors beyond childhood and adolescence that can be targeted to promote better mental health outcomes in adults with ACEs.

6.4. Potential implications

Understanding the role of early life risk factors in the development of affective disorders allows professionals to establish appropriate times for intervention and builds upon our knowledge of why affective symptoms develop, persist and diminish over time. The findings from this thesis add to the growing body of literature with a focus on the association between ACEs and affective problems across the life course.

Based on the accumulating evidence, it has already been proposed that, in order to prevent mental health problems, early intervention strategies should focus on the detection of, and reduction in exposure to ACEs and on building resilience in children and adolescents who experience adversities and trauma (Department of Health, 2009). However, there has been little effort in finding ways of helping adults who experienced various ACEs.

For example, the prevalence of different ACEs in users of mental health services, such as a primary care Improving Access to Psychological Therapies (IAPT) service, is unknown as this information is not routinely collected. Moreover,

very few studies have tested for associations of ACEs with the outcomes of and engagement with psychological treatments for depression and/or anxiety (Nanni et al., 2012). And limited conclusions can be drawn from the existing studies because of their small sample sizes and lack of control for factors that are important for adversity-driven outcomes, (e.g., types of adversities, their co-occurrence, and other potential confounders in childhood and adulthood).

Consistent with previous evidence for associations between single types of ACEs and subsequent affective symptoms, findings from Chapter 2 indicate that specific single types of ACEs are associated with adult affective symptoms. Specifically, subgroup analyses revealed that all specific single ACEs were positively associated with adulthood affective symptoms with pooled effect sizes ranging from small to medium. Notably, sexual abuse, was the highest risk factor for affective symptoms in adulthood. However and of note, effect size differences for ACE types were found to be not statistically significant. Moreover, it is known that multiple ACEs tend to co-occur, and that individuals with multiple ACEs can be at particular high risk of negative outcomes, including high risk of affective symptoms (Chapters 2 and 3). This observation has important implications for prevention and intervention strategies as it suggests that the amelioration of a single ACE might not benefit individuals' exposed to multiple types of adversity. Identifying biopsychosocial processes that are disrupted by multiple ACEs can aid better intervention strategies to prevent the onset of problems or mitigate these problems in individuals who have experiences ACEs.

However, as proposed recently, different forms of ACEs may need to be conceptualised differently, along distinct dimensions (threat versus deprivation), that may have different effects on neurodevelopment and learning mechanisms that are

crucial for later mental health (McLaughlin & Sheridan, 2016). Further empirical research using prospective longitudinal studies will be crucial in illuminating the effects of different types of ACEs on lifelong mental health and will aid the development of novel more effective preventive strategies and treatments for affective disorders in those with ACEs.

6.5. General conclusion

The present thesis addresses an important gap in the literature through investigating the long-term effects of single and cumulative ACEs on affective symptoms across the life course. Specifically, this thesis provides a comprehensive review of the existing evidence for the role of ACEs in adult affective symptoms (Studies 1 and 2). This thesis also extends the previous evidence by investigating associations between prospectively measured ACEs and affective symptoms from adolescence through late adulthood. Specifically, findings of Study 3 indicate that people who experience higher number of ACEs are at an increased risk of affective symptoms in late adulthood. These findings suggest that childhood adversity can have long lasting effects on affective disorders that may not be manifested until much later in life. As such, findings have the implications for older adults as this group may be particularly vulnerable and may benefit from specifically targeted preventive interventions. Interestingly, however, four distinct life course profiles of affective symptoms derived in Study 4 of this thesis provided little evidence to support the role of early life risk factors in these profiles. However, due to limitations of modelling approaches used in the present thesis, such as a summary score approach to accumulation of ACEs and latent class analysis to life course profiles of affective symptoms, further research is needed in order to elucidate the role of co-occurring and cumulative ACEs on affective problems across the life course.

Nevertheless, the research included in the thesis adds to the existing body of literature examining the role of adverse childhood experiences in affective disorders, by investigating the effects of a wide range of prospectively collected ACEs on affective symptoms measured at multiple time points across the extended follow-up period, from adolescence through late adulthood.

References

Abrams, R. C., Lachs, M., McAvay, G., Keohane, D. J., & Bruce, M. L. (2002). Predictors of self-neglect in community-dwelling elders. *American Journal of Psychiatry*, *159*(10), 1724–1730. http://doi.org/10.1176/appi.ajp.159.10.1724

Adams, K. B., Sanders, S., & Auth, E. A. (2004). Loneliness and depression in independent living retirement communities: Risk and resilience factors. *Aging and Mental Health*, *8*(6), 475–485. http://doi.org/10.1080/13607860410001725054

Afifi, T. O., Boman, J., Fleisher, W., & Sareen, J. (2009). The relationship between child abuse, parental divorce, and lifetime mental disorders and suicidality in a nationally representative adult sample. *Child Abuse & Neglect*, *33*(3), 139–47. http://doi.org/10.1016/j.chiabu.2008.12.009

Agorastos, A., Pittman, J. O. E., Angkaw, A. C., Nievergelt, C. M., Hansen, C. J., Aversa, L. H., … Baker, D. G. (2014). The cumulative effect of different childhood trauma types on self-reported symptoms of adult male depression and PTSD, substance abuse and health-related quality of life in a large active-duty military cohort. *Journal of Psychiatric Research*, *58*, 46–54. http://doi.org/10.1016/j.jpsychires.2014.07.014

Ahern, E., & Semkovska, M. (2017). Cognitive Functioning in the First-Episode of Major Depressive Disorder: A Systematic Review and Meta-Analysis. *Neuropsychology*, *31*(1), 52–72. http://doi.org/10.1037/neu0000319

Amato, P. R., & Keith, B. (1991). Parental Divorce and Adult Well-Being: A Meta-Analysis. *Journal of Marriage and the Family*, *53*(1), 43. http://doi.org/10.2307/353132

Anda, R. F., Whitfield, C. L., Felitti, V. J., Chapman, D., Edwards, V. J., Dube, S.

R., & Williamson, D. F. (2002). Adverse Childhood Experiences, Alcoholic Parents, and Later Risk of Alcoholism and Depression. *Psychiatric Services*, *53*(8), 1001–1009. http://doi.org/10.1176/appi.ps.53.8.1001

Appleyard, K., Egeland, B., van Dulmen, M. H. M., & Sroufe, L. A. (2005). When more is not better: The role of cumulative risk in child behavior outcomes. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *46*(3), 235–245. http://doi.org/10.1111/j.1469-7610.2004.00351.x

Arata, C. M., Langhinrichsen-rohling, J., Bowers, D., Farrill-swails, L. O., Langhinrichsen-rohling, J., & Farrill-swails, L. O. (2005). Single versus Multi-Type Maltreatment Single versus Multi-Type Maltreatment : An Examination of the Long-Term Effects of Child Abuse, *6771*(August). http://doi.org/10.1300/J146v11n04

Arboleda-Florez, J., & Wade, T. J. (2001). Childhood and adult victimization as risk factor for major depression. *International Journal of Law and Psychiatry*, *24*(4–5), 357–370. http://doi.org/10.1016/S0160-2527(01)00072-3

Bauer, D. J., & Curran, P. J. (2004). The integration of continuous and discrete latent variable models: potential problems and promising opportunities. *Psychological Methods*, *9*(1), 3–29. http://doi.org/10.1037/1082-989X.9.1.3

Beaumont, J., & Lofts, H. (2013). Measuring National Well-being - Health , (June), 1–14.

Beck, A. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry*, *165*(8), 969–977. http://doi.org/10.1176/appi.ajp.2008.08050721

Bellis, M. a., Hughes, K., Leckenby, N., Hardcastle, K. a., Perkins, C., & Lowey, H. (2014). Measuring mortality and the burden of adult disease associated with

adverse childhood experiences in England: a national survey. *Journal of Public Health*, 1–10. http://doi.org/10.1093/pubmed/fdu065

Bellis, M. A., Hughes, K., Leckenby, N., Perkins, C., & Lowey, H. (2014). National household survey of adverse childhood experiences and their relationship with resilience to health-harming behaviors in England. *BMC Medicine*, *12*(1). http://doi.org/10.1186/1741-7015-12-72

Berens, A. E., Jensen, S. K. G., & Iii, C. A. N. (2017). Biological embedding of childhood adversity : from physiological mechanisms to clinical implications, 1–12. http://doi.org/10.1186/s12916-017-0895-4

Bernet, C. Z., & Stein, M. B. (1999). Relationship of childhood maltreatment to the onset and course of major depression in adulthood. *Depression and Anxiety*, *9*(4), 169–174. http://doi.org/10.1002/(SICI)1520-6394(1999)9:4<169::AID-DA4>3.0.CO;2-2

Bifulco, A., Brown, G. W., Moran, P., Ball, C., & Campbell, C. (1998). Predicting depression in women: the role of past and present vulnerability. *Psychological Medicine*, *28*(1), 39–50. http://doi.org/10.1017/S0033291797005953

Bifulco, A., Moran, P. M., Baines, R., Bunn, A., & Stanford, K. (2002). Exploring psychological abuse in childhood: II. Association with other abuse and adult clinical depression. *Bulletin of the Menninger Clinic*, *66*(3), 241–258. http://doi.org/http://dx.doi.org/10.1521/bumc.66.3.241.23366

Broadhead, W. E., Blazer, D. G., George, L. K., & Tse, C. K. (1990). Depression, Disability Days, and Days Lost From Work in a Prospective Epidemiologic Survey. *JAMA: The Journal of the American Medical Association*, *264*(19), 2524–2528. http://doi.org/10.1001/jama.1990.03450190056028

Brown, D. W., Anda, R. F., Tiemeier, H., Felitti, V. J., Edwards, V. J., Croft, J. B., &

Giles, W. H. (2009). Adverse childhood experiences and the risk of premature mortality. *American Journal of Preventive Medicine*, *37*(5), 389–96. http://doi.org/10.1016/j.amepre.2009.06.021

Buuren, S. van, & Groothuis-oudshoorn, K. (2011). MICE: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*(3).

Cabrera, O. A., Hoge, C. W., Bliese, P. D., Castro, C. A., & Messer, S. C. (2007). Childhood adversity and combat as predictors of depression and post-traumatic stress in deployed troops. *American Journal of Preventive Medicine*, *33*(2), 77–82. http://doi.org/http://dx.doi.org/10.1016/j.amepre.2007.03.019

Caleyachetty, R., Hardy, R., Cooper, R., Richards, M., Howe, L. D., Anderson, E., … Stafford, M. (2017). Modeling Exposure to Multiple Childhood Social Risk Factors and Physical Capability and Common Affective Symptoms in Later Life. *Journal of Aging and Health*, 089826431668043. http://doi.org/10.1177/0898264316680434

Cartwright-Hatton, S., McNicol, K., & Doubleday, E. (2006). Anxiety in a neglected population: Prevalence of anxiety disorders in pre-adolescent children. *Clinical Psychology Review*, *26*, 817–833. http://doi.org/10.1016/j.cpr.2005.12.002

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., … Poulton, R. (2003). by a Polymorphism in the 5-HTT Gene Influence of Life Stress on Depression: Moderation\nAvshalom Caspi, . *Science (New York, N.Y.)*, *301*(5631), 386–389. http://doi.org/10.1126/science.1083968

Chapman, D. P., Whitfield, C. L., Felitti, V. J., Dube, S. R., Edwards, V. J., & Anda, R. F. (2004). Adverse childhood experiences and the risk of depressive disorders in adulthood. *Journal of Affective Disorders*, *82*(2), 217–25. http://doi.org/10.1016/j.jad.2003.12.013

Charles, S. T. (2010). Strength and vulnerability integration: a model of emotional well-being across adulthood. *Psychological Bulletin*, *136*(6), 1068–1091. http://doi.org/10.1037/a0021232

Chung, E. K., Mathew, L., Elo, I. T., Coyne, J. C., & Culhane, J. F. (2008). Depressive Symptoms in Disadvantaged Women Receiving Prenatal Care: The Influence of Adverse and Positive Childhood Experiences. *Ambulatory Pediatrics*, *8*(2), 109–116. http://doi.org/10.1016/j.ambp.2007.12.003

Cicchetti, D., & Toth, S. L. (1998). The Development of Depression in Children and Adolescents. *American Psychologist*, *53*(2), 221–241. http://doi.org/10.1037/0003-066X.53.2.221

Clark, C., Caldwell, T., Power, C., & Stansfeld, S. (2010). Does the influence of childhood adversity on psychopathology persist across the lifecourse? A 45-year prospective epidemiologic study. *Annals of Epidemiology*, *20*(5), 385–94. http://doi.org/10.1016/j.annepidem.2010.02.008

Clark, C., Rodgers, B., Caldwell, T., Power, C., & Stansfeld, S. (2007). Childhood and adulthood psychological ill health as predictors of midlife affective and anxiety disorders: The 1958 British Birth Cohort. *Archives of General Psychiatry*, *64*(6), 668–678. http://doi.org/10.1001/archpsyc.64.6.668

Cohen, P., Brown, J., & Smaile, E. (2001). Child abuse and neglect and the development of mental disorders in the general population. *Development and Psychopathology*, *13*(4), 981–999.

Collishaw, S., Dunn, J., O'Connor, T. G., & Golding, J. (2007). Maternal childhood abuse and offspring adjustment over time. *Development and Psychopathology*, *19*(2), 367–383. http://doi.org/10.1017/S0954579407070186

Collishaw, S., Maughan, B., Natarajan, L., & Pickles, A. (2010). Trends in

adolescent emotional problems in England: A comparison of two national cohorts twenty years apart. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *51*(8), 885–894. http://doi.org/10.1111/j.1469-7610.2010.02252.x

Colman, I., Jones, P. B., Kuh, D., Weeks, M., Naicker, K., Richards, M., & Croudace, T. J. (2014). Early development, stress and depression across the life course: pathways to depression in a national British birth cohort. *Psychological Medicine*, *44*(13), 2845–2854. http://doi.org/10.1017/S0033291714000385

Colman, I., Ploubidis, G. B., Wadsworth, M. E. J., Jones, P. B., & Croudace, T. J. (2007). A longitudinal typology of symptoms of depression and anxiety over the life course. *Biological Psychiatry*, *62*(11), 1265–71. http://doi.org/10.1016/j.biopsych.2007.05.012

Colman, I., Wadsworth, M. E. J., Croudace, T. J., & Jones, P. B. (2007). Forty-year psychiatric outcomes following assessment for internalizing disorder in adolescence. *The American Journal of Psychiatry*, *164*(1), 126–33. http://doi.org/10.1176/appi.ajp.164.1.126

Connelly, R., & Platt, L. (2014). Cohort profile: UK Millennium Cohort Study (mcs). *International Journal of Epidemiology*, *43*(6), 1719–1725. http://doi.org/10.1093/ije/dyu001

Cornwell, E. Y., & Waite, L. J. (2009). Social Disconnectedness, Percived Isolation, and Health among Older Ad. *Jourrnal of Health Sociology Behaviour*, *50*(1), 31–48.

Cuijpers, P., & Smit, F. (2002). Excess mortality in depression: A meta-analysis of community studies. *Journal of Affective Disorders*, *72*(3), 227–236. http://doi.org/10.1016/S0165-0327(01)00413-X

Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008). Psychotherapy for Depression in Adults: A Meta-Analysis of Comparative Outcome Studies. *Journal of Consulting and Clinical Psychology*, *76*(6), 909–922. http://doi.org/10.1037/a0013075

Cuijpers, P., Vogelzangs, N., Twisk, J., Kleiboer, A., Li, J., & Penninx, B. W. (2014). Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *American Journal of Psychiatry*, *171*(4), 453–462. http://doi.org/10.1176/appi.ajp.2013.13030325

D'Onofrio, B. M., Rickert, M. E., Frans, E., Kuja-Halkola, R., Almqvist, C., Sjölander, A., … Lichtenstein, P. (2014). Paternal age at childbearing and offspring psychiatric and academic morbidity. *JAMA Psychiatry*, *71*(4), 432–438. http://doi.org/10.1001/jamapsychiatry.2013.4525

Danese, A., & McEwen, B. S. (2012a). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behavior*, *106*(1), 29–39. http://doi.org/10.1016/j.physbeh.2011.08.019

Danese, A., & McEwen, B. S. (2012b). Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiology and Behavior*, *106*(1), 29–39. http://doi.org/10.1016/j.physbeh.2011.08.019

Das-Munshi, J., Goldberg, D., Bebbington, P. E., Bhugra, D. K., Brugha, T. S., Dewey, M. E., … Prince, M. (2008). Public health significance of mixed anxiety and depression: Beyond current classification. *British Journal of Psychiatry*, *192*(3), 171–177. http://doi.org/10.1192/bjp.bp.107.036707

Disner, S. G., Beevers, C. G., Haigh, E. A. P., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews Neuroscience*, *12*(8), 467–477. http://doi.org/10.1038/nrn3027

Domingue, B. W., Liu, H., Okbay, A., & Belsky, D. W. (2017). Genetic heterogeneity in depressive symptoms following the death of a spouse: Polygenic score analysis of the U.S. Health and retirement study. *American Journal of Psychiatry*, *174*(10), 963–970. http://doi.org/10.1176/appi.ajp.2017.16111209

Done, D. J., Crow, T. J., Johnstone, E. C., & Sacker, A. (1994). Childhood Antecedents of Schizophrenia and Affective-Illness - Social-Adjustment at Ages 7 and 11. *Br Med J*, *309*(6956), 699–703.

Dong, M., Anda, R. F., Felitti, V. J., Dube, S. R., Williamson, D. F., Thompson, T. J., … Giles, W. H. (2004). The interrelatedness of multiple forms of childhood abuse, neglect, and household dysfunction. *Child Abuse and Neglect*, *28*(7), 771–784. http://doi.org/10.1016/j.chiabu.2004.01.008

Driessen, E., Cuijpers, P., de Maat, S. C. M., Abbass, A. A., de Jonghe, F., & Dekker, J. J. M. (2010). The efficacy of short-term psychodynamic psychotherapy for depression: A meta-analysis. *Clinical Psychology Review*, *30*(1), 25–36. http://doi.org/10.1016/j.cpr.2009.08.010

Dube, S. R., Felitti, V. J., Dong, M., Giles, W. H., & Anda, R. F. (2003). The impact of adverse childhood experiences on health problems: Evidence from four birth cohorts dating back to 1900. *Preventive Medicine*, *37*(3), 268–277. http://doi.org/10.1016/S0091-7435(03)00123-3

Dyer, C. B., Kelly, P. A., Pavlik, V. N., Lee, J., Doody, R. S., Pickens, S., … Smith, S. M. (2006). The making of a Self-Neglect Severity Scale. *Journal of Elder Abuse & Neglect*, *18*(4), 13–23. http://doi.org/10.1300/J084v18n04

Elliott, J., & Shepherd, P. (2006). Cohort profile: 1970 British Birth Cohort (BCS70). *International Journal of Epidemiology*, *35*(4), 836–843.

http://doi.org/10.1093/ije/dyl174

Enders, C. K. (2010). *Applied Missing Data Analysis*. *Library*. http://doi.org/10.1017/CBO9781107415324.004

Evans, G. W. (2003). A Multimethodological Analysis of Cumulative Risk and Allostatic Load among Rural Children. *Developmental Psychology*, *39*(5), 924–933. http://doi.org/10.1037/0012-1649.39.5.924

Evans, G. W., Li, D., & Whipple, S. S. (2013). Cumulative risk and child development. *Psychological Bulletin*, *139*(6), 1342–1396. http://doi.org/10.1037/a0031808

Evans, G. W., Wells, N. M., & Moch, A. (2003). Housing and Mental Health: A Review of the Evidence and a Methodological and Conceptual Critique. *Journal of Social Issues*, *59*(3), 475–500. http://doi.org/10.1111/1540-4560.00074

Fallon, B., Trocmé, N., Fluke, J., MacLaurin, B., Tonmyr, L., & Yuan, Y. Y. (2010). Methodological challenges in measuring child maltreatment. *Child Abuse and Neglect*, *34*(1), 70–79. http://doi.org/10.1016/j.chiabu.2009.08.008

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., … Marks, J. S. (1998). Household Dysfunction to Many of the Leading Causes of Death in Adults The Adverse Childhood Experiences (ACE) Study, *14*(4), 245–258.

