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The Role of Early-life Psychological Factors in the Development of Chronic Disease: A Longitudinal Analysis Applied to the Onset of Cancer, Diabetes, and Asthma in Mid-life

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Abstract

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The role of early-life psychological factors in the development of chronic disease: a longitudinal analysis applied to the onset of cancer, diabetes and asthma in mid-life.

Background: There is increasing evidence that psychological factors such as stress and depression might have an influence in the onset of many physical illnesses, but less is known about their effect from early life. This study is an epidemiological life-course analysis to test: (1) the hypotheses that early-life psychological factors are linked to later development of chronic disease (cancer, diabetes, and asthma) in mid-life, (2) whether such associations can be explained by pre-existing confounding factors, and (3) whether such links are mediated by other biological, behavioural, social, and cognitive factors.

Methods: The data were from two ongoing prospective longitudinal studies following the lives of about 17,000 people born in Great Britain in one particular week in 1958 and 1970. Outcomes included diagnosis of cancer, asthma, and diabetes up to the year 2000. Psychological measures taken from ages 5 to 16 years were the main predictors. Associations were examined using discrete-time survival analysis and structural equation models, adjusting for potential confounders and mediators.

Results: In the 1958 cohort, a standard deviation increase in the scores of conduct problems at ages 11 and 16 years, indicating severe behavioural problems, was associated with 2 to 34% increase in the odds of being diagnosed with cervical or all cancers after adjusting for childhood confounders. These effects were completely mediated by adulthood psychological distress and health behaviours. Only the teacher-reported behavioural problems significantly predicted the risk of diabetes after adjusting for family history of diabetes and sex (odds ratios of 1.05 to 1.08, $p<0.01$). These associations were partly mediated by mid-life psychological distress and adiposity. Significant associations were observed between most of the childhood psychological factors and adult-onset asthma even after adjusting for possible confounders and mediators.

Conclusions: Childhood problem behaviours may predict chronic disease risk over the life-course either directly or mediated through adulthood factors. A consistent pathway among the disease groups was through adulthood psychological distress. Such continuities from childhood to adulthood psychological distress to the disease may be explained by the substantial biological plausibility of the association between psychological factors and physical health, primarily via alteration of the endocrine and the immune systems. The importance of promoting positive emotional and behavioural development in early life is stressed.

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Preface

Adult chronic disease has now become a major public health problem worldwide, and is becoming increasingly prevalent in midlife as well. Over the years, preventive measures have predominantly emphasized adult lifestyle factors such as smoking, diet and lack of physical exercise. However, this has been successfully challenged by the growing international evidence that impaired early growth and development, childhood infections, poor nutrition, and socioeconomic and psychosocial disadvantage across the life course, affect chronic disease risk later in life. As a result, many studies on the risk factors for a broad range of chronic diseases are shifting from the study of the well established risk exposures alone, but instead incorporating the early life factors and the pathways through which they have their effect on the disease. Identification of other emerging risk factors for chronic disease has now been at the heart of much research. Research into the role of psychological factors in the development of physical illness has been ongoing for a long time and new advancements in the area of psychoneuroimmunology are intended to achieve a more complete understanding of the way the interaction among the behavioural, endocrinological, and immunological changes influence health and disease. Numerous studies have examined the effects of early life experiences on chronic diseases but not much research has been done to establish the role of early life psychological factors.

This study has been undertaken to explore potential links between psychological attributes such as personality and behaviour in early life and the development of subsequent cancer, diabetes, and asthma in mid-life. This link can only be demonstrated if the diseases occur sometime after psychological attributes are measured. This is only possible if a large number of individuals are followed over long periods of time. Two of such existing ongoing long-term surveys of approximately 17,000 UK born babies during one week in 1958, and 1970 have been used in this study to test that hypothesis. The relative importance of different pathways linking childhood psychological factors to health can only be assessed if these pathways are modelled simultaneously. Statistical methods that allow for such simultaneous modelling have been used. The analysis must also reflect the temporal ordering of the variables, whereby the childhood psychological factors must temporally precede the proposed mediators, which, in turn must precede the disease outcome, since if this is neglected by treating childhood psychological variables

as another subset of factors along with the adulthood measures in multiple regression type analysis; this can systematically underestimate their role in disease aetiology.

Results from this study suggest that such links do exist, and might be detectable as early as 7 years. Research of this nature will increase our knowledge of the risk factors for chronic diseases and may help teachers, parents and doctors understand the role of personality and behaviour in long-term physical disease. Such finding is relevant for intervention programs targeting behavioural problems in children and adolescents. Addressing problematic childhood behaviour and teaching appropriate ways of interacting and self-care to vulnerable individuals will probably require early preventative intervention in order to mitigate long-term health risks.