Fergusson, D. M., McLeod, G. F. H., & Horwood, L. J. (2013). Childhood sexual abuse and adult developmental outcomes: findings from a 30-year longitudinal study in New Zealand. *Child Abuse & Neglect*, *37*(9), 664–74. http://doi.org/10.1016/j.chiabu.2013.03.013

Ferrari, A. J., Charlson, F. J., Norman, R. E., Patten, S. B., Freedman, G., Murray, C. J. L., … Whiteford, H. A. (2013). Burden of Depressive Disorders by Country,

Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Medicine*, *10*(11). http://doi.org/10.1371/journal.pmed.1001547

Flouri, E., Tzavidis, N., & Kallis, C. (2010). Adverse life events, area socioeconomic disadvantage, and psychopathology and resilience in young children: The importance of risk factors' accumulation and protective factors' specificity. *European Child and Adolescent Psychiatry*, *19*(6), 535–546. http://doi.org/10.1007/s00787-009-0068-x

Ford, E., Clark, C., & Stansfeld, S. A. (2011). The influence of childhood adversity on social relations and mental health at mid-life. *Journal of Affective Disorders*, *133*(1–2), 320–7. http://doi.org/10.1016/j.jad.2011.03.017

Fried, E. I. (2017). The 52 symptoms of major depression: Lack of content overlap among seven common depression scales. *Journal of Affective Disorders*, *208*, 191–197. http://doi.org/10.1016/j.jad.2016.10.019

Fujiwara, T., & Kawakami, N. (2011). Association of childhood adversities with the first onset of mental disorders in Japan: results from the World Mental Health Japan, 2002-2004. *Journal of Psychiatric Research*, *45*(4), 481–7. http://doi.org/10.1016/j.jpsychires.2010.08.002

Garber, J. (2006). Depression in Children and Adolescents. Linking Risk Research and Prevention. *American Journal of Preventive Medicine*, *31*, 104–125. http://doi.org/10.1016/j.amepre.2006.07.007

Garcia-Toro, M., & Aguirre, I. (2007). Biopsychosocial model in Depression revisited. *Medical Hypotheses*, *68*(3), 683–691. http://doi.org/10.1016/j.mehy.2006.02.049

Geoffroy, M.-C., Pereira, S. P., Li, L., & Power, C. (2016). Childhood maltreatment and child-to-adulthood cognition and mental health in a prospective birth

cohort, *55*(1), 33–40. http://doi.org/https://doi.org/10.1016/j.jaac.2015.10.012

Gerstorf, D., Ram, N., Mayraz, G., Hidajat, M., Lindenberger, U., Wagner, G. G., & Schupp, J. (2010). Late-Life Decline in Well-Being Across Adulthood in Germany, the UK, and the US: Something is Seriously Wrong at the End of Life. *Psychology and Aging*, *25*(2), 477–485. http://doi.org/10.1037/a0017543

Giovanelli, A., Reynolds, A. J., Mondi, C. F., & Ou, S. (2016). Adverse Childhood Experiences and Adult Well-Being in a Low- income , Urban Cohort, *137*(4). http://doi.org/10.1542/peds.2015-4016

Goldberg, D. P., & Hillier, V. F. (1979). A scaled version of the General Health Questionnaire. *Psychological Medicine*, *9*, 139–145. http://doi.org/10.1017/S0033291700021644

Green, H., McGinnity, A., Meltzer, H., & Ford, T. (2004). *Mental health of children and young people in Great Britain , 2004*. http://doi.org/10.1037/e557702010-001

Green, J. G. (2010). Childhood Adversities and adult psychopathology in the National Comorbidity Survey Replication (NCS-R) I: Associations with first onset of DSM-IV disorders, *67*(2), 1–21. http://doi.org/10.1001/archgenpsychiatry.2009.186.Childhood

Green, K. M., Fothergill, K. E., Robertson, J. a., Zebrak, K. a., Banda, D. R., & Ensminger, M. E. (2013). Early life predictors of adult depression in a community cohort of urban African Americans. *Journal of Urban Health*, *90*(1), 101–115. http://doi.org/10.1007/s11524-012-9707-5

Haaga, D. A., Dyck, M. J., & Ernst, D. (1991). Empirical status of cognitive theory of depression. *Psychological Bulletin*, *110*(2), 215–236. http://doi.org/10.1037/0033-2909.110.2.215

Hammen, C., Henry, R., & Daley, S. E. (2000). Depression and sensitization to stressors among young women as a function of childhood adversity. *Journal of Consulting and Clinical Psychology*, *68*(5), 782–787. http://doi.org/http://dx.doi.org/10.1037/0022-006X.68.5.782

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: review of the evidence. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *45*(2), 260–73. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/14982240

Hatch, S. L., Jones, P. B., Kuh, D., Hardy, R., Wadsworth, M. E. J., & Richards, M. (2007). Childhood cognitive ability and adult mental health in the British 1946 birth cohort. *Social Science & Medicine (1982)*, *64*(11), 2285–96. http://doi.org/10.1016/j.socscimed.2007.02.027

Hazel, N. A., Hammen, C., Brennan, P. A., & Najman, J. (2008). Early childhood adversity and adolescent depression: The mediating role of continued stress. *Psychological Medicine*, *38*(4), 581–589. http://doi.org/http://dx.doi.org/10.1017/S0033291708002857

Henderson, M., Hotopf, M., Shah, I., Hayes, R. D., & Kuh, D. (2011). Psychiatric disorder in early adulthood and risk of premature mortality in the 1946 British Birth Cohort. *BMC Psychiatry*, *11*(37), no pagination. http://doi.org/10.1186/1471-244X-11-37

Henry, B., Moffitt, T. E., Caspi, A., Langley, J., & et al. (1994a). On the "remembrance of things past": A longitudinal evaluation of the retrospective method. *Psychological Assessment*, *6*(2), 92–101. http://doi.org/10.1037/1040-3590.6.2.92

Henry, B., Moffitt, T. E., Caspi, A., Langley, J., & et al. (1994b). On the

"remembrance of things past": A longitudinal evaluation of the retrospective method. *Psychological Assessment*, *6*(2), 92–101. http://doi.org/10.1037/1040-3590.6.2.92

Herrenkohl, T. I. (2013). Developmental Impacts of Child Abuse and Neglect Related to Adult Mental Health, Substance Use, and Physical Health. *Changes*, *29*(6), 997–1003. http://doi.org/10.1016/j.biotechadv.2011.08.021.Secreted

Higgins, D. J., & McCabe, M. P. (2001). The Development of the Comprehensive Child Maltreatment Scale. *Journal of Family Studies*, *7*(1), 7–28. http://doi.org/10.5172/jfs.7.1.7

Horan, J. M., & Widom, C. S. (2014a). Cumulative childhood risk and adult functioning in abused and neglected children grown up. *Development and Psychopathology*, *in press*, 1–15. http://doi.org/10.1017/S095457941400090X

Horan, J. M., & Widom, C. S. (2014b). Does Age of Onset of Risk Behaviors Mediate the Relationship Between Child Abuse and Neglect and Outcomes in Middle Adulthood? *Journal of Youth and Adolescence*, *44*(3), 670–682. http://doi.org/10.1007/s10964-014-0161-4

Hughes, K., Bellis, M. A., Hardcastle, K. A., Sethi, D., Butchart, A., Mikton, C., … Dunne, M. P. (2017). The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *The Lancet Public Health*, *2*(8), e356–e366. http://doi.org/10.1016/S2468-2667(17)30118-4

Ingram, R. E. (2003). Origins of Cognitive Vulnerability to Depression. *Cognitive Therapy and Research*, *27*(1), 77–88. http://doi.org/10.1023/A

Jensen, A. R. (1958). The maudsley personality inventory. *Acta Psychologica*, *14*, 314–325.

Jones, P., Murray, R., Jones, P., Rodgers, B., & Marmot, M. (1994). Child

developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *The Lancet*, *344*(8934), 1398–1402. http://doi.org/10.1016/S0140-6736(94)90569-X

Jung, T., & Wickrama, A. (2008). An Introduction to Latent Class Growth Analysis and Growth Mixture Modeling. *Social and Personality Psychology Compass*, *2*(1), 302–317.

Kalmakis, K. a, & Chandler, G. E. (2014). Adverse childhood experiences: towards a clear conceptual meaning. *Journal of Advanced Nursing*, *70*(7), 1489–501. http://doi.org/10.1111/jan.12329

Karg, K., Burmeister, M., Shedden, K., & Sen, S. (2011). The serotonin transporter promoter variant (5-HTTLPR), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Archives of General Psychiatry*, *68*(5), 444–54. http://doi.org/10.1001/archgenpsychiatry.2010.189

Kessler, R. C., Amminger, G. P., Aguilar-Gaxiola, S., Alonso, J., Lee, S., & Ustün, T. B. (2007). Age of onset of mental disorders: a review of recent literature. *Current Opinion in Psychiatry*, *20*(4), 359–64. http://doi.org/10.1097/YCO.0b013e32816ebc8c

Kessler, R. C., Angermeyer, M., Anthony, J. C., DE Graaf, R., Demyttenaere, K., Gasquet, I., … Ustün, T. B. (2007). Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry : Official Journal of the World Psychiatric Association (WPA)*, *6*(3), 168–76. http://doi.org/10.1001/archpsyc.62.6.593

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV

Disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, *62*(June), 593–602. http://doi.org/10.1001/archpsyc.62.6.593

Kessler, R. C., Demler, O., Frank, R. G., Olfson, M., Pincus, H. A., Walters, E. E., … Zaslavsky, A. M. (2005). US prevalence and treatment of mental disorders : 1990 – 2003, *352*(24), 2515–2523. http://doi.org/10.1056/NEJMsa043266.US

Kessler, R. C., McLaughlin, K., Green, J. G., Gruber, M. J., Sampson, N. a, Zaslavsky, A. M., … Williams, D. R. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *The British Journal of Psychiatry : The Journal of Mental Science*, *197*(5), 378–85. http://doi.org/10.1192/bjp.bp.110.080499

Kessler, R. C., Petukhova, M., Sampson, N. a, Zaslavsky, A. M., & Wittchen, H.-U. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *International Journal of Methods in Psychiatric Research*, *21*(3), 169–82. http://doi.org/10.1002/mpr

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., & Moffitt, T. E. (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry*, *11*(10), 903–913. http://doi.org/10.1038/sj.mp.4001851

Korkeila, J., Vahtera, J., Nabi, H., Kivimäki, M., Korkeila, K., Sumanen, M., … Koskenvuo, M. (2010). Childhood adversities, adulthood life events and depression. *Journal of Affective Disorders*, *127*(1–3), 130–8. http://doi.org/10.1016/j.jad.2010.04.031

Kosidou, K., Magnusson, C., Mittendorfer-Rutz, E., Hallqvist, J., Hellner Gumpert, C., Idrizbegovic, S., … Dalman, C. (2010). Recent time trends in levels of self-

reported anxiety, mental health service use and suicidal behaviour in Stockholm. *Acta Psychiatrica Scandinavica*, *122*(1), 47–55. http://doi.org/10.1111/j.1600-0447.2009.01487.x

Koss, K. J., & Gunnar, M. R. (2017). Annual Research Review: Early adversity, the hypothalamic-pituitary-adrenocortical axis, and child psychopathology. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *4*, 327–346. http://doi.org/10.1111/jcpp.12784

Kraemer, H. C., Kazdin, A. E., Offord, D. R., Kessler, R. C., Jensen, P. S., & Kupfer, D. J. (1997). Coming to Terms with the Terms of Risk. *Archives of General Psychiatry*, *54*(4), 337–343.

Krokstad, S., Langhammer, A., Hveem, K., Holmen, T. L., Midthjell, K., Stene, T. R., … Holmen, J. (2013). Cohort profile: The HUNT study, Norway. *International Journal of Epidemiology*, *42*(4), 968–977. http://doi.org/10.1093/ije/dys095

Kuh, D., Lynch, J., Hallqvist, J., & Power, C. (2003). Life course epidemiology, 778–783.

Kuh, D., Pierce, M., Adams, J., Deanfield, J., Ekelund, U., Friberg, P., … Hardy, R. (2011). Cohort Profile: Updating the cohort profile for the MRC National Survey of Health and Development: A new clinic-based data collection for ageing research. *International Journal of Epidemiology*, *40*(1), e1–e9. http://doi.org/10.1093/ije/dyq231

Kuh, D., Wong, A., Shah, I., Moore, A., Popham, M., Curran, P., … Cooper, R. (2016). The MRC National Survey of Health and Development reaches age 70: maintaining participation at older ages in a birth cohort study. *European Journal of Epidemiology*, *31*(11), 1135–1147. http://doi.org/10.1007/s10654-

016-0217-8

Lacey, R. E., Bartley, M., Pikhart, H., Stafford, M., & Cable, N. (2014). Parental separation and adult psychological distress: an investigation of material and relational mechanisms. *BMC Public Health*, *14*(1), 272. http://doi.org/10.1186/1471-2458-14-272

Lacey, R. E., Bartley, M., Pikhart, H., Stafford, M., Cable, N., & Coleman, L. (2012). Parental separation and adult psychological distress: Evidence for the "reduced effect" hypothesis? *Longitudinal an Life Course Studies*, *3*(3), 359–368. http://doi.org/http://dx.doi.org/10.14301/llcs.v3i3.195

Lahey, B. B., D'Onofrio, B. M., & Waldman, I. D. (2009). Using epidemiologic methods to test hypotheses regarding causal influences on child and adolescent mental disorders. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *50*(1–2), 53–62. http://doi.org/10.1111/j.1469-7610.2008.01980.x

Langley, K., Collishaw, S., Williams, M., & Shelton, K. H. (2017). An investigation of changes in children ′ s mental health in Wales between 2007 / 2008 and 2012 / 2013. *Social Psychiatry and Psychiatric Epidemiology*, *52*(6), 639–642. http://doi.org/10.1007/s00127-017-1378-9

Last, C., Hansen, C., & Franco, N. (1997). Anxious Children In Adulthod: A Prospective Study of Adjustment. *Journal of the American Academy of Child & Adolescent Psychiatr*, *36*(5), 645–652. http://doi.org/10.1097/00004583-199705000-00015

Lee, C., Dobson, A. J., Brown, W. J., Bryson, L., Byles, J., Warner-Smith, P., & Young, A. F. (2005). Cohort Profile: The Australian longitudinal study on Women's Health. *International Journal of Epidemiology*, *34*(5), 987–991. http://doi.org/10.1093/ije/dyi098

Li, M., D'Arcy, C., & Meng, X. (2016). Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: Systematic review, meta-analysis, and proportional attributable fractions. *Psychological Medicine*, *46*(4), 717–730. http://doi.org/10.1017/S0033291715002743

Lindelow, M., Hardy, R., & Rodgers, B. (1997). Development of a scale to measure symptoms of anxiety and depression in the general UK population: the psychiatric symptom frequency scale. *Journal of Epidemiology and Community Health*, *51*(5), 549–557. http://doi.org/10.1136/jech.51.5.549

Lindert, J., von Ehrenstein, O. S., Grashow, R., Gal, G., Braehler, E., & Weisskopf, M. G. (2014). Sexual and physical abuse in childhood is associated with depression and anxiety over the life course: systematic review and meta-analysis. *International Journal of Public Health*, *59*(2), 359–72. http://doi.org/10.1007/s00038-013-0519-5

Little, T. D., Jorgensen, T. D., Lang, K. M., & Moore, E. W. G. (2014). On the joys of missing data. *Journal of Pediatric Psychology*, *39*(2), 151–162. http://doi.org/10.1093/jpepsy/jst048

Liu, R. T., Jager-Hyman, S., Wagner, C. a, Alloy, L. B., & Gibb, B. E. (2012). Number of childhood abuse perpetrators and the occurrence of depressive episodes in adulthood. *Child Abuse & Neglect*, *36*(4), 323–32. http://doi.org/10.1016/j.chiabu.2011.11.007

Lohoff, F. W. (2010). Overview of the Genetics of Major Depressive Disorder. *Current Psychiatry Reports*, *12*(6), 539–546. http://doi.org/10.1007/s11920-010-0150-6.Overview

Lowe, S. R., Quinn, J. W., Richards, C. A., Rundle, A., & Galea, S. (2017). HHS

Public Access, 212–222. http://doi.org/10.1016/j.chiabu.2015.10.007.Childhood

Lupien, S. J., King, S., Meaney, M. J., & Mcewen, B. S. (2000). Child's Stress Hormone Levels Correlate with Mother's Socioeconomic Status and Depressive State. *Biological Psychiatry*, *48*, 976–980.

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci*, *10*(6), 434–445. http://doi.org/10.1038/nrn2639

Mars, B., Collishaw, S., Hammerton, G., Rice, F., Harold, G. T., Smith, D., … Thapar, A. (2015). Longitudinal symptom course in adults with recurrent depression: Impact on impairment and risk of psychopathology in offspring. *Journal of Affective Disorders*, *182*, 32–38. http://doi.org/10.1016/j.jad.2015.04.018

McCrone, P., Dhanasiri, S., Patel, A., Knapp, M., & Lawton-Smith, S. (2008). Paying the price: the cost of mental health care in England to 2026. *The British Journal of Psychiatry : The Journal of Mental Science*, *184*, 386–92. http://doi.org/10.1192/bjp.184.5.386

McEwen, B. S. (2000). Allostasis and Allostatic Load : Implications for Neuropsychopharmacology, (99).

McLaughlin, K. A., Breslau, J., Green, J. G., Lakoma, M. D., Sampson, N. A., Zaslavsky, A. M., & Kessler, R. C. (2011). Childhood socio-economic status and the onset, persistence, and severity of DSM-IV mental disorders in a US national sample. *Social Science & Medicine (1982)*, *73*(7), 1088–96. http://doi.org/10.1016/j.socscimed.2011.06.011

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond cumulative risk: A dimensional approach to childhood adversity. *Current Directions in*

Psychological Science, *25*, 239–245. http://doi.org/10.1177/0963721416655883

McLaughlin, K. a, Conron, K. J., Koenen, K. C., & Gilman, S. E. (2010). Childhood adversity, adult stressful life events, and risk of past-year psychiatric disorder: a test of the stress sensitization hypothesis in a population-based sample of adults. *Psychological Medicine*, *40*(10), 1647–1658. http://doi.org/10.1017/S0033291709992121

McManus, S., Bebbington, P., Jenkins, R., & Brugha, T. (2016). Mental health and wellbeing in England: Adult Psychiatric Morbidity survey 2014. Leeds:NHS Digital. *Leeds: NHS Digital*, 1–405.

McManus, S., Meltzer, H., Brugha, T. T., Bebbington, P. P., & Jenkins, R. (2009). *Adult psychiatric morbidity in England, 2007 Results of a household survey*. *The Health and Social Care Information Centre, Social Care Statistics.* Retrieved from http://discovery.ucl.ac.uk/164862/

Merikangas, K., Jian-ping, H., Burstein, M., Swanson, S., Avenevoli, S., Lihong, C., … Swendsen, J. (2011). Lifetime Prevalence of Mental Disorders in US Adolescents: Results from the National Comorbidity Study-Adolescent Supplement. *Journal of the American Academy Children Adolescent Psychiatry*, *49*(10), 980–989. http://doi.org/10.1016/j.jaac.2010.05.017.Lifetime

Mersky, J. P., Topitzes, J., & Reynolds, a J. (2013). Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: a cohort study of an urban, minority sample in the U.S. *Child Abuse & Neglect*, *37*(11), 917–25. http://doi.org/10.1016/j.chiabu.2013.07.011

Moffitt, T. E., Caspi, A., Harrington, H., Milne, B. J., Melchior, M., Goldberg, D., & Poulton, R. (2007). Generalized anxiety disorder and depression: childhood risk factors in a birth cohort followed to age 32. *Psychological Medicine*, *37*(3),

441–452. http://doi.org/10.1017/S0033291706009640

Moffitt, T. E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry*, *62*(5), 473–81. http://doi.org/10.1001/archpsyc.62.5.473

Moffitt, T. E., Caspi, A., Taylor, A., Kokaua, J., Milne, B. J., Polanczyk, G., & Poulton, R. (2010). How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *October*, *40*(6), 899–909. http://doi.org/10.1017/S0033291709991036

Morton, S. M. B., Atatoa carr, P. E., Grant, C. C., Robinson, E. M., Bandara, D. K., Bird, A., … Wall, C. (2013). Cohort profile: Growing up in new zealand. *International Journal of Epidemiology*, *42*(1), 65–75. http://doi.org/10.1093/ije/dyr206

Musliner, K. L., Munk-Olsen, T., Eaton, W. W., & Zandi, P. P. (2016). Heterogeneity in long-term trajectories of depressive symptoms: Patterns, predictors and outcomes. *Journal of Affective Disorders*, *192*, 199–211. http://doi.org/10.1016/j.jad.2015.12.030

Mykletun, A., Bjerkeset, O., Øverland, S., Prince, M., Dewey, M., & Stewart, R. (2009). Levels of anxiety and depression as predictors of mortality: The HUNT study. *British Journal of Psychiatry*, *195*(2), 118–125. http://doi.org/10.1192/bjp.bp.108.054866

Nanni, V., Uher, R., Ph, D., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *American Journal of Psychiatry*, *169*(2), 141–151.

Newbury, J. B., Arseneault, L., Moffitt, T. E., Caspi, A., Danese, A., Baldwin, J. R.,

& Fisher, H. L. (2018). Measuring childhood maltreatment to predict early-adult psychopathology: Comparison of prospective informant-reports and retrospective self-reports. *Journal of Psychiatric Research*, *96*, 57–64. http://doi.org/10.1016/j.jpsychires.2017.09.020

Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS Medicine*, *9*(11), e1001349. http://doi.org/10.1371/journal.pmed.1001349

Olfson, M., Blanco, C., Wang, S., Laje, G., & Correll, C. U. (2014). National trends in the mental health care of children, adolescents, and adults by office-based physicians. *JAMA Psychiatry*, *71*(1), 81–90. http://doi.org/10.1001/jamapsychiatry.2013.3074

Oliver, B. R., Kretschmer, T., & Maughan, B. (2014). Configurations of early risk and their association with academic, cognitive, emotional and behavioural outcomes in middle childhood. *Social Psychiatry and Psychiatric Epidemiology*, *49*(5), 723–732. http://doi.org/http://dx.doi.org/10.1007/s00127-013-0756-1

Otowa, T., York, T. P., Gardner, C. O., Kendler, K. S., & Hettema, J. M. (2014). The impact of childhood parental loss on risk for mood, anxiety and substance use disorders in a population-based sample of male twins. *Psychiatry Research*, *220*(1–2), 404–409. http://doi.org/10.1016/j.psychres.2014.07.053

Paksarian, D., Cui, L., Angst, J., Ajdacic-Gross, V., Rössler, W., Merikangas, K. R., … KL, M. (2016). Latent Trajectories of Common Mental Health Disorder Risk Across 3 Decades of Adulthood in a Population-Based Cohort. *JAMA Psychiatry*, *51*(1), 8–19. http://doi.org/10.1001/jamapsychiatry.2016.1921

Park, S., Hong, J. P., Bae, J. N., Cho, S. J., Lee, D. W., Lee, J. Y., … Cho, M. J. (2014). Impact of childhood exposure to psychological trauma on the risk of psychiatric disorders and somatic discomfort: Single vs. multiple types of psychological trauma. *Psychiatry Research*, *219*(3), 443–449. http://doi.org/10.1016/j.psychres.2014.06.009

Park, S., Nam, Y., Sim, Y., & Hong, J. P. (2015). depressive symptoms in older adults, *8198*(August 2017). http://doi.org/10.3402/ejpt.v6.25178

Park, S., Pyo, J., Nam, J., Cho, S., Lee, D., Lee, J., … Je, M. (2014). Impact of childhood exposure to psychological trauma on the risk of psychiatric disorders and somatic discomfort : Single vs . multiple types of psychological trauma, *219*, 2013–2015.

Patalay, P., & Fitzsimons, E. (2017). Mental ill-health among children of the new century. Retrieved from https://www.ncb.org.uk/sites/default/files/uploads/documents/Research_reports/UCL - NCB - Mental_Ill-Health FINAL.pdf

Pine, D. S., Cohen, P., Gurley, D., Brook, J., & Ma, Y. (1998). The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of General Psychiatry*, *55*(1), 56–64. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9435761

Pirkola, S., Isomets??, E., Aro, H., Kestil??, L., H??m??l??inen, J., Veijola, J., … L??nnqvist, J. (2005). Childhood adversities as risk factors for adult mental disorders. Results from the Health 2000 study. *Social Psychiatry and Psychiatric Epidemiology*, *40*(10), 769–777. http://doi.org/10.1007/s00127-005-0950-x

Ploubidis, G., Sullivan, A., Brown, M., & Goodman, A. (2017). Psychological

Distress in Mid-Life in the UK : Evidence from the 1958 and 1970 Birth Cohorts, 1–26.

Polanczyk, G., Caspi, A., Williams, B., Price, T. S., Danese, A., Sugden, K., … Moffitt, T. E. (2009). Protective Effect of CRHR1 Gene Variants on the Development of Adult Depression Following Childhood Maltreatment. *Arch Gen Psychiatry*, *66*(9), 978–985.

Porche, M. V, Costello, D. M., & Rosen-Reynoso, M. (2016). Adverse family experiences, child mental health, and educational outcomes for a national sample of students. *School Mental Health*, 44–60. http://doi.org/10.1007/s12310-016-9174-3

Poulton, R., Caspi, A., Milne, B. J., Thomson, W. M., Taylor, A., Sears, M. R., & Moffitt, T. E. (2013). Association between children's experience of socioeconomic disadvantage and adult health: a life-course study. *Lancet*, *360*(9346), 1640–1645. http://doi.org/10.1016/S0140-6736(02)11602-3.Association

Power, C., & Elliott, J. (2006). Cohort profile: 1958 British birth cohort (National Child Development Study). *International Journal of Epidemiology*, *35*(1), 34–41. http://doi.org/10.1093/ije/dyi183

Power, C., Kuh, D., & Morton, S. (2013). From developmental origins of adult disease to life course research on adult disease and aging: insights from birth cohort studies. *Annual Review of Public Health*, *34*, 7–28. http://doi.org/10.1146/annurev-publhealth-031912-114423

Power, R. a., Lecky-Thompson, L., Fisher, H. L., Cohen-Woods, S., Hosang, G. M., Uher, R., … McGuffin, P. (2013). The interaction between child maltreatment, adult stressful life events and the 5-HTTLPR in major depression. *Journal of*

Psychiatric Research, *47*(8), 1032–1035. http://doi.org/10.1016/j.jpsychires.2013.03.017

Prescott, A., Bank, L., Reid, J. B., Knutson, J. F., Burraston, B. O., & Eddy, J. M. (2000). The veridicality of punitive childhood experiences reported by adolescents and young adults. *Child Abuse and Neglect*, *24*(3), 411–423. http://doi.org/10.1016/S0145-2134(99)00153-2

Rao, U., Chen, L.-A., Bidesi, A. S., Shad, M. U., Thomas, M. A., & Hammen, C. L. (2010). Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biological Psychiatry*, *67*(4), 357–64. http://doi.org/10.1016/j.biopsych.2009.10.017

Raposo, S. M., Mackenzie, C. S., Henriksen, C. A., & Afifi, T. O. (2014). Time does not heal all wounds: Older adults who experienced childhood adversities have higher odds of mood, anxiety, and personality disorders. *American Journal of Geriatric Psychiatry*, *22*(11), 1241–1250. http://doi.org/10.1016/j.jagp.2013.04.009

Raposo, S. M., Mackenzie, C. S., Henriksen, C. a, & Afifi, T. O. (2013). Time does not heal all wounds: older adults who experienced childhood adversities have higher odds of mood, anxiety, and personality disorders. *The American Journal of Geriatric Psychiatry : Official Journal of the American Association for Geriatric Psychiatry*, *22*(11), 1241–50. http://doi.org/10.1016/j.jagp.2013.04.009

Raven, D., Jörg, F., Visser, E., Oldehinkel, A. J., & Schoevers, R. A. (2016). Time-to-treatment of mental disorders in a community sample of Dutch adolescents. A TRAILS study. *Epidemiology and Psychiatric Sciences*, (May), 1–12. http://doi.org/10.1017/S2045796016000226

Reiser, S. J., McMillan, K. a, Wright, K. D., & Asmundson, G. J. G. (2014). Adverse childhood experiences and health anxiety in adulthood. *Child Abuse & Neglect*, *38*(3), 407–13. http://doi.org/10.1016/j.chiabu.2013.08.007

Remigio-Baker, R. A., Hayes, D. K., & Reyes-Salvail, F. (2014). Adverse Childhood Events and Current Depressive Symptoms Among Women in Hawaii: 2010 BRFSS, Hawaii. *Maternal and Child Health Journal*, *18*(10), 2300–2308. http://doi.org/10.1007/s10995-013-1374-y

Reuben, A., Moffitt, T. E., Caspi, A., Belsky, D. W., Harrington, H., Schroeder, F., … Danese, A. (2016). Lest we forget: comparing retrospective and prospective assessments of adverse childhood experiences in the prediction of adult health. *Journal of Child Psychology and Psychiatry*, *57*(10), 1103–1112. http://doi.org/10.1111/jcpp.12621

Richards, M., Hardy, R., & Wadsworth, M. (1997). The effects of divorce and separation on mental health in a national UK birth cohort. *Psychological Medicine*, *27*(5), 1121–1128. http://doi.org/10.1017/S003329179700559X

Risch, N., Herrell, R., & Lehner, T. (2009). Interaction Between the Serotonin Transporter Gene (5-HTTLPR), Stressful Life Events, and Risk of Depression. *Jama*, *301*(23), 2462–2472. http://doi.org/10.1001/jama.2009.878

Risch, N., Herrell, R., Lehner, T., Liang, K.-Y., Eaves, L., Hoh, J., … Merikangas, K. R. (2009). Interaction Between the Serotonin Transporter Gene (5-HTTLPR), Stressful Life Events, and Risk of Depression A Meta-analysis. *Jama*, *301*(23), 2462–2472. http://doi.org/10.1001/jama.2009.878

Roberts, R. E., Clifford Attkisson, C., & Rosenblatt, A. (1998). Prevalence of psychopathology among children and adolescents. *American Journal of Psychiatry*, *155*(6), 715–725.

Rodgers, B. (1990). Adult affective disorder and early environment. *The British Journal of Psychiatry*, *157*(4), 539–550. http://doi.org/10.1192/bjp.157.4.539

Rodgers, B. (1994). Pathways between parental divorce and adult depression. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *35*(7), 1289–1308.

Roshanaei-Moghaddam, B., Katon, W. J., & Russo, J. (2009). The longitudinal effects of depression on physical activity. *General Hospital Psychiatry*, *31*(4), 306–315. http://doi.org/10.1016/j.genhosppsych.2009.04.002

Roy, A., & Raver, C. (2014). Are all risks equal? Early experiences of poverty-related risk and children's functioning. *Journal of Family Psychology*, *28*(3), 391–400. http://doi.org/10.1037/a0036683

Rudenstine, S., Cohen, G., Prescott, M., Sampson, L., Liberzon, I., Tamburrino, M., … Galea, S. (2017). Adverse Childhood Events and the Risk for New-Onset Depression and Post-Traumatic Stress Disorder Among U . S . National Guard Soldiers, *180*(September 2015). http://doi.org/10.7205/MILMED-D-14-00626

Rudolph, K. D., & Flynn, M. (2011). Childhood Adversity and Youth Depression: Influence of Gender and Pubertal Status. *Development and Psychopathology*, *19*(2), 497–521. http://doi.org/10.1017/S0954579407070241.Childhood

Rutter, M. (1967). A children's behaviour questionnaire for completion by teachers: preliminary findings. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *8*(1), 1–11. http://doi.org/10.1111/j.1469-7610.1967.tb02175.x

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities

in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*(3–4), 276–295. http://doi.org/10.1111/j.1469-7610.2006.01614.x

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene-environment interplay and psychopathology: Multiple varieties but real effects. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *47*(3–4), 226–261. http://doi.org/10.1111/j.1469-7610.2005.01557.x

Sacks, V., Murphey, D., & Moore, K. (2014). Adverse Childhood Expereinces: National and State-Level Prevalence. *Child Trends*, *2014–28*, 1–5. http://doi.org/10.1007/BF03312070

Sands, A., Thompson, E. J., & Gaysina, D. (2017). Long-term influences of parental divorce on offspring affective disorders: A systematic review and meta-analysis. *Journal of Affective Disorders*, *218*(November 2016), 105–114. http://doi.org/10.1016/j.jad.2017.04.015

Saris, I. M. J., Aghajani, M., van der Werff, S. J. A., van der Wee, N. J. A., & Penninx, B. W. J. H. (2017). Social functioning in patients with depressive and anxiety disorders. *Acta Psychiatrica Scandinavica*, 352–361. http://doi.org/10.1111/acps.12774

Schafer, J. L., & Graham, J. W. (2002). Missing data: Our view of the state of the art. *Psychological Methods*, *7*(2), 147–177. http://doi.org/10.1037//1082-989X.7.2.147

Schilling, E. a, Aseltine, R. H., & Gore, S. (2008). The impact of cumulative childhood adversity on young adult mental health: measures, models, and interpretations. *Social Science & Medicine (1982)*, *66*(5), 1140–51. http://doi.org/10.1016/j.socscimed.2007.11.023

Schoevers, R. A., Beekman, A. T. F., Deeg, D. J. H., Geerlings, M. I., Jonker, C., & Van Tilburg, W. (2000). Risk factors for depression in later life; results of a prospective community based study (AMSTEL). *Journal of Affective Disorders*, *59*(2), 127–137. http://doi.org/10.1016/S0165-0327(99)00124-X

Schotte, C. K. W., Bossche, B. Van Den, Doncker, D. De, Claes, S., & Cosyns, P. (2006). A Biopsychosocial Model As A Guide For Psychoeducation And Treatment Of Depression. *Depression and Anxiety*, *23*(1), 312–324. http://doi.org/10.1002/da

Secinti, E., Thompson, E. J., Richards, M., & Gaysina, D. (2017). Research Review: Childhood chronic physical illness and adult emotional health - a systematic review and meta-analysis. *Journal of Child Psychology and Psychiatry*. http://doi.org/10.1111/jcpp.12727

Sellers, R., Maughan, B., Pickles, A., Thapar, A., & Collishaw, S. (2015). Trends in parent- and teacher-rated emotional, conduct and ADHD problems and their impact in prepubertal children in Great Britain: 1999-2008. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *56*(1), 49–57. http://doi.org/10.1111/jcpp.12273

Shanahan, L., Copeland, W. E., Costello, E. J., & Angold, A. (2011). Child-, adolescent- and young adult-onset depressions: differential risk factors in development? *Psychological Medicine*, *41*(11), 2265–2274. http://doi.org/http://dx.doi.org/10.1017/S0033291711000675

Sheridan, M. a., Peverill, M., Finn, A. S., & McLaughlin, K. a. (2017). Dimensions of childhood adversity have distinct associations with neural systems underlying executive functioning. *Development and Psychopathology*, *29*(5), 1777–1794. http://doi.org/10.1126/science.1249098.Sleep

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased Amygdala and Decreased Dorsolateral Prefrontal BOLD Responses in Unipolar Depression: Related and Independent Features. *Biological Psychiatry*, *61*(2), 198–209. http://doi.org/10.1016/j.biopsych.2006.05.048

Solomon, A., Haaga, D. A. F., & Arnow, B. A. (2001). Is clinical depression distinct from subthreshold depressive symptoms? A review of the continuity issue in depression research. *Journal of Nervous and Mental Disease*, *189*(8), 498–506. http://doi.org/10.1097/00005053-200108000-00002

Sourander, A., Multimäki, P., Nikolakaros, G., Haavisto, A., Ristkari, T., Helenius, H., … Almqvist, F. (2005). Childhood predictors of psychiatric disorders among boys: a prospective community-based follow-up study from age 8 years to early adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*(8), 756–767. http://doi.org/10.1097/01.chi.0000164878.79986.2f

Spiers, N., Bebbington, P., McManus, S., Brugha, T. S., Jenkins, R., & Meltzer, H. (2011). Age and birth cohort differences in the prevalence of common mental disorder in England: National psychiatric morbidity surveys 1993-2007. *British Journal of Psychiatry*, *198*(6), 479–484. http://doi.org/10.1192/bjp.bp.110.084269

Stafford, M., Black, S., Shah, I., Hardy, R., Pierce, M., Richards, M., … Kuh, D. (2013). Using a birth cohort to study ageing: Representativeness and response rates in the National Survey of Health and Development. *European Journal of Ageing*, *10*(2), 145–157. http://doi.org/10.1007/s10433-013-0258-8

Stafford, M., Gale, C. R., Mishra, G., Richards, M., Black, S., & Kuh, D. L. (2015). Childhood Environment and Mental Wellbeing at Age 60-64 Years: Prospective Evidence from the MRC National Survey of Health and Development. *Plos*

One, *10*(6), e0126683. http://doi.org/10.1371/journal.pone.0126683

Stanfeld, S., Clark, C., Bebbington, P., King, M., Jenkins, R., & Hinchliffe, S. (2014). Common Mental Disorders. *Adult Psychiatric Morbidity Survey 2014*, 213–17. http://doi.org/10.1002/9780470684214.ch17

Stansfeld, S. A., Clark, C., Rodgers, B., Caldwell, T., & Power, C. (2008). Childhood and adulthood socio-economic position and midlife depressive and anxiety disorders. *British Journal of Psychiatry*, *192*(2), 152–153. http://doi.org/10.1192/bjp.bp.107.043208

Stansfeld, S., Clark, C., Bebbington, P., King, M., Jenkins, R., & Hinchliffe, S. (2014). Common mental disorders. *Ethnic Minority Psychiatric Illness Rates in the Community (EMPIRIC): Quantitative Report*. Retrieved from http://content.digital.nhs.uk/catalogue/PUB21748

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., … Thacker, S. B. (2015). Meta-analysis of Observational Studies.

Takizawa, R., Maughan, B., & Arseneault, L. (2014). Adult health outcomes of childhood bullying victimization: Evidence from a five-decade longitudinal British birth cohort. *American Journal of Psychiatry*, *171*(7), 777–784. http://doi.org/10.1176/appi.ajp.2014.13101401

Taylor, S. E., Way, B. M., & Seeman, T. E. (2011). Early adversity and adult health outcomes. *Development and Psychopathology*, *23*(3), 939–54. http://doi.org/10.1017/S0954579411000411

Thompson, E. J., Kazantseva, A., & Gaysina, D. (2017). Internalizing psychopathology across the life course: from genes and environment to gene-environment interaction. *Psychopathology Review*, *2*, 1–25. http://doi.org/10.5127/pr.00

Thoresen, S., Myhre, M., Wentzel-larsen, T., Aakvaag, H. F., Thoresen, S., Myhre, M., … Aakvaag, H. F. (2015). general Norwegian population, *8198*(August 2017). http://doi.org/10.3402/ejpt.v6.26259

Thornicroft, G., Sartorius, N. . (1993). The Course and Outcome of Depression in Different Cultures: 10years Follow-up of the WHO Collaborative Study on the Assessment of Depressive Disorder. *Psychol. Med.*, *23*(4), 1023–32.

Tiet, Q. Q., Bird, H. R., Davies, M., Hoven, C., Cohen, P., Jensen, P. S., & Goodman, S. (1998). Adverse life events and resilience. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37*(11), 1191–200. http://doi.org/10.1097/00004583-199811000-00020

Turner, H. A., & Butler, M. J. (2003). Direct and indirect effects of childhood adversity on depressive symptoms in young adults. *Journal of Youth and Adolescence*, *32*(2), 89–103. http://doi.org/http://dx.doi.org/10.1023/A:1021853600645

Tyrka, A. R., Wier, L., Price, L. H., Ross, N. S., & Carpenter, L. L. (2008). Childhood parental loss and adult psychopathology: effects of loss characteristics and contextual factors. *International Journal of Psychiatry in Medicine*, *38*(3), 329–344. http://doi.org/10.2190/PM.38.3.h

Vachon, D. D., Krueger, R. F., Rogosch, F. A., & Cicchetti, D. (2015). Assessment of the Harmful Psychiatric and Behavioral Effects of Different Forms of Child Maltreatment. *JAMA Psychiatry*, (November), 1135. http://doi.org/10.1001/jamapsychiatry.2015.1792

van der Vegt, E. J. M., Tieman, W., van der Ende, J., Ferdinand, R. F., Verhulst, F. C., & Tiemeier, H. (2009). Impact of early childhood adversities on adult psychiatric disorders: a study of international adoptees. *Social Psychiatry and*

Psychiatric Epidemiology, *44*(9), 724–731. http://doi.org/10.1007/s00127-009-0494-6

Velders, F. P., Dieleman, G., Cents, R. A. M., Bakermans-kranenburg, M. J., Jaddoe, V. W. V, Hofman, A., … Verhulst, F. C. (2012). Variation in the Glucocorticoid Receptor Gene at rs41423247 Moderates the Effect of Prenatal Maternal Psychological Symptoms on Child Cortisol Reactivity and Behavior. *Neuropsychopharmacology*, *37*(11), 2541–2549. http://doi.org/10.1038/npp.2012.118

Veldman, K., Bultmann, U., Almansa, J., & Reijneveld, S. A. (2015). Childhood Adversities and Educational Attainment in Young Adulthood: The Role of Mental Health Problems in Adolescence. *Journal of Adolescent Health*, *57*(5), 462–467. http://doi.org/10.1016/j.jadohealth.2015.08.004

Veldman, K., Reijneveld, S. A., Almansa Ortiz, J., Verhulst, F. C., & Bultmann, U. (2015). Mental health trajectories from childhood to young adulthood affect the educational and employment status of young adults: results from the TRAILS study. *Journal of Epidemiology & Community Health*, 1–6. http://doi.org/10.1136/jech-2014-204421

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., … Moradi-Lakeh, M. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, *380*(9859), 2163–2196. http://doi.org/10.1016/S0140-6736(12)61729-2

Wadsworth, M., Kuh, D., Richards, M., & Hardy, R. (2006). Cohort profile: The 1946 National Birth Cohort (MRC National Survey of Health and Development). *International Journal of Epidemiology*, *35*(1), 49–54.

http://doi.org/10.1093/ije/dyi201

Weissman, M. M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D. J., & Verdeli, H. (2006). Offspring of depressed parents. 20 Years later. *Archives of General Psychiatry*, *54*(10), 932–940. http://doi.org/10.1001/archpsyc.1997.01830220054009

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., … Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet*, *382*(9904), 1575–1586. http://doi.org/10.1016/S0140-6736(13)61611-6

WHO. (2011). International statistical classification of diseases and related health problems - 10th revision. *World Health Organisation*, *2*(5), 1–252. http://doi.org/978924 549165

Wickramaratne, P., & Weissman, M. M. (1998). Onset of Psychopathology in Offspring by Developmental Phase and Parental Depression. *Journal of the American Academy of Child and Adolescent Psychiatry*, *37*(9), 933–942.

Williams, J. M. G., & Scott, J. (2009). Autobiographical memory in depression. *Psychological Medicine*, *18*(03), 689. http://doi.org/10.1017/S0033291700008370

Wing, J. K., Cooper, J. E. & Sartorius, N. (1974). *The Measurement and Classification of Psychiatric Symptoms.* Cambridge University Press: London.

Wing, J. K., Cooper, J. E., & Sartorius, N. (2011). *Measurement and classification of psychiatric symptoms: An instruction manual for the PSE and CATEGO program*. Cambridge University Press.

Wood, J. J., & Wood, J. (2006). Effect of anxiety reduction on children's school

performance and social adjustment. *Developmental Psychology*, *42*(2), 345–9. http://doi.org/10.1037/0012-1649.42.2.345

Wood, N., Bann, D., Hardy, R., Gale, C., Goodman, A., Crawford, C., & Stafford, M. (2017). Childhood socioeconomic position and adult mental wellbeing: Evidence from four British birth cohort studies. *PLoS ONE*, *12*(10), 1–13. http://doi.org/10.1371/journal.pone.0185798

Zivin, K., Yosef, M., Miller, E. M., Valenstein, M., Duffy, S., Kales, H. C., … Kim, H. M. (2015). Associations between depression and all-cause and cause-specific risk of death: A retrospective cohort study in the Veterans Health Administration. *Journal of Psychosomatic Research*, *78*(4), 324–331. http://doi.org/10.1016/j.jpsychores.2015.01.014

Appendices

Appendices for chapter 2 (study1)

Appendix 2A. Inclusion and Exclusion Criteria

Appendix 2B. STROBE Checklist

Appendix 2C. Authors Contacted

Appendix 2D. Forest plot of all studies included in the analysis (incl. filled studies)

Appendix 2E. Funnel plot of all studies included in the analysis (incl. filled studies)

Appendix 2F. Funnel plot of depression studies

Appendix 2G. Forest plot of depression studies (incl. filled studies)

Appendix 2H. Funnel plot of depression studies (incl. filled studies)

Appendix 2I. Funnel plot of anxiety studies

Appendix 2J. Funnel plot of unspecified internalising symptoms.

Appendix 2K. Forest plot of unspecified internalising symptoms (incl. filled studies)

Appendix 2L. Funnel plot of unspecified internalising symptoms (incl. filled studies)

Appendix 2M. Supplementary References

Appendix 2A. Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met the following criteria:

(a) An assessment of family-related adverse childhood experiences was implemented
(b) Either a dichotomous or continuous measures of internalizing disorder was implemented.
(c) The study reported on a single family-related adverse childhood experience. E.g. childhood maltreatment, parental loss, parental divorce / separation, parental illness or parental mental illness.
(d) The study reported on multiple adverse childhood experiences

Exclusion criteria

Studies were excluded from the analysis if the met any of the following criteria:

(a) An adverse childhood experience assessment was not conducted
(b) A link between adverse childhood experience and internalizing disorder / symptoms is not apparent.
(c) Only 1 ACE (Unless that ACE is a search term specified)
(d) Only pre-natal adverse childhood experience was measured.
(e) No empirical or peer reviewed data is reported
(f) Case-report design
(g) There is no valid control group
(h) Outcomes aren't a valid measure of internalizing disorders (e.g. drug abuse, crime);
(i) The sample was <18 years old when assessed for internalizing disorders / symptoms
(j) There is only one outcome measure of bipolar disorder
(k) Exposure to adverse childhood experience took place after the age of 18
(l) Inappropriate analysis
(m) Overlapping Sample

Appendix 2B. STROBE Checklist

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any pre specified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