Acknowledgement

My success in this PhD programme would not be possible without the contribution of many whom deserve my appreciation. My deepest thanks to God almighty for the blessings, strength and courage He has given me in achieving this degree and throughout my lifetime.

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My loving wife Matilda and daughter Lynn have patiently stood by me throughout this programme. I would have not been able to complete this work without their support and understanding. My parents have also contributed to my success in every aspect of my life and I would like to extend my sincere appreciation to them. All my brothers and sisters have all been there whenever I needed them during my academic work.

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Author's Declaration

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2 Research Student's Declaration

Statement of any advanced studies undertaken in connection with the programme of research.

I declare that the work in this dissertation is original except where indicated by special reference in the text and any views expressed in the dissertation are those of the author and in no way represent those of Bournemouth University.

Concurrent registration for two or more academic awards *(tick one)*

I declare that while registered as a candidate for the University's research award, I have not been a registered candidate or enrolled as a student for an award of any other academic or professional institution. ☒

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I/We declare that I/we **have** read the above named Research Student's completed thesis and **support** its submission. ☐

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List of Acronyms

ADHD	Attention Deficit/Hyperactivity Disorder
AGA	Appropriate Weight for Gestational Age
BAS	British Ability Scale
BBS	British Births Survey
BCS70	1970 British Birth Cohort Study
BMI	Body Mass Index
BNF	British National Formulary
BRCA1	Breast Cancer Type 1: early onset
BRCA2	Breast Cancer Type 2: susceptibility protein
BSAG	Bristol Social Adjustment Guide
CAPI	Computer-assisted Personal Interviewing
CARALOC	Children's Attribution of Responsibility and Locus of Control
CASI	Computer-assisted Self-administered Interview
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CHD	Coronary Heart Disease
CHES	Child Health and Education Study
CI	Confidence Interval
CLS	Centre for Longitudinal Studies
CNS	Central Nervous System
CVD	Cardiovascular Disease
CWP	Chronic Widespread Pain
EBV	Epstein-Barr Virus
ECRHS	European Community Respiratory Health Survey
EM	Expectation Maximization
ESEM	Exploratory Structural Equation Modelling
ETS	Environmental Tobacco Smoke
FEV_1	Forced Expiratory Volume in one Second
FVC	Forced Vital Capacity
GB	Great Britain
GDM	Gestational Diabetes Mellitus
GHQ	General Health Questionnaire
GI	Glycaemic Index
GINA	Global Initiative for Asthma
GL	Glycaemic Load
GLUT4	Glucose Transporter Type 4
GWA	Genome-wide Association
HbA_{1c}	Glycated Haemoglobin
HDM	House Dust Mite
HIV	Human Immunodeficiency Virus
HMW	High Molecular Weight
HPA	Hypothalamic Pituitary Adrenocortical Axis
HPV	Human Papilloma Viruses
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICE	The Imputation by Chained Equations
IgE	Immunoglobulin E
IL	Interleukin

LAWSEQ	Lawrence Self Esteem Questionnaire
LGA	Large for Gestational Age
LISREL	Linear Structural Relations
LMW	Low Molecular Weight
MAR	Missing at Random
MCAR	Missing Completely at Random
MET	Metabolic Equivalent of Task
MI	Multiple Imputation
MICE	Multivariate Imputation by Chained Equations
ML	Maximum Likelihood
MNAR	Missing not at Random
MODY	Maturity Onset Diabetes of the Young
MRC	Medical Research Council
NCDS	National Child Development Study
NFER	National Foundation for Educational Research
NHS	Nurses' Health Study
NINR	Non-ignorable Non-response
NK	Natural Killer
NSP	Non Starch Polysaccharides
OA	Occupational Asthma
OC	Oral Contraception
OGTT	Oral Glucose Tolerance Test
OR	Odds Ratios
PEFR	Peak Expiratory Flow Rate
PMS	Perinatal Mortality Survey
PNI	Psychoneuroimmunology
RMSEA	Root Mean Square Error of Approximation
RR	Risk Ratio
SAM	Sympathetic Adrenal Medullary System
SEM	Structural Equation Modelling
SEN	State Enrolled Nurse
SES	Socioeconomic Status
SGA	Small for Gestational Age
SGRT	Southgate Group Reading Test
SNS	Sympathetic Nervous System
T2DM	Type 2 Diabetes Mellitus
TLI	Tucker and Lewis Index
TNF	Tumour Necrosis Factor
UK	United Kingdom
USA	United States of America
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist-to-hip Ratio
WSR	Waist-to-stature Ratio

SECTION I

INTRODUCTION, DATABASES, AND ANALYTICAL METHODS

Chapter 1

Introduction

Chronic diseases- mainly cancer, chronic respiratory diseases, heart disease, stroke, and diabetes- are shaping up as one of the greatest health challenges for the industrialised countries, and indeed, the world in the 21st century. Figures from the World Health Organization (WHO) (2005) show that chronic diseases account for about 60% of the projected 58 million deaths (in 2005) and about half of the global burden of disease. The contribution from the low and middle-income countries, where most of the world's population lives almost counts for over 80% of this global burden.