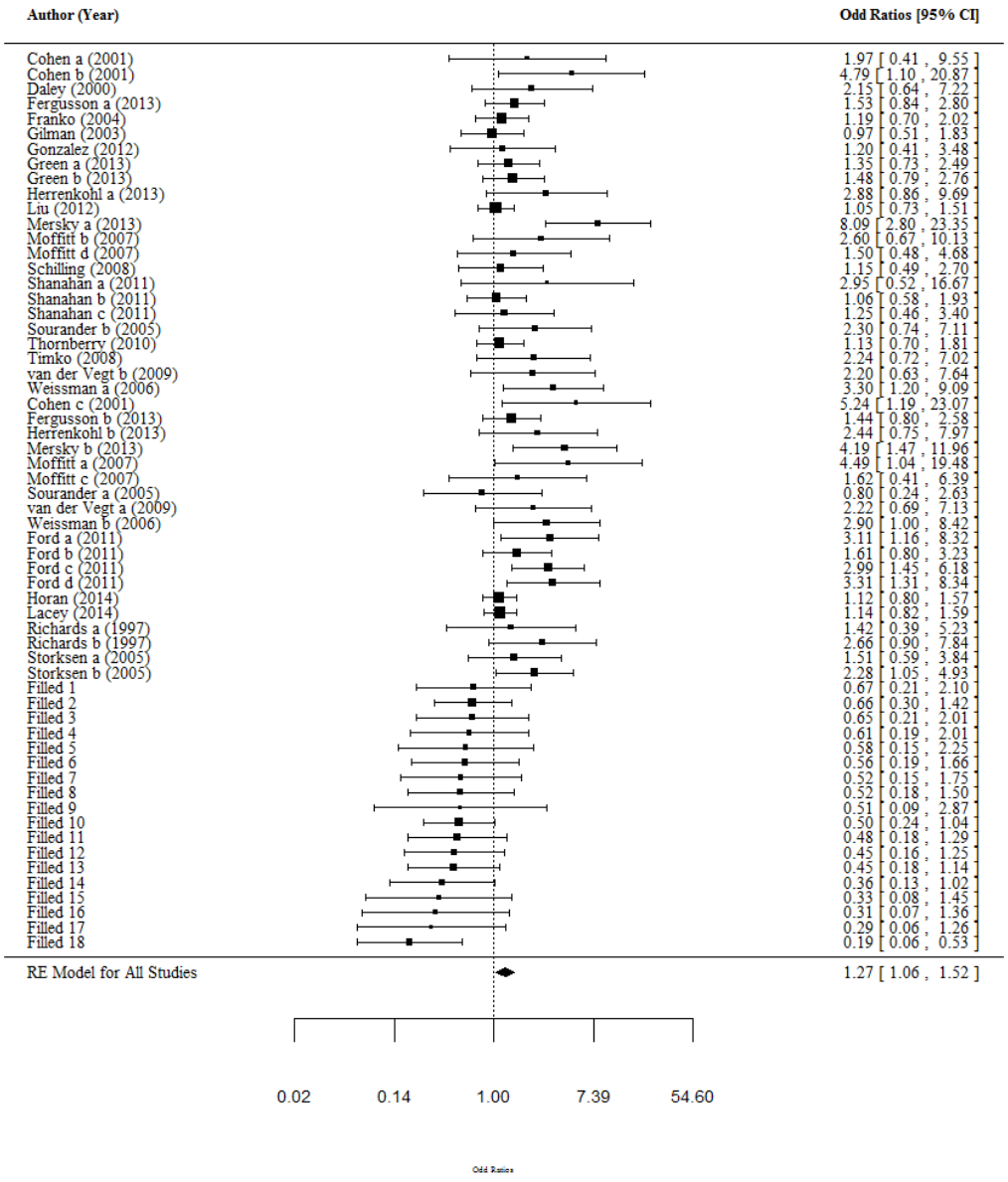
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence

		interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

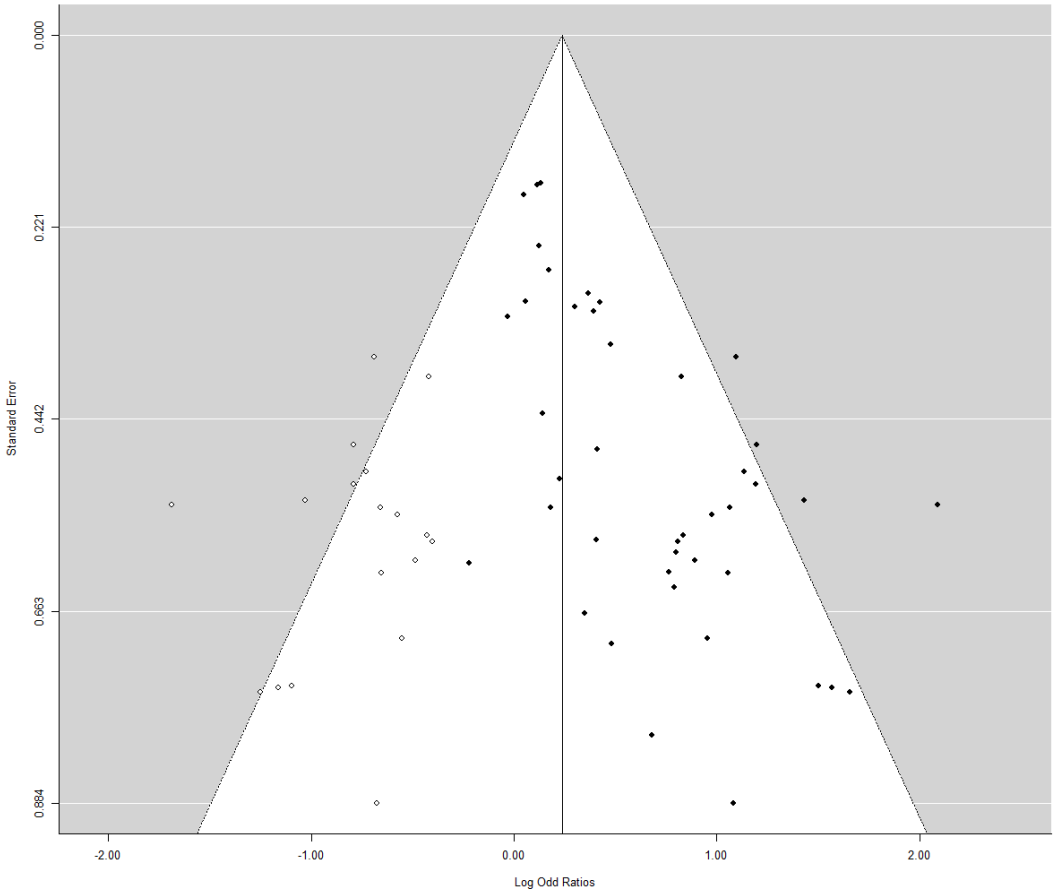
Appendix 2C. Authors contacted

Reason for contact	Authors responses	Data retrieved
Unpublished data from recognised experts in the field, of papers included in the analysis	5 contacted: 2 responders 3 non-responders	0 data sources retrieved

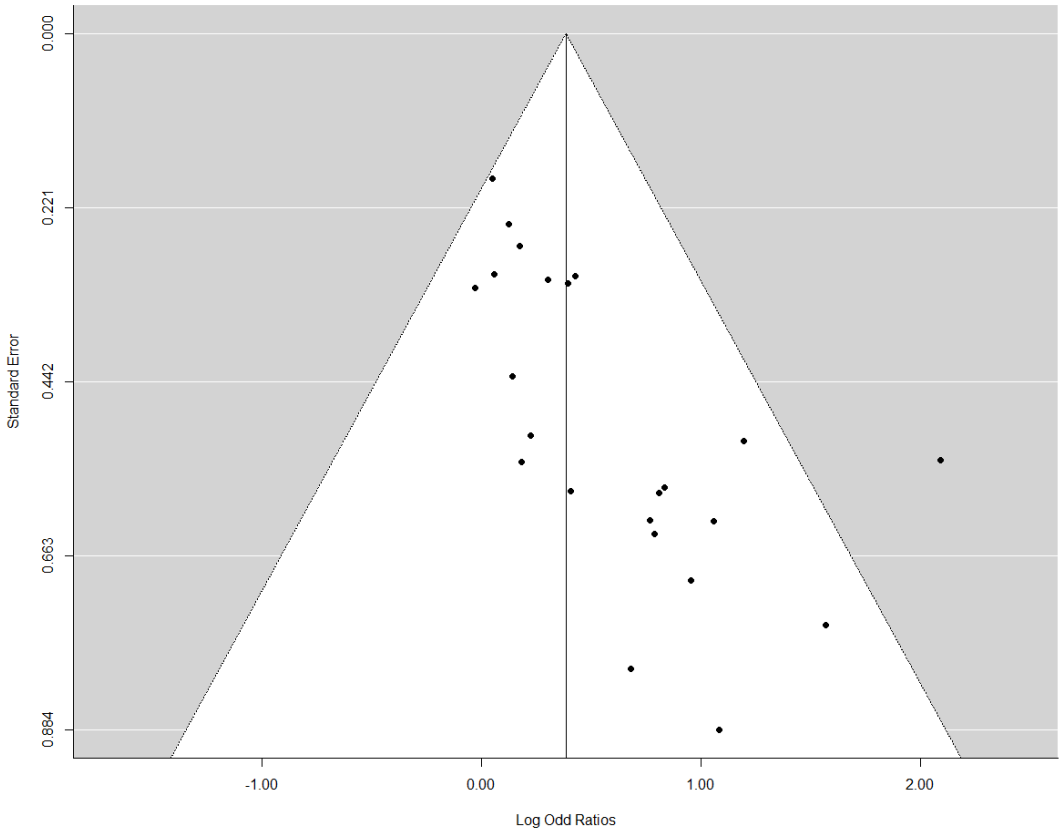
Appendix 2D. Forest plot of all studies included in the analysis (incl. filled studies)



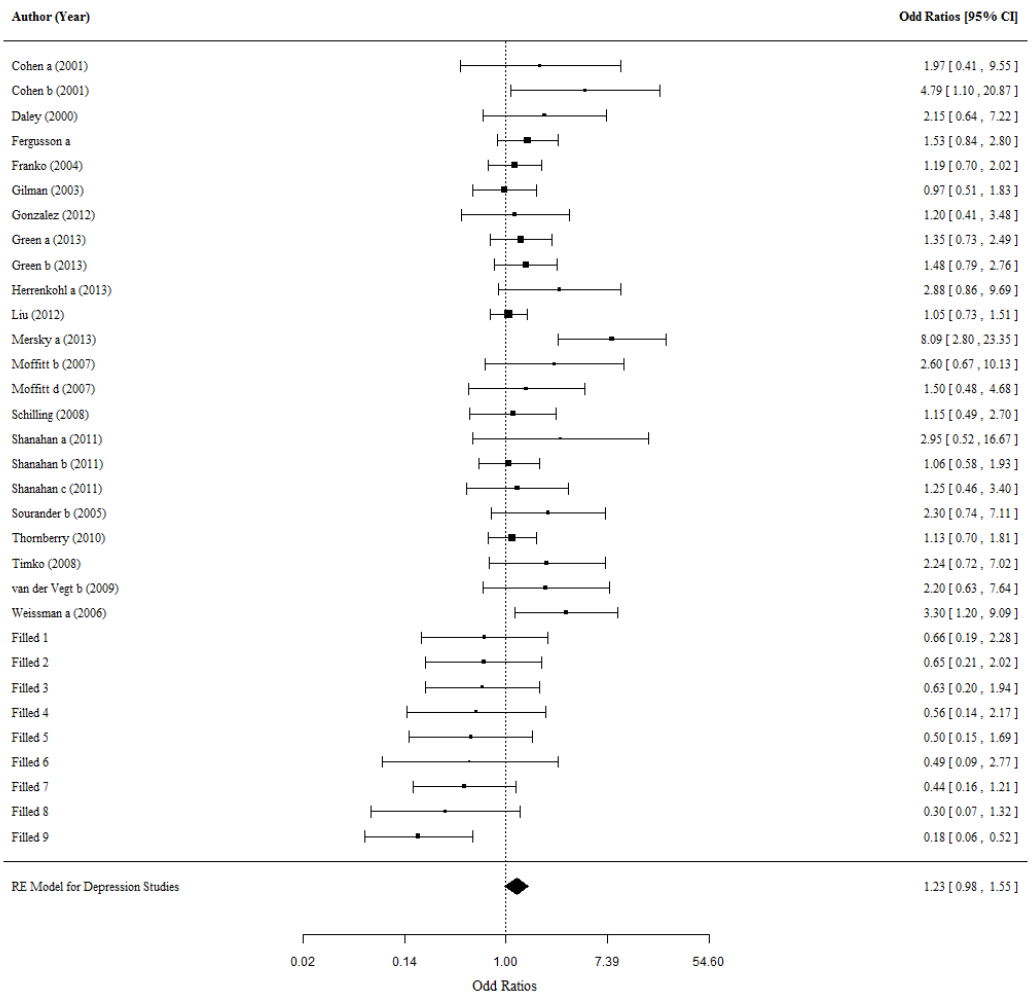
Appendix 2E. Funnel plot of all studies included in the analysis (incl. filled studies)



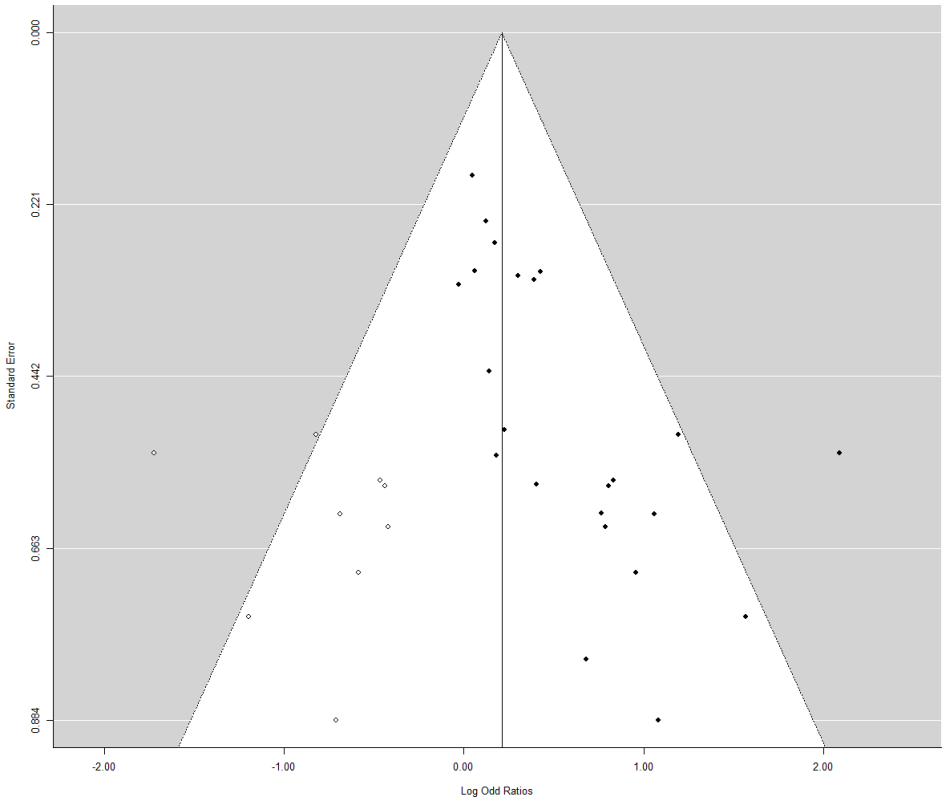
Appendix 2F. Funnel plot of depression studies



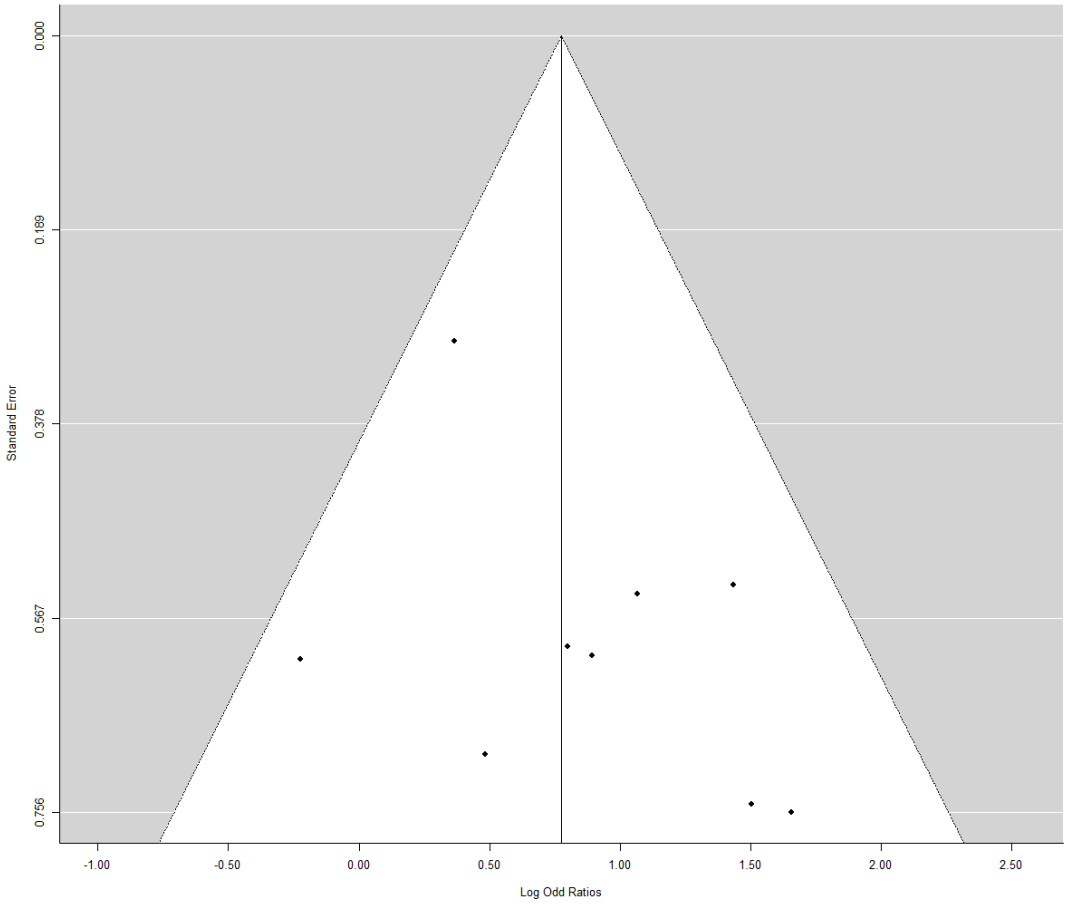
Appendix 2G. Forest plot of depression studies (incl. filled studies)



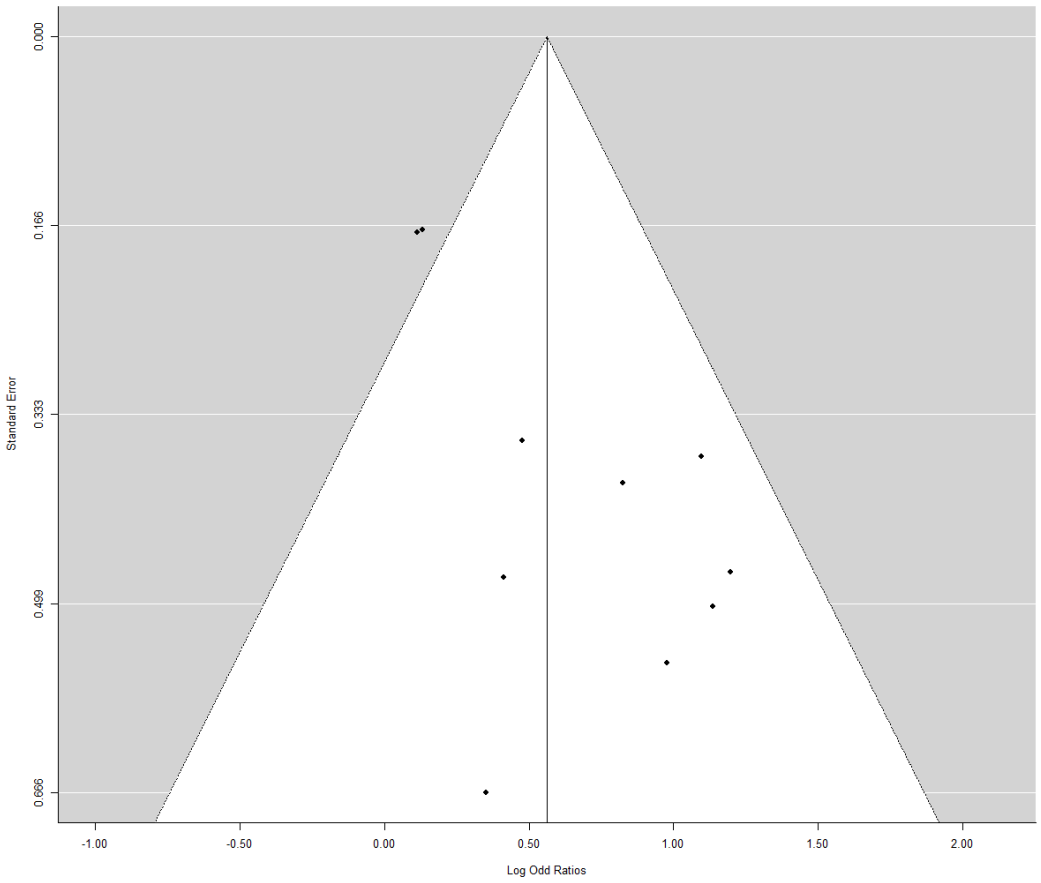
Appendix 2H. Funnel plot of depression studies (incl. filled studies)



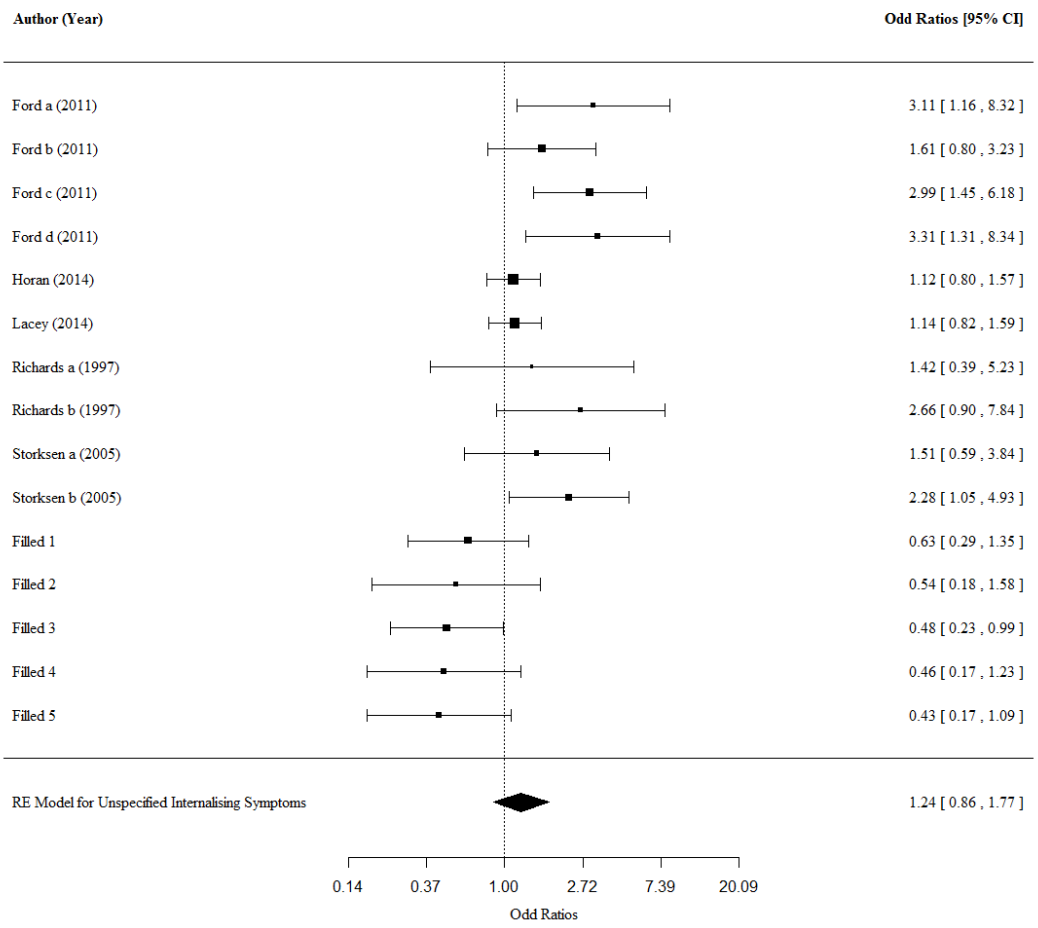
Appendix 2I. Funnel plot of anxiety studies



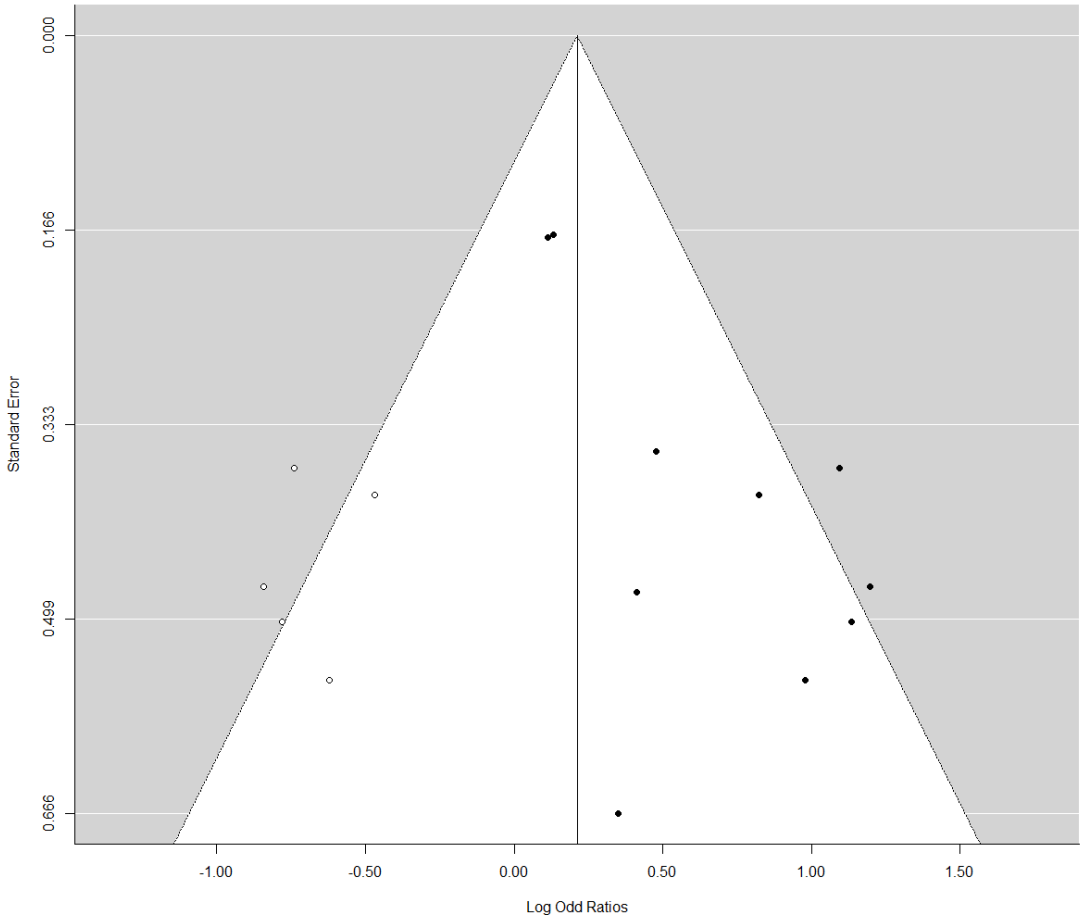
Appendix 2J. Funnel plot of unspecified internalising symptoms



Appendix 2K. Forest plot of unspecified internalising symptoms (incl. filled studies)



Appendix 2L. Funnel plot of unspecified internalising symptoms (incl. filled studies)



Appendix 2M. Supplementary References

Coffino, B. (2009). The role of childhood parent figure loss in the etiology of adult depression: findings from a prospective longitudinal study. *Attachment & Human Development*, *11*(5), 445–470. doi:10.1080/14616730903135993

Cohen, P., Brown, J., & Smaile, E. (2001). Child abuse and neglect and the development of mental disorders in the general population. *Development and Psychopathology*, *13*(4), 981–999.