The prevailing aetiological models for most of adult chronic diseases have emphasized adult risk factors and determinants, which are common to most of these conditions. These risk factors, which are largely preventable- high cholesterol, high blood pressure, obesity, and smoking–, cause the majority of the chronic disease burden. They are majorly a result of unhealthy diet, physical inactivity, and tobacco use. Dozens of other risk factors also have been proposed, but they account for a smaller proportion of chronic disease. These include infectious agents that are responsible for cervical and liver cancers, and some environmental factors, such as air pollution, which contribute to a range of chronic diseases including asthma and other chronic respiratory diseases.

How well can we predict chronic diseases from the well established risk factors?

Despite decades of research in the risk factors for the chronic conditions and the knowledge of a large number of well established and seemingly important risk factors, there are still significant gaps in our understanding of other crucial risk factors. The extent to which classic risk factors account for the occurrence of chronic disease, especially the coronary heart disease (CHD), is a matter of long-term debate (Syme, 1996; Magnus and Beaglehole, 2001; Beaglehole and Magnus, 2002). Earlier studies on the risk factors of CHD have found the accuracy of the prediction of the disease based on the traditional risk factors very low, explaining no more than half of the occurrence of CHD in the population (Heller *et al.*, 1984). However, recent evidence has shown a larger contribution of the established risk factors to the CHD epidemic. One of the major contributions was the study by Stamler *et al.* (1999) based on two large prospective

studies, involving five cohorts. The result of their studies indicated that lifetime favourable status in regard to all the three major risk factors (serum cholesterol level, blood pressure, and smoking) led to low mortality rates from CHD, cardiovascular disease (CVD), and all causes. They found that about 75% of the CHD deaths could be attributed to the three classical risk factors. This debate on the proportion of the chronic disease attributable to the well established risk factors has stimulated further research into genetic markers, other adult risk factors to do with psychosocial environment, more detailed assessment of adult dietary intake and childhood risk factors (Marmot and Elliott, 2005) to update the information on the well established risk factors. Despite a debate on the limitations of the "risk factors" approach (Mckinlay and Marceau, 1999), there is still a strong support for continuing to search for new alternative approaches to risk factors.

What roles do psychological factors play in chronic disease epidemiology?

That there might be a link between psychological factors (personality, behaviour, motivation, cognition, affect) and the development of chronic disease is not a new idea. In the latter part of the last century, interest was rekindled with the identification of coronary prone (so called Type A) personality. This is supported by the evidence that individuals exhibiting high levels of aggressiveness and hostility are more likely to develop coronary heart disease (Sanderman and Ranchor, 1997). Depression has also been linked to CHD. Two independent meta-analyses of studies of depression as a risk factor for incident coronary heart disease (Rugulies, 2002; Wulsin and Singal, 2003) established a link between depressed mood and development of myocardial infarctions in initially healthy people. Sundquist *et al.* (2005) also found out that even after accounting for socioeconomic status and geographic region, depression remained a clinically significant risk factor for developing CHD, especially in men and women aged 25 to 50.

There has also been considerable interest in the role that personality and affect have in the development of cancer, particularly breast cancer, although evidence is less consistent (Sanderman and Ranchor, 1997; Bleiker, 1999; Butow *et al.*, 2000). The idea of a type C (cancer prone) personality has also emerged, characterised by repression/suppression of negative emotions, unassertiveness and low self esteem (Sanderman and Ranchor, 1997; Thomas *et al.*, 2000). Psychological factors (hopelessness) have been implicated in incident hypertension especially in men (Everson

et al., 2000), with those reporting high levels of hopelessness at baseline almost 3 times more likely to become hypertensive after adjusting for other factors as compared to those who are not hopeless. Huovinen *et al.* (2001) in their study of the psychological factors (including extroversion and neuroticism scales, subjective stress, and life satisfaction) and prevalent asthma found out that high extroversion score was significantly associated with the risk of adult onset asthma among women. Death in elderly people has also been associated with lack of improvement in symptoms of depression and anxiety (Lavretsky *et al.*, 2002). Psychological factors too have been linked to various psychosomatic conditions (alexithymia)(Lumley *et al.*, 1996), unexplained hospital admission (extroversion, poor concentration) (Hotopf *et al.*, 2000), fatal (but not non-fatal) strokes (psychological distress)(May *et al.*, 2002), somatic multi-morbidity and psychiatric ill-health (temperamental and behavioural features) (Neeleman *et al.*, 2002).

Can early life experience determine health in later life?