Daley, S. E., Hammen, C., & Rao, U. (2000). Predictors of first onset and recurrence of major depression in young women during the 5 years following high school graduation. *Journal of Abnormal Psychology*, *109*(3), 525–533. doi:http://dx.doi.org/10.1037/0021-843X.109.3.525

Fergusson, D. M., McLeod, G. F. H., & Horwood, L. J. (2013). Childhood sexual abuse and adult developmental outcomes: findings from a 30-year longitudinal study in New Zealand. *Child Abuse & Neglect*, *37*(9), 664–74. doi:10.1016/j.chiabu.2013.03.013

Ford, E., Clark, C., & Stansfeld, S. A. (2011). The influence of childhood adversity on social relations and mental health at mid-life. *Journal of Affective Disorders*, *133*(1-2), 320–7. doi:10.1016/j.jad.2011.03.017

Franko, D. L., Striegel-Moore, R. H., Brown, K. M., Barton, B. a, McMahon, R. P., Schreiber, G. B., … Daniels, S. R. (2004). Expanding our understanding of the relationship between negative life events and depressive symptoms in black and white adolescent girls. *Psychological Medicine*, *34*(7), 1319–1330. doi:10.1017/S0033291704003186

Gilman, S. E., Kawachi, I., Fitzmaurice, G. M., & Buka, S. L. (2003). Socio-economic status, family disruption and residential stability in childhood: Relation to onset, recurrence and remission of major depression. *Psychological Medicine*, *33*(8), 1341–1355. doi:http://dx.doi.org/10.1017/S0033291703008377

Gonzalez, A., Boyle, M. H., Kyu, H. H., Georgiades, K., Duncan, L., & MacMillan, H. L. (2012). Childhood and family influences on depression, chronic physical conditions, and their comorbidity: Findings from the Ontario Child Health Study. *Journal of Psychiatric Research*, *46*(11), 1475–1482. doi:10.1016/j.jpsychires.2012.08.004

Green, K. M., Fothergill, K. E., Robertson, J. a., Zebrak, K. a., Banda, D. R., & Ensminger, M. E. (2013). Early life predictors of adult depression in a community cohort of urban African Americans. *Journal of Urban Health*, *90*(1), 101–115. doi:10.1007/s11524-012-9707-5

Herrenkohl, T. I. (2012). Developmental Impacts of Child Abuse and Neglect Related to Adult Mental Health, Substance Use, and Physical Health. *Changes*, *29*(6), 997–1003. doi:10.1016/j.biotechadv.2011.08.021.Secreted

Horan, J. M., & Widom, C. S. (2014). Cumulative childhood risk and adult functioning in abused and neglected children grown up. *Development and Psychopathology, in press*, 1–15. doi:10.1017/S095457941400090X

Lacey, R. E., Bartley, M., Pikhart, H., Stafford, M., & Cable, N. (2014). Parental separation and adult psychological distress: an investigation of material and relational mechanisms. *BMC Public Health*, *14*(1), 272. doi:10.1186/1471-2458-14-272

Liu, R. T., Jager-Hyman, S., Wagner, C. a, Alloy, L. B., & Gibb, B. E. (2012). Number of childhood abuse perpetrators and the occurrence of depressive episodes in adulthood. *Child Abuse & Neglect*, *36*(4), 323–32. doi:10.1016/j.chiabu.2011.11.007

Mersky, J. P., Topitzes, J., & Reynolds, a J. (2013). Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: a cohort study of an urban, minority sample in the U.S. *Child Abuse & Neglect*, *37*(11), 917–25. doi:10.1016/j.chiabu.2013.07.011

Moffitt, T. E., Caspi, A., Harrington, H., Milne, B. J., Melchior, M., Goldberg, D., & Poulton, R. (2007). Generalized anxiety disorder and depression: childhood risk factors in a birth cohort followed to age 32. *Psychological Medicine*, *37*(3), 441–452. doi:10.1017/S0033291706009640

Moretti, M. M., & Craig, S. G. (2013). Maternal versus paternal physical and emotional abuse, affect regulation and risk for depression from adolescence to early adulthood. *Child Abuse and Neglect*, *37*(1), 4–13. doi:10.1016/j.chiabu.2012.09.015

Oldehinkel, A. J., & Ormel, J. (2014). A longitudinal perspective on childhood adversities and onset risk of various psychiatric disorders. *European Child & Adolescent Psychiatry*, 641–650. doi:10.1007/s00787-014-0540-0

Raposa, E. B., Hammen, C. L., & Brennan, P. a. (2014). Close Friends' Psychopathology as a Pathway From Early Adversity to Young Adulthood Depressive Symptoms. *Journal of Clinical Child & Adolescent Psychology*, (July 2015), 1–9. doi:10.1080/15374416.2014.910788

Richards, M., Hardy, R., & Wadsworth, M. (1997). The effects of divorce and separation on mental health in a national UK birth cohort. *Psychological Medicine*, *27*(5), 1121–1128. doi:10.1017/S003329179700559X

Schilling, E. a, Aseltine, R. H., & Gore, S. (2008). The impact of cumulative childhood adversity on young adult mental health: measures, models, and interpretations. *Social Science & Medicine (1982)*, *66*(5), 1140–51. doi:10.1016/j.socscimed.2007.11.023

Shanahan, L., Copeland, W. E., Costello, E. J., & Angold, A. (2011). Child-, adolescent- and young adult-onset depressions: differential risk factors in

development? *Psychological Medicine*, *41*(11), 2265–2274. doi:http://dx.doi.org/10.1017/S0033291711000675

Sourander, A., Multimäki, P., Nikolakaros, G., Haavisto, A., Ristkari, T., Helenius, H., … Almqvist, F. (2005). Childhood predictors of psychiatric disorders among boys: a prospective community-based follow-up study from age 8 years to early adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry*, *44*(8), 756–767. doi:10.1097/01.chi.0000164878.79986.2f

Størksen, I., Røysamb, E., Moum, T., & Tambs, K. (2005). Adolescents with a childhood experience of parental divorce: A longitudinal study of mental health and adjustment. *Journal of Adolescence*, *28*(6), 725–739. doi:10.1016/j.adolescence.2005.01.001

Thornberry, T. P., Henry, K. L., Ireland, T. O., & Smith, C. a. (2010). The Causal Impact of Childhood-Limited Maltreatment and Adolescent Maltreatment on Early Adult Adjustment. *Journal of Adolescent Health*, *46*(4), 359–365. doi:10.1016/j.jadohealth.2009.09.011

Timko, C., Cronkite, R. C., Swindle, R., Robinson, R. L., Turrubiartes, P., & Moos, R. H. (2008). Functioning status of adult children of depressed parents: a 23-year follow-up. *Psychological Medicine*, *38*(3), 343–352. doi:10.1017/S0033291707002073

Van der Vegt, E. J. M., Tieman, W., van der Ende, J., Ferdinand, R. F., Verhulst, F. C., & Tiemeier, H. (2009). Impact of early childhood adversities on adult psychiatric disorders: a study of international adoptees. *Social Psychiatry and Psychiatric Epidemiology*, *44*(9), 724–731. doi:10.1007/s00127-009-0494-6

Weissman, M. M., Warner, V., Wickramaratne, P., Moreau, D., & Olfson, M. (1997). Offspring of depressed parents. 10 Years later. *Archives of General Psychiatry*, *54*(10), 932–940. doi:10.1001/archpsyc.1997.01830220054009

Appendices for chapter 4 (study 3)

Appendix 4A. Information on early life predictors.

Appendix 4B. Count and percentage of survey member in original and imputed variable.

Appendix 4C. Information on auxiliary variables used when conducting multiple imputation on original variables.

Appendix 4D. Correlations (unstandardized) for latent factor scores of affective symptoms.

Appendix 4E. Number of participants that had information on affective symptoms at each time

Appendix 4A. Count and percentage of survey member in original and imputed variable

Adversity Category	Adversity Type	Comparison groups (0, 1)	Original Variable *N* (%)	Imputed variable *N* (%)
Family Instability	Parental Divorce (by age 15)	no divorce	4246 (93.4)	4688 (87.4)
		divorce	300 (6.6)	674 (12.6)
	Death of any parent (by age 15)	no death	4516 (93.4)	4983 (92.9)
		death	321 (6.6)	379 (7.1)
	Break with Mother (before 15 years)	no	5072 (94.6)	5072 (94.6)
		yes	289 (5.4)	289 (5.4)
	Residential Moves	0-2 moves	3720 (69.4)	4472 (83.4)
		3+ moves	799 (14.9)	890 (16.6)
Family Socio-economic circumstances	Fathers Education	> primary	1808 (42.2)	2273 (42.4)
		primary only	2477 (57.8)	3089 (57.6)
	Mothers Education	> primary	1582 (29.5)	1973 (36.8)
		primary only	2759 (51.5)	3389 (63.2)
	Lack of home amenities	3 or less	2974 (82.9)	4562 (85.1)
		>3	615 (11.5)	800 (14.9)
	Crowding	<3 per room	4491 (83.8)	5178 (96.6)
		3 or more per room	162 (3)	184 (3.4)
	Fathers social class	non-manual	1926 (41.2)	2198 (41)
		Manual	2747 (51.2)	3164 (59)
Parents Age	Teen Father	20+ years	4156 (99.5)	5303 (98.9)
		<20 years	22 (0.5)	59 (1.1)

	Teen Mother	20+ years	4101 (97.9)	5215 (97.3)
		<20 years	86 (2.1)	147 (2.7)
	Mid aged father	40 years or less	3744 (89.6)	4725 (88.1)
		>40 year	434 (10.4)	637 (11.9)
	Mid aged mother	40 years or less	4059 (96.9)	5147 (96)
		>40 year	128 (3.1)	215 (4)
Childrearing environment and Parenting	Breastfeeding	Yes	3651 (76.3)	4101 (76.5)
		No	1261 (23.5)	1261 (23.5)
	Mothers management and understanding	Among the best	2157 (48.3)	2579 (48.1)
		Average/Among the worse	2307 (51.7)	2783 (51.9)
	Parents interest in child education	Average or high interest in primary and/or secondary education	2624 (83)	4250 (79.2)
		Low interest in both primary and secondary education	537 (17)	1112 (20.8)
	Cleanliness of child (1950)	Average / among the most clean	2833 (61.7)	3280 (61.2)
		Among the least clean	1762 (38.3)	2082 (38.8)
	Cleanliness of house (1950)	Among the most clean	1121 (59.40)	146 (57)
		Average / Among the least clean	766 (40.60)	110 (43)
	Clothes repair (1950)	Satisfactory state of repair	4541 (98.1)	5257 (98)

		Unsatisfactory state of repair	90 (1.9)	105 (2)
	Shoes repair (1950)	Satisfactory size and type	4492 (83.8)	5218 (97.3)
		Unsatisfactory size and type	115 (2.5)	144 (2.7)
	Fathers perceived health	Excellent	3104 (80)	4282 (79.9)
		Average / poor	776 (20)	1080 (20.1)
	Mother perceived health	Excellent	3072 (76.5)	4104 (76.5)
		Average / poor	944 (23.5)	1258 (23.5)
Parents Health	Maternal neuroticism	no	3917 (97.3)	5227 (97.5)
		yes	110 (2.1)	135 (2.5)
Childhood Health	Birth Weight	>2500	5010 (94)	5041 (94)
		2500 or less	317 (6)	321 (6)
	Chronic Illness (before age 15)	no (or after 15 years)	4333 (80.8)	4333 (80.8)
		yes	1029 (19.2)	1029 (19.2)

Appendix 4B. Information on auxiliary variables used when conducting multiple imputation on original variables

		Variable description	Variable Name	Date Collected	Notes / categories	Missing Data Code	*N missing (%)*	Imputation type	Auxiliary variables used
Family Instability	1.	**Parental Divorce**	DIV15	1961	Parents' divorce by age 15y 0 = no 1 = yes	none	816	Binary "logreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.
	2.	**Death of any parent**	DP0TO15	1961	Death of any parent between 0-15 years 0 = no 1 = yes	none	525	Binary "logreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.
	3.	Break with Mother	DABNR	1961	Age at break with mother 0 = no or after 15 1 = before 15	none	**1**	**na**	-
	4.	Residential Moves	TOTMOV61	1961	Label: How many times SM had moved within G.B. from 1946-1961. See Note TOTMOV48.	0 = None. See note to TOTMOV48 9 = No information	843	Numerical "norm"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.

Family SES	5.	Fathers Education	fed	1946	1 = Primary only 2 = Primary & no diploma 3 = Primary & no diploma 4 = Primary & Professional degree, diploma 5 = Secondary only 6 = Secondary & no diploma 7 = Secondary & tech/course diploma 8 = Secondary & Professional degree, diploma	-9989 = unknown	1077	Categorical, "polyreg"	none
	6.	Mothers Education	med	1946	1 = Primary only 2 = Primary & no diploma 3 = Primary & no diploma 4 = Primary & Professional degree, diploma 5 = Secondary only 6 = Secondary & no diploma 7 = Secondary & tech/course diploma 8 = Secondary & Professional degree, diploma	-9989 = unknown	1021	Categorical, "polyreg"	none
	7.	Lack of home amenities	AML215	1948-1961	Continuous variable of lack of home amenities between the ages of 2 and 15.	none	1773	Numerical "norm"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.
	8.	Crowding	crow50	1950	1 = 1/2 person per room 2 = 1 person per room 3 = 1 1/2 person per room 4 = 2 persons per room 5 = 2 1/2 persons per room	-9989 = unknown -9799 unknown	709	Categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education and father's occupational status,

					6 = 3 persons per room 7 = 3 1/2 persons per room 8 = 3 1/2+ persons per room				
	9.	**Father's occupational status**	chsc	1946	1 = professional etc 2 = intermediate 3 = skilled(Non-Manual) 4 = skilled(Manual) 5 = partly skilled 6 = unskilled	9 = unknown	689	Categorical, "polyreg"	none
	10.	Family Size	FAM61	1961	Number of children in family when this child was 15 = complete family size	-9969 = unknown (blank on rubric card)	1192	Numerical "norm"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.
Parental age	11.	Fathers age at birth	PAB46	1946	Father's age at birth of survey child. Actual age in years coded (PAB = FAB)	-9999 = unknown -9699 = unknown	1186	numerical, "norm"	none
	12.	Mothers age at birth	MAB46	1946	Mother's age at birth of survey child	-9999 = unknown	1177	numerical, "norm"	none
Childrearing and parenting	13.	Breastfeeding	BRE	1946	0 = Never breast fed 1 = Stopped 1st month 2 = Stopped 2nd month 3 = Stopped 3rd month 4 = Stopped 4th month 5 = Stopped 5-7 months 6 = Stopped 8-10 months 7 = Stopped after 10 months	-9999 = unknown -9899 = unknown	580	categorical, "polyreg"	none

14.	Mothers management and understanding	man50	1950	Mother's management and understanding of child compared with others in H.V. (Health Visitor) care 1950 (not cleanliness of child or home) 1 = average 2 = among the best 3 = among the worse	-9899 = no answer -9799 = 19 cases no label	898	categorical	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education and father's occupational status,
18.	Parent's interest in child education	PARPS	1961	Parents' interest - primary and secondary 1 = High interest Secondary and Primary 2 = High interest Secondary and medium interest Primary 3 = High interest Secondary and low interest Primary 4 = Average interest Secondary and high interest Primary 5 = Average interest Secondary and medium interest Primary 6 = Average interest Secondary and low interest Primary 7 = Low interest Secondary and high interest Primary 8 = Low interest Secondary and medium interest Primary 9 = Low interest Secondary and low interest Primary	-9999 = unknown -9899 = unknown -9799 = not at school	2738	Categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.
19.	Cleanliness of child (1950)	clc50	1950	Cleanliness of child 1950 (Health Visitor's opinion) 1 = Average, compared with others in Health Visitor's care 2 = Among the most clean 3 = Among the least clean	-9899 = no answer -9799 = 6 cases no label	767	categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education and father's occupational status,

20.	Cleanliness of house (1950)	clh50	1950	Cleanliness of house 1950 - Health Visitor's opinion 1 = Average, compared with others in Health Visitor's care 2 = Among the most clean 3 = Among the least clean	-9899 = no answer -9799 = 6 cases no label	908	categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education and father's occupational status,
21.	Clothes repair (1950)	clo50	1950	Clothes repair 1950 (health visitor's opinion) 1 = Satisfactory state of repair 2 = Unsatisfactory state of repair	-9899 = no answer -9799 = 7 cases no label	731	categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education and father's occupational status,
22.	Shoes repair (1950)	sho50	1950	Child's shoes 1950 1 = Satisfactory size and type 2 = Unsatisfactory size and type	-9899 = no answer -9799 = 7 cases no label	755	categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education and father's occupational status,
23.	Fathers perceived health	FHS61	1961	Husband's health 1961 0 = Excellent, Good 1 = Excellent, Good but complaint/disability 2 = Average 3 = Average but complaint/disability 4 = Poor	-9999 = unknown -9899 = unknown -9799 = dead or away	1484	categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.
24.	Mother perceived health	MHS61	1961	Summary of mother's health 1961 0 = Excellent, Good 1 = Excellent, Good but complaint/disability 2 = Average 3 = Average but complaint/disability 4 = Poor	-9999 = unknown -9899 = unknown	1348	categorical "polyreg"	Birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, father's occupational status, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.

Parental health Childhood health	25.	Maternal neuroticism	MPI61	1961	Maudsley Personality Inventory (neuroticism scale only) completed by mother MPI on a scale from 0-6?	-9999 = unknown -9899 = unknown -9799 = Mother dead	1377	Numerical “norm”	Birth weight, breastfeeding, paternal age, maternal age, fathers’ education, mothers’ education, father’s occupational status, crowding, mother’s management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Cognition at age 8 and cognition at age 11.
	26.	Birth Weight	MBWTU	1946	1946 Birth Weight in Metric units gms	none	35	Numerical, "norm"	none
	27.	Chronic Illness	ILS	1961	Chronic illness before age 15y 0 = no 1 = yes’		**0**	**na**	-

Appendix 4C. Number of participants that had information on affective symptoms at each time point

Age affective symptom measure was taken	Ordinal affect symptom levels	Males n (%) *N* = 2815	Females n (%) *N* = 2547	Total n (%) *N* = 5362
13	No symptoms	981 (34.8)	877 (34.4)	1858 (34.7)
	Mild symptoms	465 (16.5)	445 (17.5)	910 (17)
	Moderate symptoms	292 (10.4)	259 (10.2)	551 (10.3)
	Severe symptoms	195 (6.9)	172 (6.8)	367 (6.8)
	Total Valid	1933 (68.7)	1753 (68.8)	3686 (68.7)
	Total Missing	882 (31.1)	794 (31.2)	1678 (31.3)
15	No symptoms	1073 (38.1)	1013 (39.8)	2086 (38.9)
	Mild symptoms	389 (13.8)	342 (13.4)	731 (13.6)
	Moderate symptoms	300 (10.7)	266 (10.4)	566 (10.6)
	Severe symptoms	197 (7)	174 (6.8)	371 (6.9)
	Total Valid	1959 (69.6)	1795 (70.5)	3754 (70)
	Total Missing	856 (30.4)	752 (29.5)	1608 (30)

36	No symptoms	898 (31.9)	784 (30.8)	1682 (31.4)
	Mild symptoms	414 (14.7)	399 (15.7)	813 (15.2)
	Moderate symptoms	261(9.3)	234 (9.2)	495 (9.2)
	Severe symptoms	180 (6.4)	152 (6)	332 (6.2)
	Total Valid	1753 (62.3)	1569 (61.6)	3322 (62)
	Total Missing	1062 (37.7)	978 (38.4)	2040 (38)
43	No symptoms	857 (30.4)	766 (30.1)	1623 (30.3)
	Mild symptoms	414 (14.7)	397 (15.6)	811 (15.1)
	Moderate symptoms	262 (9.3)	226 (8.9)	488 (9.1)
	Severe symptoms	187 (6.6)	136 (5.3)	323 (6)
	Total Valid	1720 (61.1)	1525 (59.9)	3245 (60.5)
	Total Missing	1095 (38.9)	1022 (40.1)	2117 (39.5)
53	No symptoms	798 (28.3)	720 (28.3)	1518 (28.3)
	Mild symptoms	365 (13)	319 (12.5)	684 (12.8)
	Moderate symptoms	237 (8.4)	203 (8)	440 (8.2)
	Severe symptoms	157 (5.6)	133 (5.2)	290 (5.4)

	Total Valid	1557 (55.3)	1375 (54)	2932 (54.7)
	Total Missing	1258 (44.7)	1172 (46)	2430 (45.3)
60-64	No symptoms	577 (20.5)	515 (20.2)	1092 (20.4)
	Mild symptoms	249 (8.8)	290 (11.4)	539 (10.1)
	Moderate symptoms	156 (5.5)	170 (6.7)	326 (6.1)
	Severe symptoms	61 (2.2)	154 (6)	215 (4)
	Total Valid	1043 (37.1)	1129 (44.3)	2172 (40.5)
	Total Missing	1772 (62.9)	1418 (55.7)	3190 (59.5)
69	No symptoms	684 (24.3)	603 (23.7)	1287 (24)
	Mild symptoms	144 (5.1)	172 (6.8)	316 (5.9)
	Moderate symptoms	142 (5)	174 (6.8)	316 (5.9)
	Severe symptoms	70 (2.5)	141 (5.5)	211 (3.9)
	Total Valid	1040 (36.9)	1090 (42.8)	2130 (39.7)
	Total Missing	1775 (63.1)	1457 (57.2)	3232 (60.3)

Appendix 4D. Correlations (unstandardized) for latent factor scores of affective symptoms.