There is now extensive evidence from many countries that conditions before birth and in early childhood influence health in adult life. In fact, the idea that events occurring during the early development of an individual and specifically during intrauterine life have profound consequences on future health, the so called “foetal origins of adult disease”, is well established and has been termed "programming” in developmental biology (Morley, 2006; Rinaudo and Lamb, 2008). Low birth weight, a marker of intrauterine stress, has been linked to predisposition to many conditions including hypertension, cardiovascular diseases, diabetes, and stroke (Barker, 1998, 2001; Boo and Harding, 2006; Rinaudo and Lamb, 2008).

The idea that adverse psychosocial experiences and psychological factors in childhood may influence adult physical health and early mortality is not new either. Evidence from longitudinal studies shows that early child development, socioeconomic and psychosocial environment, and psychological well being of childhood are empirically linked to adult health status. A study by Martin *et al.* (2002) demonstrated a link between personality traits measured during childhood and all causes of mortality 70 years later and found this relationship to be independent of subsequent health behaviours. Recent studies have also demonstrated a link between several childhood psychological attributes such as aggression (Temcheff *et al.*, 2010), adverse experiences (Danese *et al.*, 2009; Jones *et al.*, 2009), abuse (Wegman and Stetler, 2009), personality (Kubzansky *et al.*, 2009), stress

(Dube *et al.*, 2009) and depressive symptoms (Hasler *et al.*, 2005), and negative adult physical health outcomes. These evidences suggest that psychological factors that influence the development of chronic disease may be identifiable in early life. These ideas are expressed in the lay press as well as in the scientific literature (Burne, June 14 2004).

A life course perspective

Recently, attention has been paid to the ways in which such early life environment might influence health in later life. Three major and sometimes conflicting models have been proposed: first, latent effects by which the early life environment affects adult health independent of intervening experience; second, pathway effects, through which the early life environment sets individuals onto life trajectories that in turn affect health status over time; and, third, cumulative effects whereby the intensity and duration of exposure to unfavourable environments adversely affects health status, according to a dose–response relationship (Kuh and Ben-Shlomo, 1997; Hertzman, 1999; Kuh *et al.*, 2003). All these can be summed up within the concept of life course approach to disease epidemiology. Kuh and Ben-Shlomo (2004) define the life course approach as the study of long-term biological, behavioural, and psychosocial process that link adult health and disease risk to physical or social exposure, earlier in adult life, or across generations.

The latency model also referred to as the "critical period model" or "biological programming" (Kuh and Ben-Shlomo, 1997), emphasises the strong independent effects on health status late in life, of discrete events that tend to occur early in life and is the basis of the "foetal origins of adult disease" hypothesis. In its purest form, this model advocates that an exposure in a critical period results in permanent and irreversible damage or disease. Several lines of evidence support this model including the existence of critical or sensitive periods in brain development (Cynader, 1994); and the associations between birthweight, placenta size and weight gain in the first year of life with several conditions later in life (Barker, 1998, 2001).

The pathways model, which recognizes the importance of later life effect modifiers, emphasises the role of early environment on subsequent life trajectories, which in turn influence adult health. According to this model, a life course approach studies the biological, psychological, and social pathways that link early life experiences and conventional adult risk factors to the health outcome in later life. It resembles what has

been described as "a chain of risk model" (Kuh *et al.*, 2003), which refers to a sequence of linked exposures that raise disease risk because one bad experience or exposure tends to lead to another and then another; and usually involve mediating factors and often modifying factors.

In the third model, factors that raise disease risk or promote good health may accumulate gradually over the life course, although there may be developmental periods when their effects have greater impact on later health than factors operating at other times. These life course models are not mutually exclusive, but may operate simultaneously; for example, in practice, latent effects can be difficult to disentangle from pathway effects.

Thus, a life course approach is vital in testing not only the direct effects of early-life exposures on later disease, but also the possible pathways with potential intermediaries or confounding factors, and takes into account the temporal ordering of the exposure variables. The approach does not deny the contribution of the well established risk factors such as smoking and obesity, but is aimed at studying the contribution of early life factors jointly with these later life risk factors to identify the risks and protective pathways across life course. It therefore provides a good conceptual framework in which the relationship between the childhood psychological factors and later chronic disease development are examined. The psychological factors in childhood are thought to have both direct and indirect effects on later health outcome. Direct effects result from both latency and cumulative mechanisms. The psychological distress during critical periods of child development may have independent, long-standing effects on biological processes throughout the life course. In addition, psychosocial development may influence an individual's ability to respond to repeated stressful exposures throughout childhood and into adolescence and adulthood. Indirect effects occur through pathway mechanisms involving the role of psychological factors in the development of other known risk factors for chronic diseases including smoking, and obesity.

Pathways linking psychological factors and physical disorders

Many chronic diseases cluster in individuals, so that several co-morbidities can exist at once. At least 35% of men over 60 years of age have been found to have two or more chronic conditions and the number of co-morbidities increases progressively with age, with higher levels among women (Guralnik and National Center for Health, 1989). Similarly, strong interrelationships between physical and mental health have been

observed, with 41% of patients with chronic medical illness having had or concurrently having psychiatric disorder (Katon and Sullivan, 1990). Thus, co-morbidity of psychological and physical disorders seems quite substantial.

A number of pathways potentially accounting for the relationship between psychological factors and physical illness have been proposed to help explain the co-morbidity of physical and psychological health problems. One of such conceptual framework, proposed by Cohen and Rodriguez (1995), provides explanations for the development and maintenance of the co-occurrence of psychological and physical disorders. Their model has been adopted in this study since it presents a broad theoretical framework for identifying factors that contribute to and maintain comorbid conditions of physical and psychological health problems.

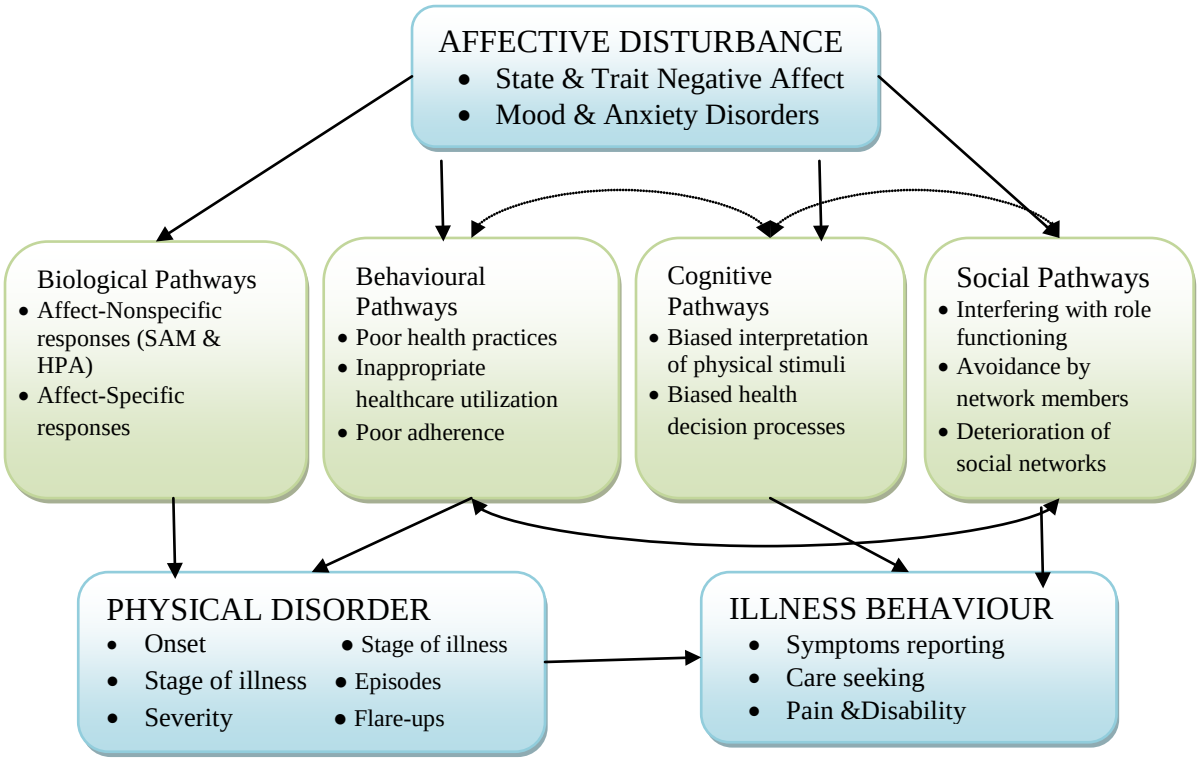


Figure 1-1: Pathways linking affective disturbances to physical disorders.
Taken from Figure 1 of Cohen and Rodriguez (1995). The paths identified in the model move in only one direction from affective disturbance to physical disorder. SAM = sympathetic-adrenal medullary system; HPA = hypothalamic-pituitary-adrenocortical axis.

The Cohen and Rodriguez's model identifies four pathways, biological, behavioural, cognitive, and social pathways that may mediate the link between psychological factors

and physical disorder (Figure 1-1), and provide explanations for the development and maintenance of the co-occurrence of the two disorders. Although their discussion of psychological disorders was limited to the role of affective disturbances (subclinical negative moods as well as mood and affective disorders), the pathways they identified are thought to contribute to co-occurrences of other psychological disorders and physical disease as well. The relations between psychological and physical disorder are likely to be bi-directional and involve multiple feedback loops. However, we only focus on the role of psychological factors as contributors to physical disorders.