	13	15	36	43	53	60-64	69
13	1						
15	.424***	1					
36	.060**	.071***	1				
43	0.67**	.083***	.333***	1			
53	0.51**	.084***	.213***	.332***	1		
60-64	.026	.014	.035	.117***	.102***	1	
69	.034	.013	.193***	.250***	.273***	.151***	1

Appendix 4E. Complete case analysis (i.e. those who had information on affective symptoms available at every time point, *n* = 4788).

		Model 3 adjusted for sex, cognition by age 8, education attainment by age 26, and social class by age 53 OR (95% CI)		
			Count (%)	
Age	**No symptoms (ref)**	**Mild Symptoms**	**Moderate symptoms**	**Severe symptoms**
13	-	1.08 (.99;1.18)	1.02 (.92; 1.12)	.91 (.79; 1.03)
	247 (49.6)	118 (23.7)	83 (16.7)	50 (10)
15	-	.95 (.86; 1.03)	1.02 (.92; 1.13)	.92 (.82; 1.05)
	284 (57)	103 (20.7)	64 (12.9)	47 (9.4)
36	-	.99 (.92; 1.08)	1.12 (1.01; 1.24).	.99 (.88; 1.13)
	245 (49.2)	133 (26.7)	75 (15.1)	45 (9)
43	-	1.02 (.94; 1.11)	1.02 (.92; 1.14)	1.11 (.96; 1.28)
	263 (52.8)	141 (28.3)	62 (12.4)	32 (6.4)
53	-	.97 (.89; 1.06)	.98 (.89; 1.09)	1.01 (.91; 1.13)
	248 (49.8)	113 (22.7)	79 (15.9)	58 (11.6)
60-64	-	1.01 (.93; 1.10)	1.01 (.90; 1.12)	1.06 (.94; 1.20)
	278 (50)	155 (27)	76 (13.2)	56 (9.8)
69	-	1.00 (.90; 1.10)	1.01 (.91; 1.12)	1.11 (.98; 1.26)
	369 (64.3)	82 (14.3)	82 (14.3)	41 (7.1)

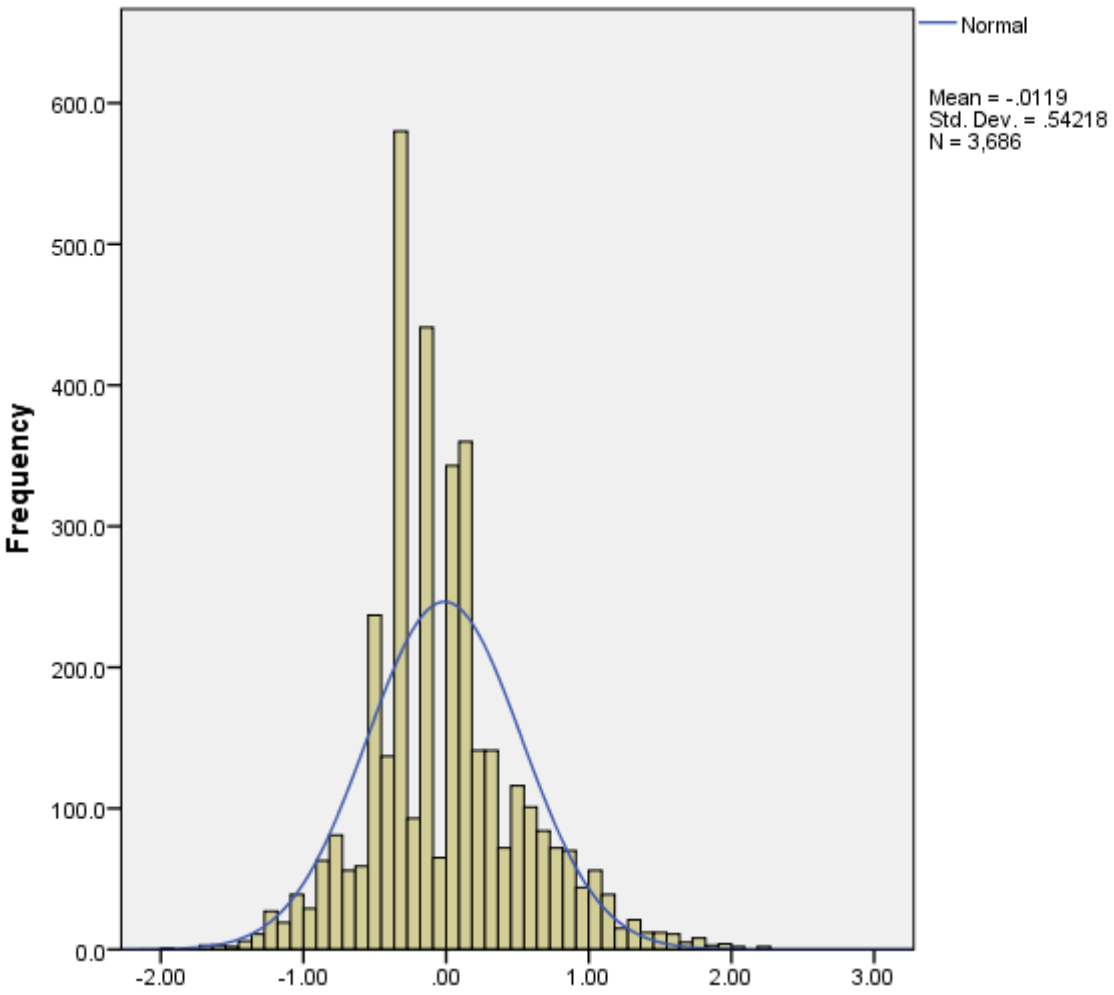
Appendix 4F. Results of association analysis using multinomial logistic regression analysis for the quadratic relationship between ACEs and affective symptom severity at different ages (no depression is the control group).

			Model 1b (unadjusted) OR (95% CI)		
Age	**Number of ACEs**	**No symptoms (ref)**	**Mild Symptoms**	**Moderate symptoms**	**Severe symptoms**
13	0-3 ACEs	-	1.01 (.83;1.23)	1.06 (.84; 1.35)	1.01 (.76; 1.33)
	4-6 ACEs (ref)	-	-	-	-
	7-20 ACEs		1.03 (.85;1.25)	1.12 (.89; 1.40)	1.09 (.83; 1.42)
15	0-3 ACEs	-	.99 (.80; 1.21)	1.12 (.88; 1.41)	.90 (.63; 1.31)
	4-6 ACEs (ref)	-	-	-	-
	7-20 ACEs		.90 (.74; 1.10)	1.11 (.89; 1.39)	1.07 (.82; 1.41)
36	0-3 ACEs	-	1.00 (.81; 1.23)	1.13 (.88; 1.45)	.98 (.75; 1.28)
	4-6 ACEs (ref)	-	-	-	-
	7-20 ACEs	-	1.04 (.85; 1.27)	1.16 (.91; 1.48)	1.15 (.86; 1.53)

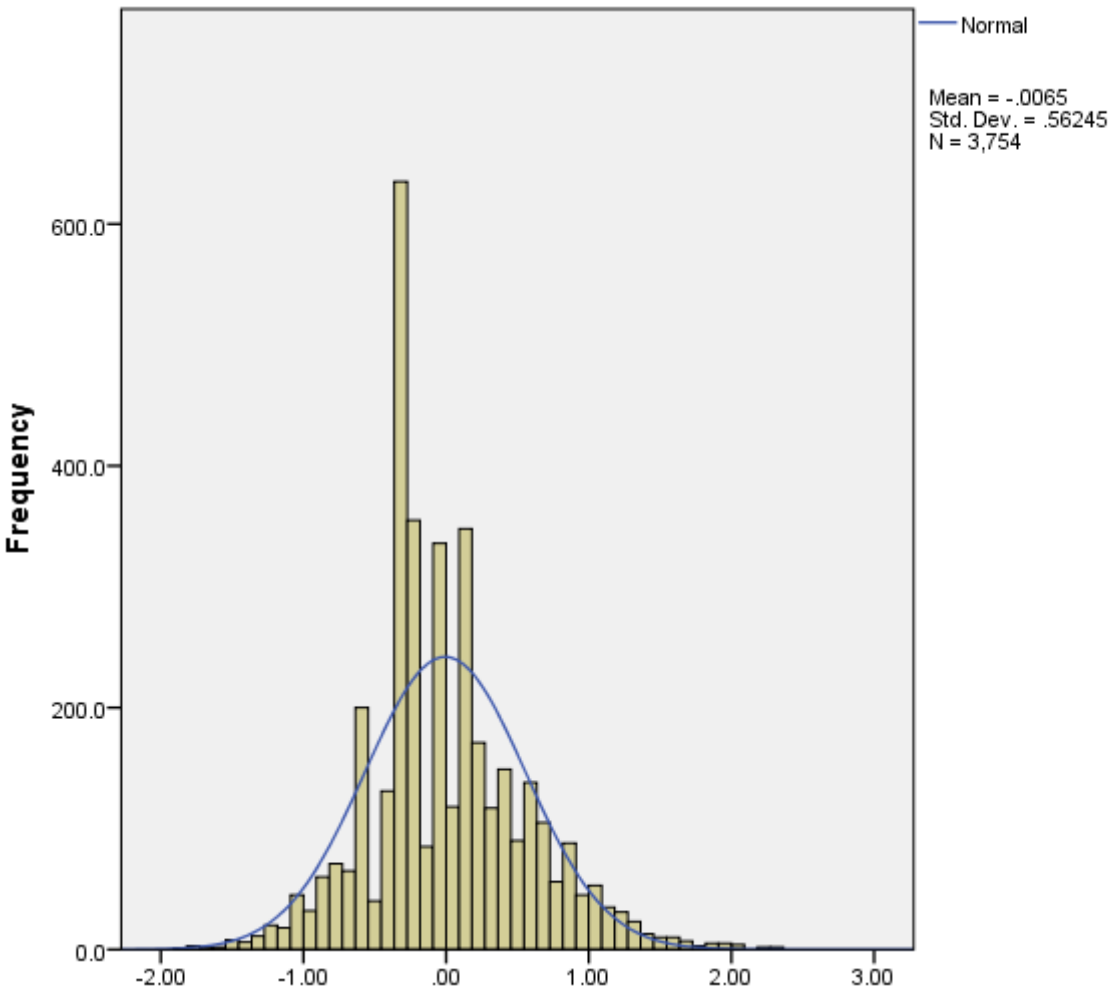
43	0-3 ACEs	-	1.02 (.83; 1.26)	.89 (.68; 1.13)	1.06 (.78; 1.42)
	4-6 ACEs (ref)	-	-	-	-
	7-20 ACEs		.96 (.78; 1.17)	.90 (.71; 1.15)	1.05 (.79; 1.40)
53	0-3 ACEs	-	1.02 (.81; 1.28)	.94 (.72; 1.22)	.90 (.66; 1.22)
	4-6 ACEs (ref)	-	-	-	-
	7-20 ACEs		1.17 (.94; 1.45)	.98 (.76; 1.26)	.84 (.62; 1.13)
60-64	0-3 ACEs	-	.83 (.65; 1.06)	.93 (.69; 1.24)	.94 (.66;1.35)
	4-6 ACEs (ref)	-	-	-	-
	7-20 ACEs		1.16 (.90; 1.51)	.97 (.71; 1.33)	1.44 (1.00; 2.07)
69	0-3 ACEs	-	.88 (.66; 1.18)	1.01 (.76; 1.36)	.91 (.63; 1.30)
	4-6 ACEs (ref)	-	-	-	-
	7-20 ACEs		.96 (.70; 1.31)	1.03 (.75; 1.42)	1.45 (1.01; 2.07)

Appendices for chapter 5 (study 4)

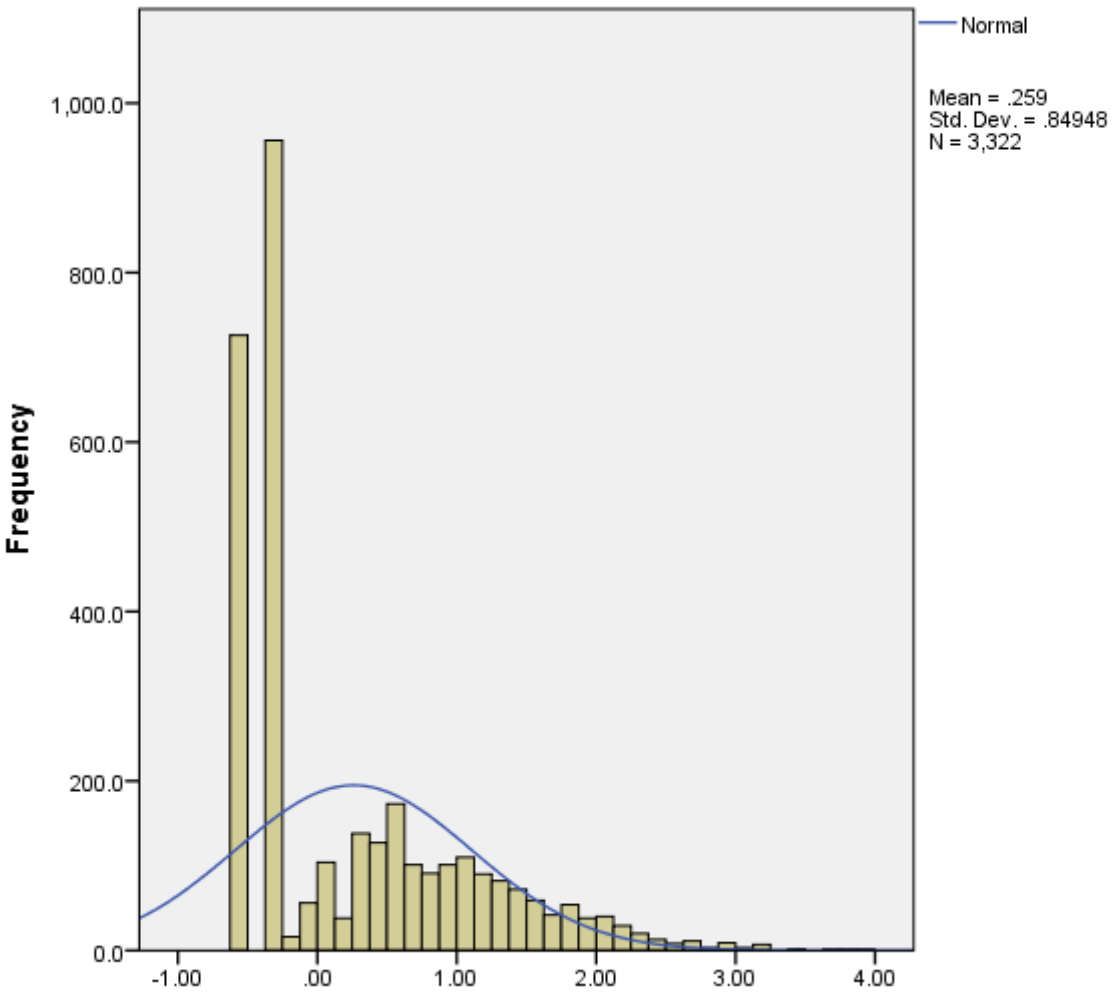
Appendix 5Q. Results of association analysis using multinomial logistic regression analysis for different types of adverse childhood experiences and life course profiles of affective symptoms excluding those who died by age 69 (no affective symptoms is the control group)



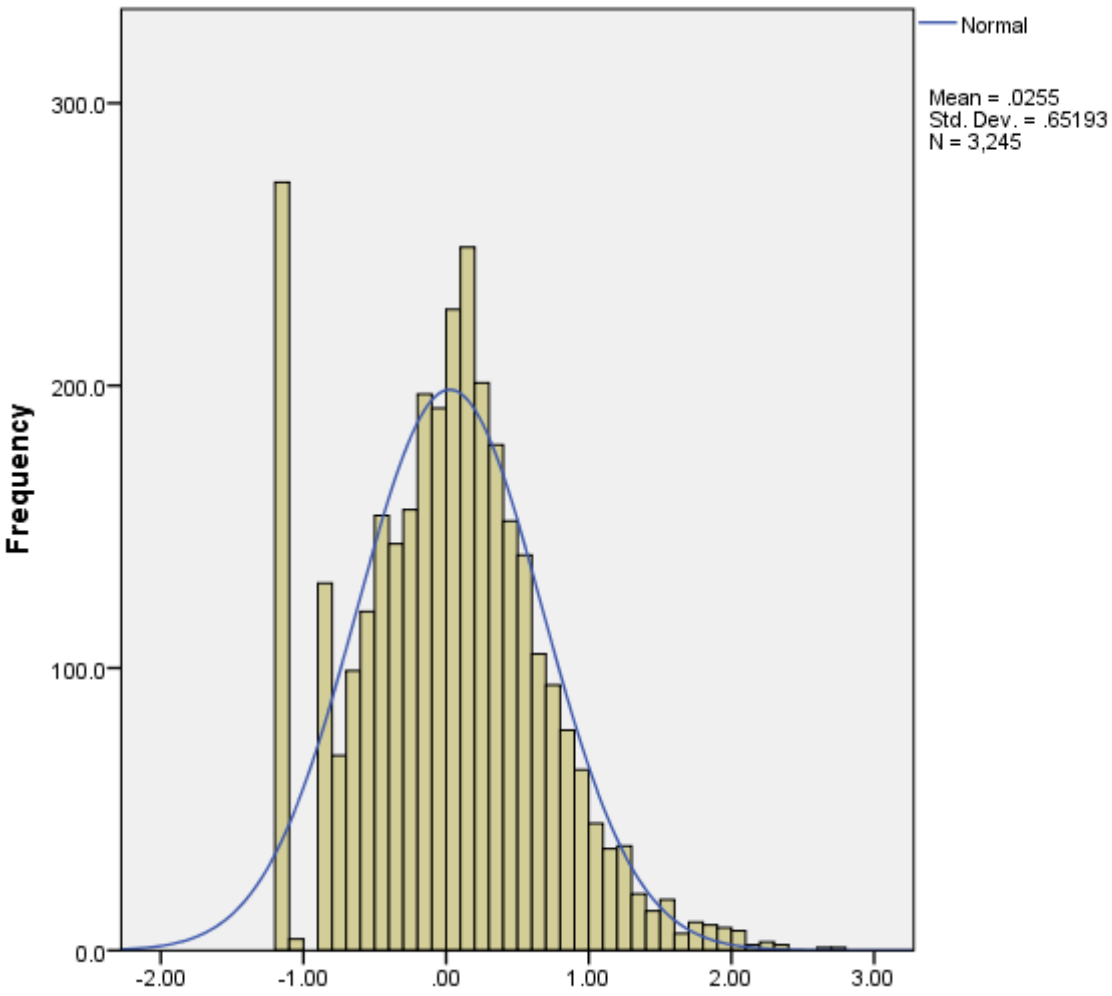
Appendix 5A. Distribution of latent factor scores for affective symptoms at age 13



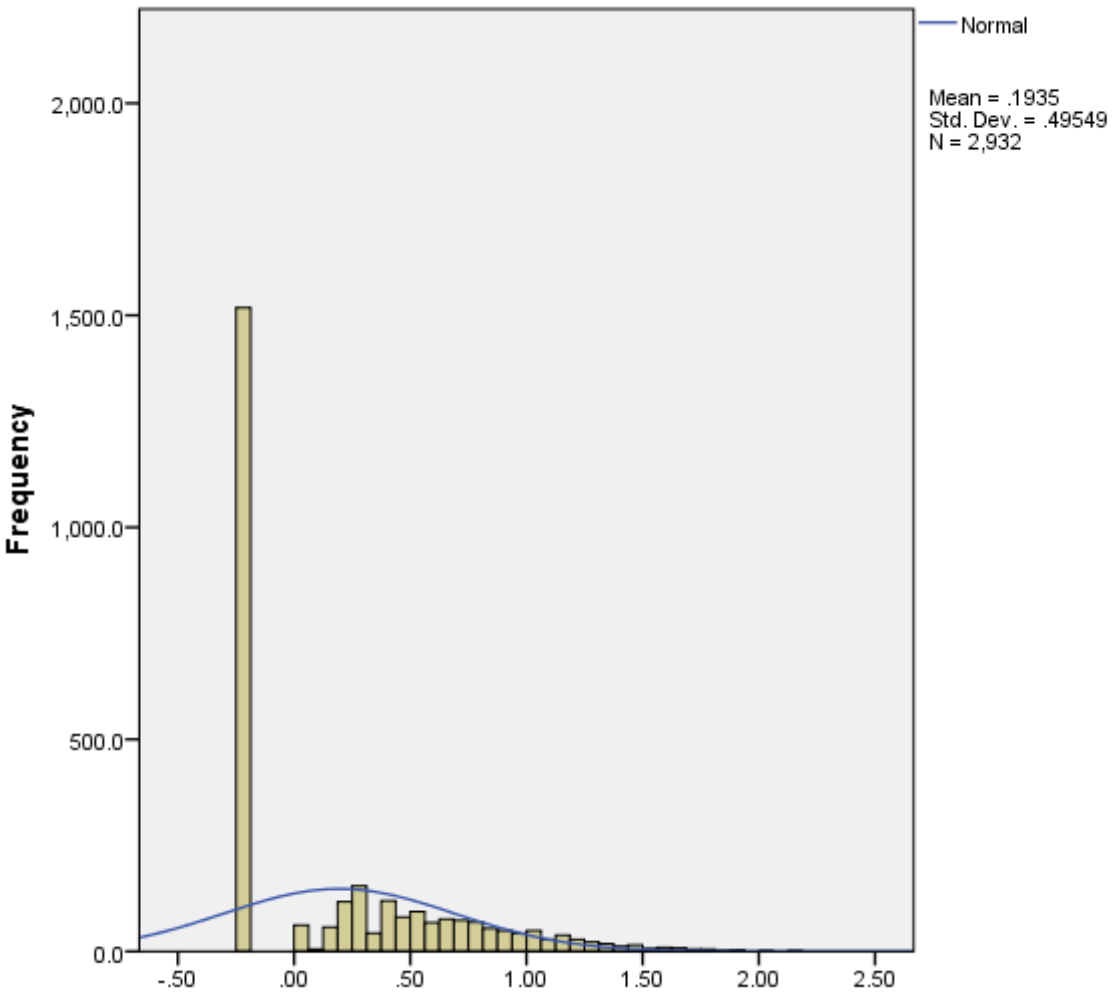
Appendix 5B. Distribution of latent factor scores for affective symptoms at age 15



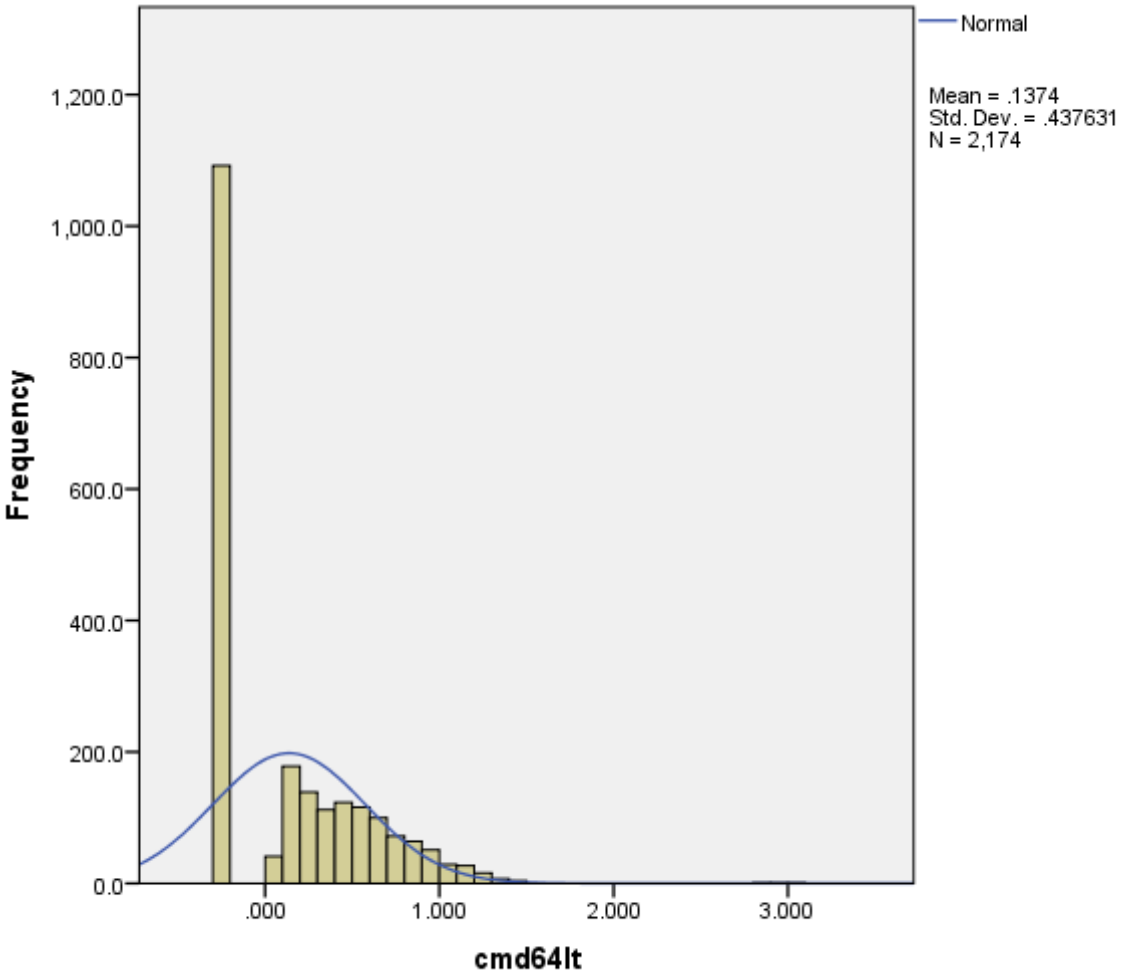
Appendix 5C. Distribution of latent factor scores for affective symptoms at age 36



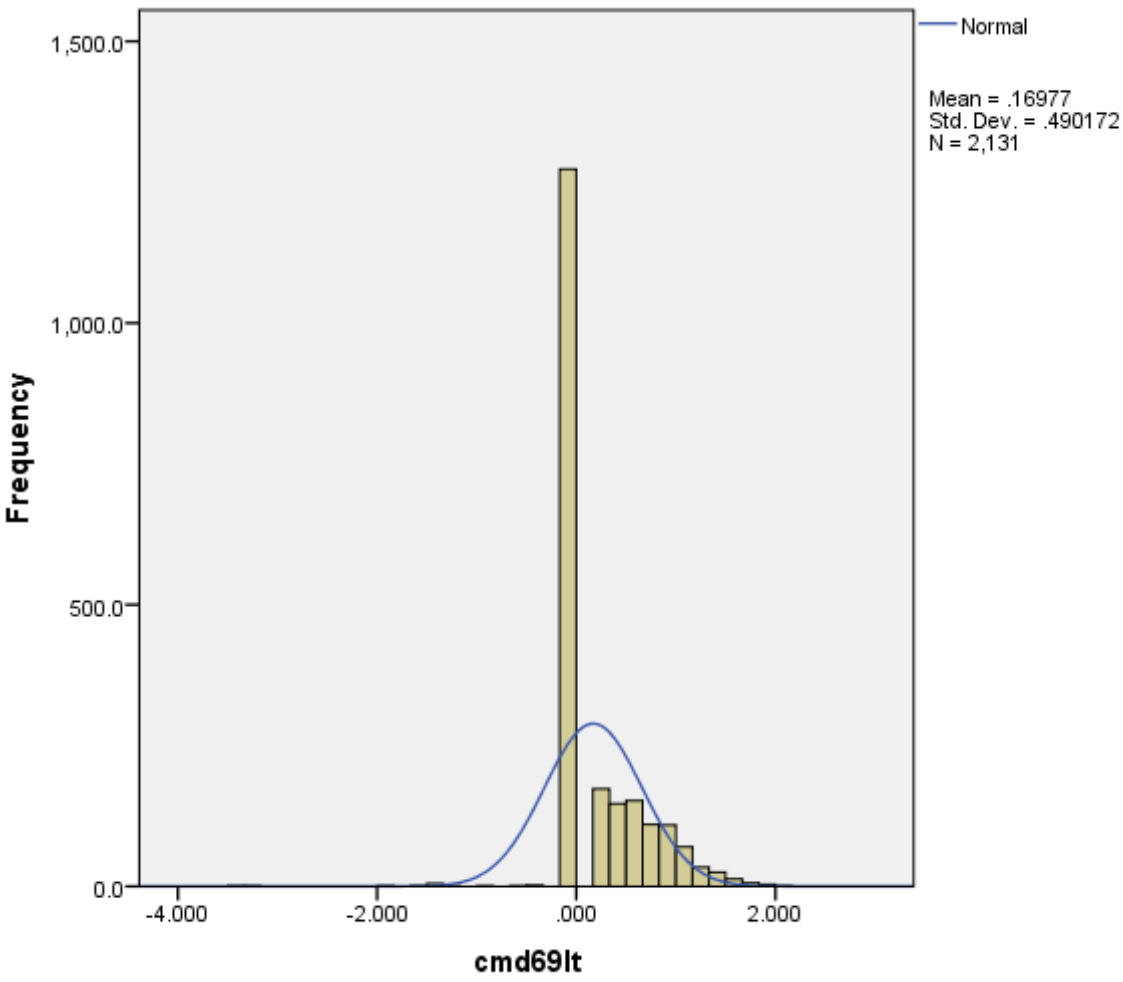
Appendix 5D. Distribution of latent factor scores for affective symptoms at age 43



Appendix 5E. Distribution of latent factor scores for affective symptoms at age 53



Appendix 5F. Distribution of latent factor scores for affective symptoms at age 60-64



Appendix 5G. Distribution of latent factor scores for affective symptoms at age 69

Appendix 5H. Number of participants who have information on affective symptom trajectories and adversities

Adversity Category	Adversity Type	Absence of symptoms	Adolescent symptoms only	Adult symptoms only	Adolescent onset repeated symptoms	Adolescent and adult symptoms	Later life symptoms only	Total *N*
		N	***N***	***N***	***N***	***N***	***N***	
Total		2888	671	575	174	198	468	4974
Family Instability	Parental Divorce (by age 15)	2432	584	492	140	171	391	4210
	Death of any parent (by age 15)	2071	269	655	1631	178	419	4484
	Break with mother (before 15 years)	2887	671	575	174	198	468	4973
	Residential Moves (by age 15)	2428	568	469	156	169	431	4221
Family Socioeconomic circumstances	Fathers education	2294	535	449	151	164	400	3993
	Mothers education	2331	546	453	149	164	407	4050
	Lack of home amenities	1908	472	379	130	128	335	3352
	Crowding	2486	580	489	163	174	440	4385

	Father's occupational status	2502	587	494	160	175	436	4354
	Family Size	2237	537	445	153	156	405	3993
Parents Age	Teenage father	2243	523	432	146	153	402	3899
	Teenage mother	2248	523	432	144	153	399	3908
	Mid aged father	2243	523	432	146	153	402	3899
	Mid aged mother	2248	523	432	147	155	403	3908
Childrearing environment and parenting	Breastfeeding	2555	611	512	166	177	437	4458
	Mothers management and understanding	2399	557	466	153	163	419	4157
	Paternal neglect (PBI)	1529	335	310	126	113	385	2798
	Maternal neglect (PBI)	1561	340	305	129	112	384	2831
	Parents interest in child education (primary and secondary)	1686	380	345	113	119	312	2955
	Cleanliness of child (1950)	2450	578	481	162	175	431	4277

	Cleanliness of house (1950)	2450	588	465	158	165	413	4139
	Clothes repair (1950)	2480	579	482	162	172	437	4312
	Shoes repair (1950)	2467	579	481	160	172	431	4290
Parental Health	Fathers perceived health	2071	499	405	134	140	373	3622
	Mothers perceived health	2152	511	414	144	148	381	3750
	Maternal neuroticism	2163	510	414	145	146	382	3760
Childhood Health	Birth weight	2869	669	567	174	196	467	4942
	Chronic Illness (before age 15)	2888	671	575	174	198	468	4974

Appendix 5I. Contingency table for non-imputed early life risk factors across six life course profiles of affective symptoms

Adversity Category	**Adversity Type**	**Comparison groups (0, 1, 2)**	**Absence of symptoms *N* (%)**	**Adolescent symptoms only *N* (%)**	**Adult symptoms only *N* (%)**	**Adolescent onset repeated symptoms *N* (%)**	**Adolescent and adult symptoms *N (%)***	**Later life symptoms only**	**Total *N* (%)**
Family Instability	Parental Divorce (by age 15)	no divorce	2268(93.3)	548(93.8)	458(93.1)	128(91.4)	160(93.6)	365(93.4)	3927(93.3)
		divorce	164(6.7)	36(6.2)	34(6.9)	12(8.6)	11(6.4)	26(6.6)	283(6.7)
	Death of any parent (by age 15)	no death	2423(93)	581(94.3)	486(94.2)	136(91.3)	166(93.3)	388(32.6)	4180(93.2))
		death	183(7)	35(5.7)	30(5.8)	13(8.7)	12(6.7)	31(7.4)	304(6.8)
	Break with Mother (before 15 years)	no	2730(94.6)	635(94.6)	543(94.4)	163(93.7)	187(94.4)	443(94.7)	4701(94.5)
		yes	157(5.4)	36(5.4)	32(5.6)	11(6.3)	11(5.6)	25(5.3)	272(5.5)
	Residential Moves	0 (ref)	605(24.9)	129(22.8)	109(10.6)	35(3.4)	47(4.6)	107(24.8)	1032(24.5)
		1 – 3 moves	1664(68.6)	401(70.7)	329(11.3)	114(73.1)	114(67.5)	295(68.4)	2917(69.1)
		4+ moves	158(6.5)	37(6.5)	31(6.6)	7(4.5)	8(4.7)	29(6.7)	270(6.4)
Family Socio-economic circumstances	Fathers Education	> primary	555(24.2)	114 (21.3)	124(27.6)	39(25.8)	50(30.5)	107(26.8)	989(24.8)
		primary only	1739(75.8)	421(78.7)	325(72.4)	112(74.2)	114(69.5)	293(73.3)	3004(75.2)
	Mothers Education	> primary	444 (19)	111(20.3)	88(19.4)	34(22.8)	39(23.8)	106(26)	822(20.3)
		primary only	1887 (81)	435(79.7)	365(80.6)	115(77.2)	125(76.2)	301(74)	3228(79.7)

	Lack of home amenities	Lacks 0 or 1(ref)	1067(55.9)	256(54.2)	196(51.7)	74(56.9)	62(48.4)	201(62.7)	1865(55.6)
		Lacks 2 or 3	504(26.4)	134(28.4)	114(30.1)	33(25.4)	44(34.4)	87(26)	916(27.3)
		Lacks 4+	337(17.7)	82(17.4)	69(18.2)	23(17.7)	22(17.2)	38(11.3)	571(17)
	Crowding	½ - 1 person per room (ref)	1364(56.1)	322 (55.5)	279(57.1)	90(55.2)	95(54.6)	255(58)	2435(56.2)
		1 – 2 ½ people per room	1009(40.6)	236(40.7)	195(39.9)	65(39.9)	72(41.4)	171(38.9)	1748(40.4)
		3+ people per room	83(3.3)	22(3.8)	15(3.1)	8(4.9)	7(4)	14(3.2)	149(3.4)
	Father's occupational status	non-manual	1032(41.2)	242(41.2)	199(40.3)	64(40)	70(40)	197(45.2)	1804(41.4)
		Manual	1470(58.8)	345(58.8)	295(59.7)	96(60)	105(60)	239(54.8)	2550(58.6)
	Family size	0-3 children	1591(71.1)	372(69.3)	316(71)	107(69.9)	110(70.5)	290(71.6)	2786(70.8)
		4+ children	646(28.9)	165(30.7)	129(29)	46(30.1)	46(29.5)	115(28.4)	1147(29.2)
Parents Age	Teen Father	20+ years	2228(99.3)	522(99.8)	428(99.1)	146(100)	153(100)	401(99.8)	3878(99.5)
		<20 years	15(0.7)	1(0.2)	4(0.9)	0(0)	0(0)	1(0.2)	21(0.5)
	Teen Mother	20+ years	2197(97.7)	513(98.1)	424(98.1)	144(98)	153(98.7)	399(99)	3830(98.0)
		<20 years	51(2.3)	10(1.9)	8(1.9)	3(2)	2(1.3)	4(1)	78(2.0)
	Mid aged father	40 years or less	2023(90.2)	464(88.7)	387(89.6)	130(89)	128(83.7)	362(90)	3494(89.6)
		>40 year	220(9.8)	59(11.3)	45(10.4)	16(11)	25(16.3)	40(10)	405(10.4)
	Mid aged mother	40 years or less	2183(97.1)	510(97.5)	413(95.6)	143(97.3)	150(96.8)	386(95.8)	3758(96.9)
		>40 year	65(2.9)	13(2.5)	19(4.4)	43.2)	5(3.2)	17(4.2)	123(3.1)

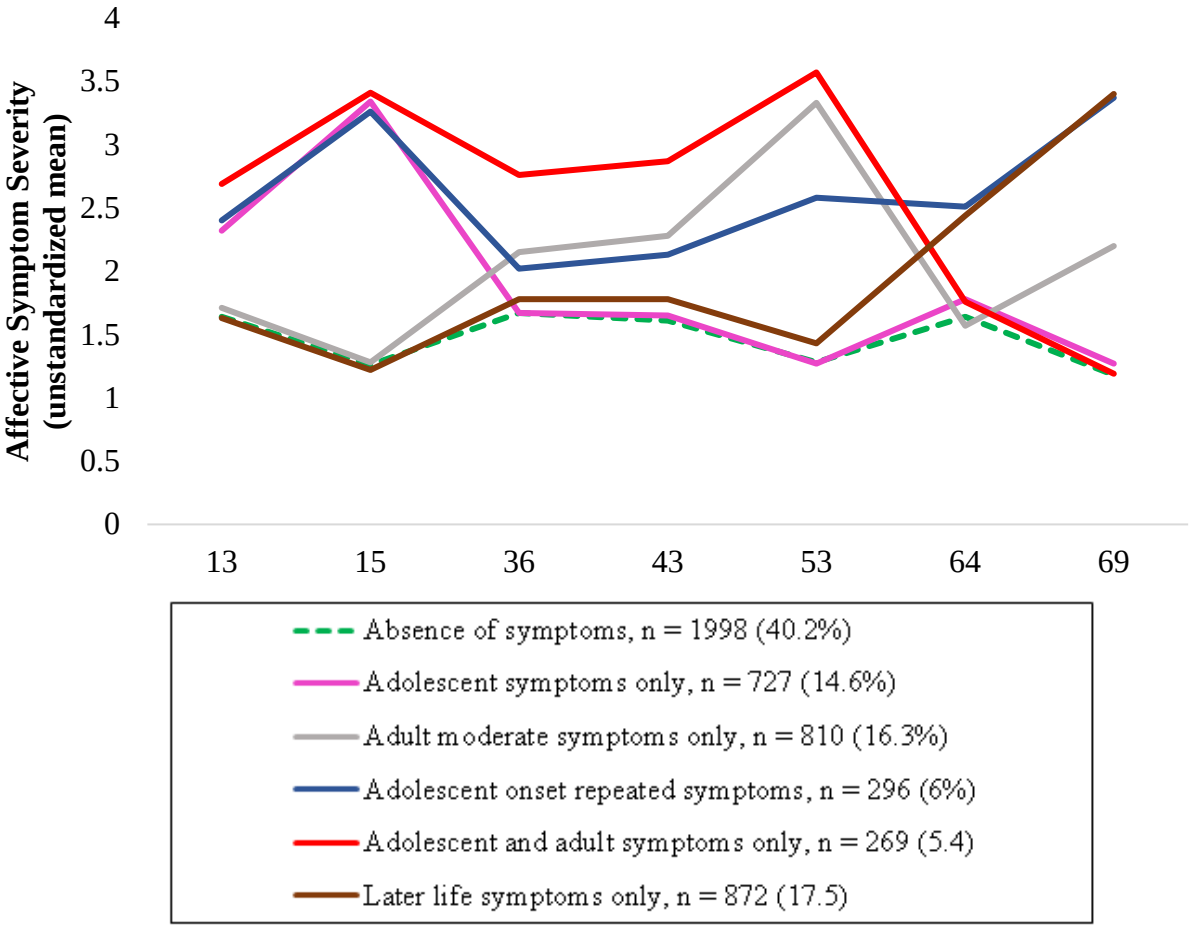
Childrearing environment and Parenting	Breastfeeding	Breastfed for 5+ months (ref)	1076(42.1)	244(40)	189(36.9)	74(44.6)	72(40.7)	197(45.1)	1852(41.6)
		Breastfed for 1-4 months	882(34.5)	209(34.3)	185(36.1)	58 (34.9)	59(33.3)	165 (37.8)	1558 (35)
		Never breastfed	596(23.3)	157(25.7)	138(27)	34(20.5)	46(26)	75(17.2)	1046(23.5)
	Mothers management and understanding	Among the best	1139(47.5)	278 (49.9)	229(49.1)	73(47.7)	78(47.9)	230(54.9)	2027(48.8)
		Average / Among the worse	1260(52.5)	279(50.1)	237(50.9)	80(52.3)	85(52.1)	189(45.1)	2130(51.2)
	Paternal neglect (PBI)	No neglect	1035(67.7)	241(71.9)	207(66.8)	96(76.2)	70(61.9)	281(73)	1930(69)
		Neglect	494(32.3)	94(28.1)	103(33.2)	30(23.8)	43(38.1)	104(27)	721(31)
	Maternal neglect (PBI)	No neglect	1066(68.3)	229(67.4)	196(64.3)	89(70.5)	79(70.5)	274(71.4)	1933(68.3)
		Neglect	495(31.7)	111(32.6)	109(35.7)	40(31)	33(29.5)	110(28.6)	898(31.7)
	Parents interest in child education	High interest in primary or secondary education (ref)	619(36.7)	132(34.8)	119(34.5)	37(32.7)	49(41.2)	122(39.1)	1078(36.5)
		Average interest in primary or secondary education	542(32.2)	99(26.1)	123(35.7)	29(25.7)	28 (23.5)	90 (28.8)	911(30.8)
		Low interest in primary or secondary education	524 (31.1)	148(39.1)	103(29.9)	47(41.6)	42 (35.3)	100(32.1)	964(32.6)
	Cleanliness of child (1950)	Among the most clean	1503(61.3)	358(61.9)	306(63.6)	100(61.7)	113(64.6)	270(62.6)	2650(62)

		Average/Among the least clean	947(38.7)	220(38.1)	175(36.4)	62(38.3)	62(35.4)	161(37.4)	1627(38)
	Cleanliness of house (1950)	Among the most clean	1380(58)	328(58.8)	282(60.6)	87(55.1)	99(60)	241(58.4)	2417(58.4)
		Average / Among the least clean	1000(42)	230(41.2)	183(39.4)	71(44.9)	66(40)	172(41.6)	1722(41.6)
	Clothes repair (1950)	Satisfactory state of repair	2431(98)	572(98.8)	471(97.7)	161(99.4)	167(97.1)	430(98.4)	4232(98.1)
		Unsatisfactory state of repair	49(2)	7(1.2)	11(2.3)	1(0.6)	5(2.9)	7(1.6)	80(1.9)
	Shoes repair (1950)	Satisfactory size and type	2402(97.4)	567(97.9)	467(97.1)	154(96.3)	169(98.3)	424(98.4)	4183(97.5)
		Unsatisfactory size and type	65(2.6)	12(2.1)	14(2.9)	6(3.8)	3(1.7)	7(1.6)	107(2.5)
Parents Health	Fathers perceived health	Good	1021(49.3)	228(45.8)	199(49.1)	68(50.7)	60(42.9)	178(47.7)	1754 (48.5)
		Average	655(31.6)	173(34.7)	126(31.1)	35(26.1)	49(35)	113(30.3)	1151(31.8)
		Poor	394(19)	97(19.5)	80(19.8)	31(23.1)	31(22.1)	82(22)	715(19.8)
	Mother perceived health	Good	914(42.5)	202(39.6)	164(39.6)	55(38.2)	51(34.5)	148(38.8)	1534 (40.9)
		Average	742(34.5)	176(34.5)	172(41.5)	50(34.7)	57(38.5)	138(36.2)	1335(35.6)
		Poor	495(23)	132(25.9)	78(18.8)	39(27.1)	40(27)	95(24.9)	879(23.5)
	Maternal neuroticism	no	2104(97.3)	498(97.6)	402(97.1)	139(95.9)	140(95.9)	372(97.4)	3655(97.2)
		yes	59(2.7)	12(2.4)	12(2.9)	6(4.1)	6(4.1)	10(2.6)	105(2.8)
Childhood Health	Birth Weight	2500 – 4000 grams	2389(83.3)	560(83.7)	443 (78.1)	140(80.5)	169(86.2)	407(87.2)	4108 (83.1)

		>4000 grams	309 (10.8)	70 (10.5)	75 (13.2)	20(11.5)	18 (9.2)	43 (9.2)	535 (10.8)
		2500 or less grams	171(6)	39(5.8)	49(8.6)	14(8)	9(4.6)	17(3.6)	299(6.1)
	Chronic Illness (before age 15)	no (or after 15 years)	2334(80.8)	540(80.5)	462(80.3)	140(80.5)	161(81.3)	388(82.9)	4025(80.9)
		yes	554(19.2)	131(19.5)	113(19.7)	34(19.5)	37(18.7)	80(17.1)	949(19.1)

Note. Early life predictors of life course profiles of affective symptoms (6 profiles): A total of 4974 participants were included in the association analyses testing for the effects of individual early life predictors on six life course profiles of affective symptoms. Two early life predictors (teenage mother and teenage father) were omitted from the analysis due to low sample sizes. For the profile of adolescent symptoms only, one early life predictor – interest in child's education – was identified: those whose parents had a low interest in their education were 1.32 times more likely to develop adolescent symptoms only compared to those who had a high interest in child's education (b =.28, Wald χ^2 =4.42, p = .035). For the profile of adult symptoms only, several early life predictors were identified: individuals who were never breastfed were 1.32 times more likely to develop adult affective symptoms only than individuals who were breastfed for 5-10 months (b =.28, Wald χ^2 = 5.04, p = .025); offspring of Mother's who perceived their health to be excellent / average (with complaint or disability) were 1.29 times more likely to develop adult symptoms only than those who Mother's perceived health was perceived to be excellent / average (without complaint or disability) (b =.26, Wald χ^2 = 4.57, p = .033); those who weighed >4000 grams at birth were 1.31 times more likely to develop adult symptoms only compared to those who weighed between 2500 and 4000 grams (b =.27, Wald χ^2 = 3.77, p = .052); those who weighed <2500 grams at birth were 1.55 times more likely to develop adult

symptoms only compared to those who weighed between 2500 and 4000 grams (b =.43, Wald χ^2 =6.55, p = .011). For the profile of adolescent onset repeated symptoms no early life predictors were identified. For the profile of adolescent and adult symptoms only, two early life predictors were identified: individuals who lacked 2 or 3 home amenities in childhood were 1.5 times more likely to develop adolescent and adult symptoms only compared to those who lacked 0 or 1 home amenity (b =.41, Wald χ^2 =3.40, p = .046); those whose father was over 40 years at birth were 1.8 times more likely to develop moderate adolescent and adulthood symptoms than those whose father was under 40 years at birth (b = .59, Wald χ^2 = 6.49, p = .011). For the profile of later life symptoms only, several early life predictors were identified: offspring of mothers with a primary level of education were 1.5 times less likely to develop symptoms in later life than offspring of mother with a higher level of education (b = -.40, Wald χ^2 = 10.47, p = .001); individuals who lacked 3 or more home amenities in childhood were 1.7 times less likely to develop affective symptoms in later life (b = -.53, Wald χ^2 = 8.87, p = .003); individuals who were never breastfed were 1.46 times less likely to develop later life symptoms than those who were breastfed for 5-10 months (b =-38, Wald χ^2 = 6.69, p = .010); offspring whose mother's management and understanding was average / among the worse were less likely to develop symptoms in later life than those whose mothers management and understanding was among the best (b = -.38, Wald χ^2 = 8.07, p = .004); those who experienced neglect by fathers were less likely to develop symptoms in later life than those who experienced neglect (b = -.25, Wald χ^2 = 4.00, p = .045); those who weighed <2500 grams at birth were 1.72 times less likely to develop later life symptoms compared to those who weighed between 2500 and 4000 grams (b =-.54, Wald χ^2 = 4.30, p = .038).