As presented in Figure 1-1, the model proposes that affective disturbances can influence physical disorder through biological, behavioural, cognitive, and social pathways. The model also distinguishes between physical disorder (biologically verifiable disease) and illness behaviours. In the case of physical disorder, the primary pathways are biological and behavioural. In the case of illness behaviours, the pathways include direct manifestations of disease pathology, cognitive biases in interpreting bodily sensations, and social pressures influencing care seeking.

1. Biological pathways: Several biological pathways that might influence physical disorder have been suggested including the non specific responses that occur to most or all negative emotions and disorders, and those that occur to a specific disorder but not the other. Of relevance to chronic disease is that affect may be linked to alterations in immune and neuroendocrine function (Watkins, 1997). Reviews by Cohen and Herbert (1996) and Kiecolt-Glaser *et al.* (2002a) address the importance of studies of human psychoneuroimmunology in understanding the role of psychological factors in physical health. They discuss how psychological factors might influence immunity and immune system-mediated disease. For example, for the case of cancer, because the immune system is thought to play important roles in tumour surveillance and in preventing the progression and metastatic spread of tumours, psychological factors associated with immunity are considered potential contributors to cancer onset and progression illness (see Section 4.3.1 for further discussion).

2. Behavioural pathways: Behavioural changes (e.g. increased smoking, poor diets, alcohol consumption, drug-taking, and less exercise) that are associated with personality characteristics or that occur as adaptations or coping responses in the face of stressful events or negative emotional states may place persons at risk for disease

onset, progression or increased severity. Behaviours that indirectly influence health such as utilization of health care services, participation in screening programs, and adherence to medical treatment might also be important and can be affected by cognitive pathways. Baum and Posluszny (1999) present a comprehensive discussion on how behaviour influences disease processes particularly for the initiation or progression of cancer, HIV, cardiovascular disease, and other illnesses.

3. Cognitive pathways: Cognitive interpretation of symptoms and decisions regarding engaging with health services may affect illness behaviour. Many studies examining psychological aspects of self-assessed health have focused on a fairly rational set of processes such as how symptoms are perceived and interpreted (Martin et al., 2003), and understanding self-assessed health and adherence to medical regimens (Leventhal et al., 1992).

4. Social pathways: Psychological distress may interfere with an individual's social networks, emotional support, and normative social role in family and society that can influence behavioural and cognitive pathways and affect illness behaviour. Social networks support physical health by promoting positive health practices, positive views of the world, and providing resources for facing and avoiding stressful life events (Cohen, 1988), hence, interfering with these networks can increase the risk of physical disorder.

Biological and behavioural pathways are most likely to influence disease onset directly. Cognitive and social pathways are more likely to influence illness behaviours such as reporting symptoms, seeking of care, and degree of pain and disability experienced. These pathways have been incorporated in our study to guide the research and hypotheses concerning how psychological factors might affect chronic disease. The model has general application to different chronic diseases, although it is likely that the relative importance of each pathway might differ for different diseases.

The need for prospective longitudinal data on risks factors and disease onset

In order to demonstrate a link between early life psychological factors and later development of chronic disease it is imperative to use prospective, longitudinal research of sufficient duration that the two measures are temporally distinct. In this way, the information about circumstances and experience early in life is used to predict the

outcomes later in life domains. Such design requires a prospective study that begins at birth and continues to collect data thereafter into adulthood. This design has the advantages of recalled data only over short periods between data collections (Wadsworth *et al.*, 2003). By collecting data prospectively, the problems of recall bias that occur in retrospective studies are avoided, and there is less need to rely on administrative records. Britain has three such studies, still in progress, that have collected data from birth (in 1946, 1958 and 1970) and continue to do so on the same population during childhood, adolescence and adulthood (Ferri, E *et al.*, 2003). This study uses the data from two of these studies, the 1958 and the 1970 cohorts.

A recognised flaw in much of the existing evidence in this area is in the use of cross-sectional and case-control research designs where disease status is measured either at the same time or preceding the psychological measures. Since changes in psychological factors often occur as a result of being diagnosed and living with a chronic disease, and indeed, might affect the progression of the disease, this design makes it impossible to assess the role of psychological factors in the development of disease. The high cost of long term prospective designs has led many researchers to use quasi-prospective designs that focus on high risk groups who have been referred for diagnostic tests. A criticism of this approach is that the onset of chronic disease and the psychological factors are often not temporally distinct.

1.1. Aims and Objectives

Psychological factors have been associated with poorer physical health in adulthood, but less is known about childhood psychological factors broadly, including behavioural and emotional problems or the pathways from childhood psychological factors to adult disease. This study uses two existing large British longitudinal birth cohort studies– the 1958 national Child Development Study (NCDS) and the 1970 British Cohort Study (BCS70)- to examine the role of early-life psychological factors in the development of chronic disease. The specific objectives of the study are as follows:

1. To test the hypothesis that there is a temporal relationship between psychological factors (personality, behaviour, motivation, cognition, affect) measured during the life course and the development of chronic diseases (cancer, Type 2 diabetes mellitus, and, asthma) in middle age.