Affective Symptom Severity (unstandardized mean)
4
3.5
3
2.5
2
1.5
1
0.5
0
13
15
36
43
53
64
69
Absence of symptoms, n = 1998 (40.2%)
Adolescent symptoms only, n = 727 (14.6%)
Adult moderate symptoms only, n = 810 (16.3%)
Adolescent onset repeated symptoms, n = 296 (6%)
Adolescent and adult symptoms only, n = 269 (5.4)
Later life symptoms only, n = 872 (17.5)

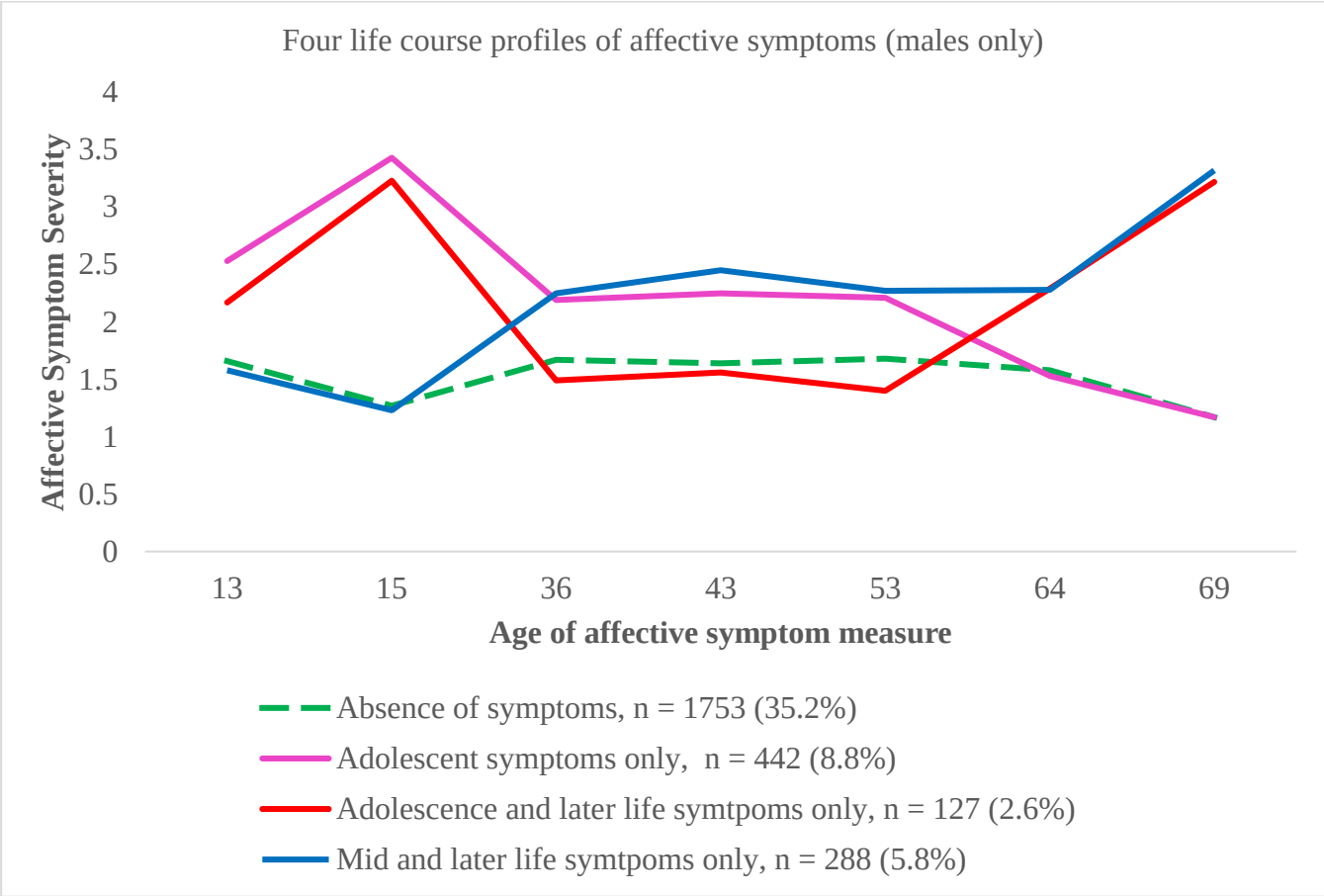
Appendix 5J. Six life course profiles of affective symptoms from ages 13 to 69 years

Note. Latent Profile Analysis: Six-class solution. These six profiles indicated: 1) those with no symptoms *(n* = 1998; 40.2%); 2) those who had symptoms in adolescence only (*n* = 727; 14.6%); 3) those who had symptoms in adulthood only (*n* = 810; 16.3%); 4) those with repeated symptoms across the life course (*n* = 296; 6%); 5) those who had symptoms in adolescence and mid adulthood but no symptoms in later life (*n* = 269; 5.4%); and 6) those with symptoms in later life only (*n* = 872; 17.5%).

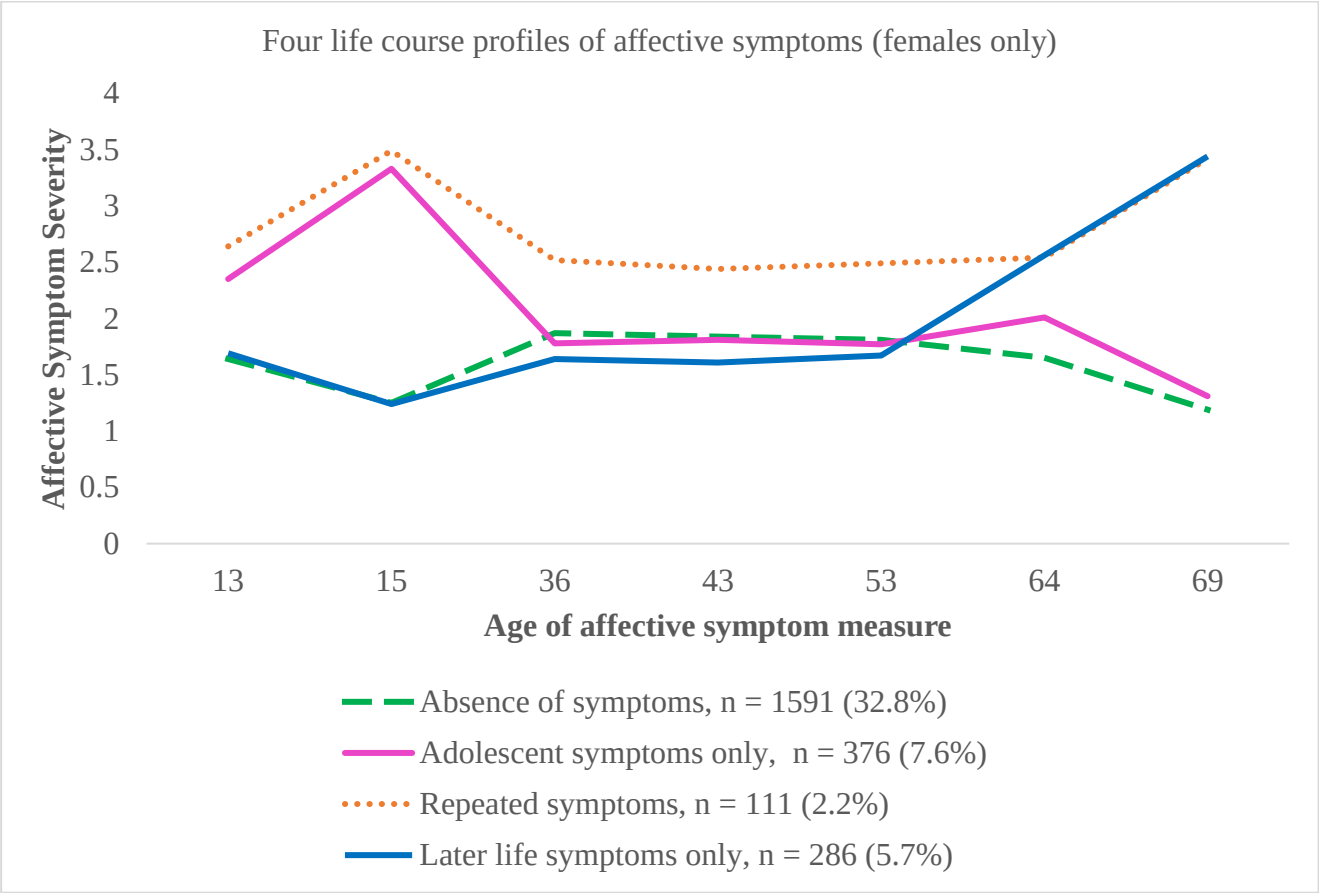
Appendix 5K. Indices for a model fit for a latent profile model (with sex as a grouping variable)

	3 classes	**4 classes**	**5 classes**	**6 classes**	**7 classes**
Likelihood ratio bootstrap *p* value[a]	<.001	**<.001**	<.001	<.001	<.001
Bayesian Information Criteria[b]	65209.83	**64382.56**	63731.61	63424.60	63294.02
Akaike's Information Criteria[c]	64858.18	**63926.72**	63171.58	62760.38	62525.61
Entropy[d]	.81	**.79**	.76	.77	.75

N = 4974. [a]*p*>.01 indicates good fit; [b]lowest value indicates better fit; [c]lowest value indicates better fit; [d]value closest to 1 indicates high certainty in classification.



Appendix 5L. Four life course profiles of affective symptoms from ages 13 to 69 years for males (*n* = 2610)

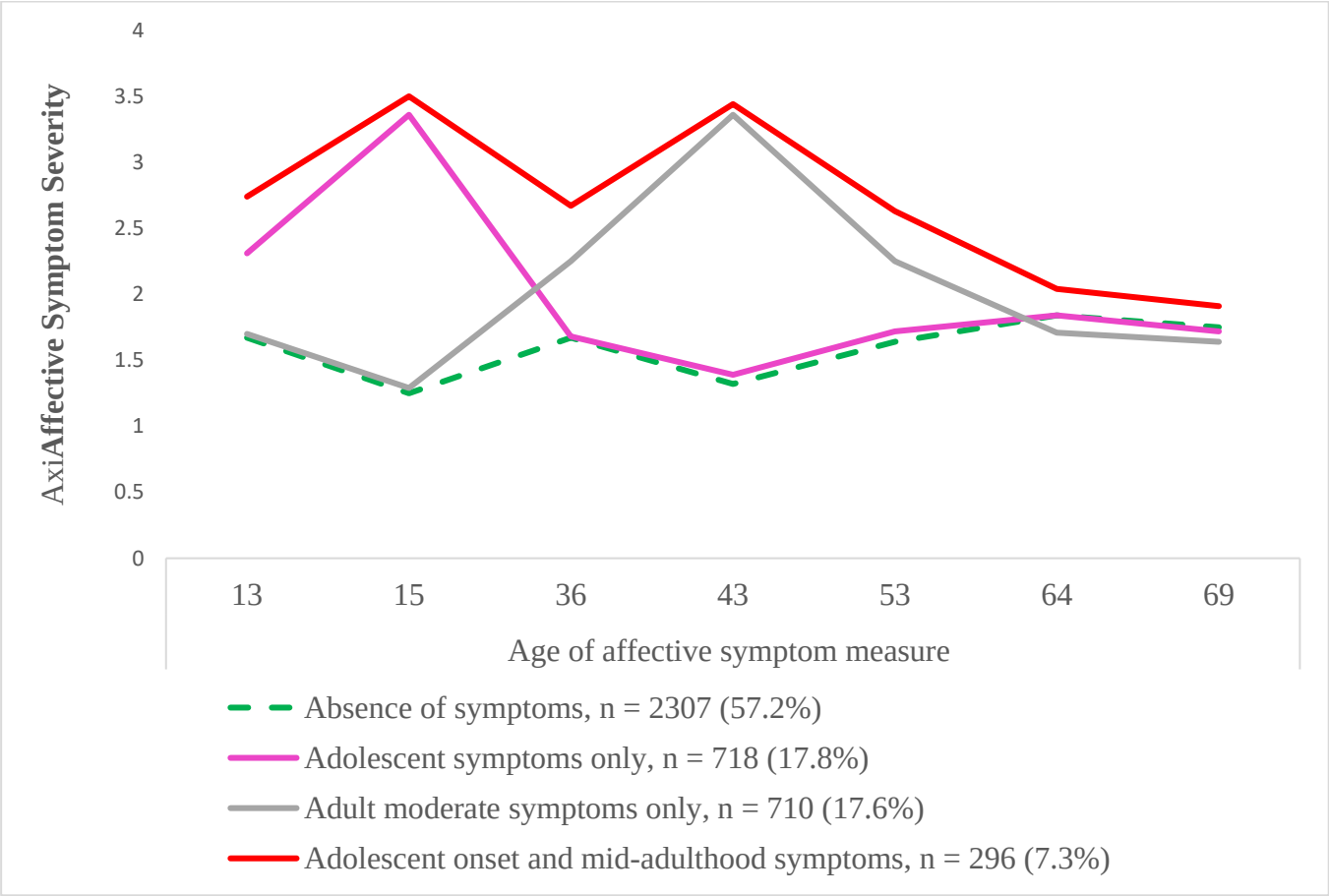


Appendix 5M. Four life course profiles of affective symptoms from ages 13 to 69 years for females (*n* = 2364)

Appendix 5N. Indices for a model fit latent profile analysis with those who died by age 69 excluded

	3 classes	**4 classes**	**5 classes**	**6 classes**	**7 classes**
Likelihood ratio bootstrap *p* value[a]	<.001	**<.001**	<.001	<.001	<.001
Bayesian Information Criteria[b]	48426.98	**47911.08**	47168.87	46975.71	46587.81
Akaike's Information Criteria[c]	48237.93	**47671.62**	46878.99	46635.42	46197.10
Lo-Mendell-Rubin bootstrap *p* value of likelihood ratio test comparing current model to previous model[d]	<.001	**<.001**	<.001	.072	<.001
Entropy[e]	.68	**.73**	.67	.67	.69

N = 4031. [a]*p*>.01 indicates good fit; [b]lowest value indicates better fit; [c]lowest value indicates better fit; [d]indicates addition of this class significantly improves fit; [e]value closest to 1 indicates high certainty in classification.



Appendix 5O. Four life course profiles of affective symptoms from ages 13 to 69 years (excluding those who died)

Appendix 5P. Multiple Imputation

Notably, as a large amount of data was missing across different types of early life predictors, multiple imputation was implemented to impute missing data for each predictor variable. Predictors of dropout have been previously identified including low education attainment, mild cognitive impairment and socioeconomic disadvantage (Kuh et al., 2016; Stafford et al., 2013).

As predictor variables were collected at three distinct time points (i.e. at birth, at age 4 and by age 15), three steps were carried out in order to impute missing data. Firstly, multiple imputation (MI) was used to impute missing data for variables collected at the birth of the survey member (i.e. in 1946). Seven predictors were imputed including birth weight, breastfeeding, paternal age, maternal age, fathers' education, mothers' education, and father's occupational status. Secondly, MI was used to impute missing data for variables collected in 1950 (i.e. at age 4). Six predictors were imputed including, crowding, mother's management and understanding, cleanliness of child, cleanliness of house, clothes repair and shoes repair. Variables collected at birth were used as auxiliary variables when running MI for these variables. Thirdly, MI was used to impute missing data for variables collected in 1961 (i.e. age 15). Nine predictors were imputed including, parental divorce by age 15, death of any parent by age 15, number of residential moves, lack of home amenities, family size, parents interest in primary and secondary education, husbands perceived health, mothers perceived health and maternal neuroticism. Two predictors measured by age 15 (age at break with mother and childhood chronic illness) were not imputed as there was little or no missing data on these variables (see table 2 for n of missingness on each variable). Auxiliary variables include all those predictors that took place before age 15 (i.e. those recorded in 1946 and 1950) and cognitive ability, recorded in 1954 (age 8 years) and 1957 (age 11 years).

Appendix 5Q. Results of association analysis using multinomial logistic regression analysis for different types of adverse childhood experiences and life course profiles of affective symptoms excluding those who died by age 69 (no affective symptoms is the control group)

			Associations with AS profiles OR (95% CI)		
			Adolescent symptoms only	Adult symptoms only	Adolescent onset and mid adulthood symptoms
Family Instability	Parental Divorce		1.07 (.82; 1.40)	1.08 (.81; 1.44)	.54 (.73; 1.80)
	Death of any parent		1.10 (.78; 1.55)	1.16 (.79; 1.70)	1.18 (.66; 2.10)
	Break with Mother		.99 (.67; 1.47)	.90 (.61; 1.36)	.95 (.51;1.79)
	Residential Moves	1 – 3 moves	.95 (.78; 1.16)	1.01 (.81; 1.26)	1.40 (.98; 2.00)
		4+ moves	.95 (.63; 1.45)	1.37 (.91; 2.07)	1.20 (.59; 2.45)
	Fathers Education		.92 (.77; 1.10)	1.10 (.91; 1.33)	.94 (.71; 1.26)

Family Socioeconomic circumstances	Mothers Education		.95 (.79; 1.14)	.93 (.76; 1.13)	1.01 (.76; 1.36)
	Lack of home amenities	Lacks 2 or 3	1.00 (.76; 1.30)	.93 (.71; 1.23)	1.37 (.83; 2.25)
		Lacks 4+	1.01 (.77; 1.32)	.84 (.63; 1.12)	1.59 (.97; 2.62).
	Crowding	1 – 2 ½ people per room	.86 (.72; 1.04)	.82 (.68; 1.01)	1.01 (.75; 1.36)
		3+ people per room	.96 (.57; 1.61)	.94 (.54; 1.66).	1.56 (.76; 3.20)
	Father's occupational status		.93 (.78; 1.11)	.93 (.77; 1.13)	.97 (.72; 1.30)
	Family Size		1.01 (.83; 1.22)	1.33 (1.06; 1.66)*	.91 (.67; 1.24)
Parents age	Older aged father		.82 (.63; 1.06)	1.22 (.89; 1.68)	.81 (.53; 1.23)
	Older aged mother		1.28 (.79;2.05)	1.61 (.92; 2.82).	1.27 (.58; 2.76)
Childrearing and Parenting	Breastfeeding	Breastfed for 1-4 months	.80 (.64; 1.01)	.88 (.68; 1.13)	.92 (.61; 1.36)
		Never breastfed	.79 (.63; 1.01)	.80 (.62; 1.02)	1.04 (.72; 1.52)

Mothers management and understanding		1.12 (.94; 1.33)	.92 (.76; 1.12)	.86 (.65; 1.15)
Parent's interest in child education	Average interest in education	.86 (.64; 1.14)	1.18 (.89; 1.56)	.89 (.54; 1.48)
	Low interest in education	1.32 (1.02; 1.72)	1.02 (.77; 1.36)	1.50 (.96; 2.34).
Cleanliness of child (1950)		1.04 (.87; 1.26)	.97 (.80; 1.18)	1.00 (.74; 1.35)
Cleanliness of house (1950)		1.02 (.85; 1.22)	.87 (.72; 1.06)	.96 (.71; 1.28)
Clothes repair (1950)		1.87 (.80; 4.37)	1.32 (.60; 2.93)	.92 (.33; 2.56)
Shoes repair (1950)		.90 (.51;1.60)	1.13 (.57; 2.21)	.74 (.32; 1.73)
Fathers perceived health	Average	1.02 (.84; 1.25)	.98 (.79; 1.22)	1.09 (.45; 1.61)
	Poor	.95 (.75; 1.21)	.79 (.61; 1.04).	1.24 (.90; 1.72)

	Mother perceived health	Average	1.05 (.86; 1.28)	.90 (.72; 1.11)	.92 (.65; 1.29)
		Poor	1.07 (.85; 1.34)	.91 (.71; 1.17)	1.36 (.95; 1.93).
	Maternal neuroticism		1.16 (.65; 2.07)	1.51 (.75; 3.03)	.76 (.34; 1.67)
Childhood Health	Birth Weight	>4000 grams	.99 (.71; 1.27)	1.13 (.84; 1.52)	.76 (.45; 1.27)
		2500 or less grams	.99 (.65; 1.50)	1.01 (.64; 1.58)	1.07 (.52; 1.96)
	Chronic Illness		.97 (.75; 1.25)	1.37 (1.10; 1.75)*	1.18 (.80; 1.73)