2. To test whether such associations can be explained by pre-existing physical, social, and environmental confounding factors.

3. To use an existing theoretical model of the link between psychological factors and disease (Cohen and Rodriguez, 1995) to test whether associations are mediated by biological, behavioural, social, and /or cognitive pathways.

4. To test whether physical, social, and environmental factors have a moderating (i.e. intensifying or diminishing) effect on the temporal association between psychological factors and chronic disease.

The life course perspective (Kuh and Ben-Shlomo, 2004) and pathway model (Cohen and Rodriguez, 1995) have been used as conceptual and theoretical framework since these approaches emphasize and accommodate the complex temporal interplay that occurs throughout life between biological, social, environmental and psychological risk processes.

1.2. Structure of the Thesis

This thesis consists of five major sections, each divided into three chapters except the final section which has a single chapter. Section 1 comprises the introduction, description of the databases and measures, and description of the analytical methods used in the subsequent sections. The second chapter, which describes the databases and the measures, also discusses how different psychological variables were derived from the respective items of the scales. In chapter three, the statistical methods are described as well as the methods for handling missing data. Section two focuses on cancer, with chapter four giving a brief literature review of the risk factors for cancer, a motivation for the choice of the particular cancer site, and the specific analytical strategies applied to cancer analysis. The results and discussion of the risks factors for cancer are presented in chapters five and six, respectively. The third section covers the literature review for Type 2 diabetes mellitus in chapter seven, diabetes results in chapter eight, and discussion and conclusions for diabetes in chapter nine. Section 4 deals with asthma- a literature review of the aetiology and epidemiology of asthma, results, discussion and conclusions. The final section summarises the whole thesis, describes the strength and limitations of the study and the contribution to knowledge.

Chapter 2

Data and Measures

2.1. Databases

This study pools 11,419 participants from the National Child Development Study for whom adult follow-up data were available at age 42, and 11,261 participants from the British Cohort Study for whom adult follow-up data were available at age 30.

2.1.1. The National Child Development Study

The National Child Development Study (NCDS) is a continuing longitudinal study that seeks to follow the lives of about 17,000 people born in Great Britain in the week of 3rd to 9th March 1958. It has its origins in the Perinatal Mortality Survey (PMS) which was designed to examine the social and obstetric factors associated with stillbirth and death in early infancy among the children born in Great Britain in that one week (Butler and Bonham, 1963). Following the initial birth survey, there have been seven attempts to trace all members of the birth cohort in order to monitor their physical, educational and social development. These follow-ups were carried out when the children were 7 years in 1965, 11 years in 1969, 16 years in 1974, 23 years in 1981, 33 years in 1991, 41-42 years in 1999-2000, and 46 years in 2004. The immigrant children born in the same week were added to the sample at the 7-, 11- and 16-year contacts, therefore, in total there are records with some information on 18,558 children. Power and Elliott (2006) give a full description of the study and what was covered for each sweep.

The eighth follow-up marking the 50th anniversary of the study ended in spring 2009, though the complete data from this sweep was not ready at the time of analysis. The core aim was to update the social, economic and health information collected in 2004 but new areas of data collection included more detailed questions about the care needs of cohort members' parents; a new module covering symptoms of the menopause and a module featuring a series of cognitive ability tests.

The questionnaire used for the birth survey was completed by the midwife in attendance at delivery with reference to all available records and after an interview with the mother.

Information recorded included: social and family background, details of past obstetric history, antenatal care and abnormalities during pregnancy, length and abnormalities of labour, analgesia and anaesthesia as well as sex, weight, progress, management and outcome of the infant.

At each of the first three follow-ups, information was obtained from four main sources: the children themselves (from questionnaires and ability tests), the parents (most commonly the mother alone), local authority medical officers (full medical examination), and schools (usually the head teacher and class teacher(s)). The information collected covered areas such as the father's and mother's occupation, length of parents' education, smoking habits, aspirations and expectations for child's future education and occupation, family relationships, parent-school contacts, sources of income and indices of poverty (including at sixteen only, details of household income), housing circumstances, child's general health and information on accidents, hospital admissions and visits to the doctor, and details of medical history relating to vision, hearing, speech therapy, convulsions, asthma, migraine, enuresis, psychiatric problems, dental care and pubertal development. Parents also answered questions which combine to give an index of behaviour in the home (Rutter *et al.*, 1970) .

The 1981 survey information was obtained from the subjects (who were interviewed by a professional survey research interviewer) and from the 1971 and 1981 censuses (from which variables describing area of residence were taken). In the further follow-ups, the information was collected from the cohort member; husband, wife, or cohabitee if any; from the natural or adopted children of 1 in 3 cohort families; and from the mother of these children (Ferri, 1993). The adult sweeps have collected data over a number of domains, including physical and mental health, demographic circumstances, employment, and housing.

Over the years, there has inevitably been some attrition from lost contact, refusals, emigration, and death, but response rates remain high. The adult surveys each include information on approximately 11,000 individuals who are still participating in the survey (Hawkes and Plewis, 2006).

2.1.2. Biomedical survey

The first biomedical assessment of the NCDS cohort members in adulthood was conducted by a research nurse visiting the home between September 2002 and March 2004 when the participants were aged 44-45 years, following the funding award from Medical Research Council (MRC) in 1999. The survey was designed to obtain objective measures of ill-health and biomedical risk factors in order to address a wide range of specific hypotheses relating to anthropometry; cardiovascular, respiratory and allergic diseases; visual and hearing impairment; and mental ill-health.

The target sample comprised some 12,037 cohort members who responded to NCDS sweeps 4, 5 or 6. Levels of co-operation with the survey were high, with a total of 9,377 cohort members taking part, and only a minority declining to provide samples of blood and saliva. Consent was lowest for the blood and saliva components (93.7% and 97.7% of participants, respectively); virtually all participants consented to the mental health and physical components, with little variation in consent for individual physical measurements (Atherton *et al.*, 2008). Of the 9,377 participants, 8,585 (91.6%) consented to all four interview components. Blood samples were collected from 88% of those examined, and 97% of these gave consent to creation of immortalised cell lines, extraction and storage of deoxyribonucleic acid (DNA) for medical research purposes. A total of 8,018 blood samples were received from subjects who gave consent to extraction of DNA, and 7,980 of these also gave consent for creation of immortalised cell cultures.

The elements in the computer-assisted personal interviewing (CAPI) used in the main survey included: blood pressure and pulse- three measures of systolic and diastolic blood pressure and resting pulse were taken; prescription drugs- all prescribed drugs taken, by name and BNF code; standing height, sitting height, weight, waist circumference, hip circumference; lung function- three measures (from up to five attempts) of forced vital capacity (FVC), forced expiratory volume (FEV_1) and peak expiratory flow rate (PEFR); and non-fasting blood sample- four tubes filled and sent by nurses to laboratories in London, Newcastle and Bristol. In addition, respondents completed a CASI (computer-assisted self-administered interview) section, covering smoking and drinking habits; and adverse childhood experiences. The scale used for the adverse childhood experiences was taken from the Australian path through life study (Rosenman and Rodgers, 2004, 2006).

This consists of 17 items which are retrospectively rated as having occurred or not (coded 0 = no, 1 = yes) by 16 years of age.

Respondents also filled in a paper self-completion questionnaire with supplementary questions about diet, physical activity, working conditions, social support, life events and pain. Pain was assessed by a questionnaire sent in advance of the nurse interview, using blank body manikins on which the respondents shaded areas of pain lasting for one day or longer in the past month; participants were then asked whether they had been aware of the pain for at least 3 months. Chronic widespread pain (CWP) was defined according to the American College of Rheumatology criteria for fibromyalgia—namely, contralateral body quadrant pain and axial skeleton pain lasting for at least 3 months (Wolfe *et al.*, 1990).

Biochemical analyses of blood samples included measures of Glycosylated haemoglobin (HbA1c) on whole citrated blood by ion exchange high performance liquid chromatography, using the Tosoh A_{1c} 2.2 Glycohemoglobin Analyser HLC-723GHb; and immunoglobulin E (IgE), house dust mite Allergen (HDM), cat allergen, and grass pollen allergen. The IgE was measured on serum by the HYTEC enzyme immunoassay (Nolte and Dubuske, 1997), with positive and negative controls. Total IgE was assayed on all specimens, and allergen-specific IgE to house dust mite, mixed grasses, and cat fur, were measured on specimens with a total IgE concentration above the median (30kU/L). The ethical approval for the biomedical study was obtained from the South East Multi-Centre Research Ethics Committee.

2.1.3. The 1970 British Cohort Study

Twelve years after the 1958 cohort study, the 1970 British Birth Cohort Study (BCS70) began as the British Births Survey (BBS), when data was collected about the births and families of 17,198 babies born in England, Scotland, Wales and Northern Ireland in the week of 5^{th}-11^{th} April 1970. The first wave, the BBS, was sponsored by the National Birthday Trust Fund in association with the Royal College of Obstetricians and Gynaecologists. The aims of the survey were to look at the social and biological characteristics of the mother in relation to neonatal morbidity, and to compare the results with those of the NCDS. Participants from Northern Ireland, who had been included in

the birth survey, were dropped from the study in all subsequent sweeps, which only included respondents from Great Britain.

Since its inception, there have been seven full data collection exercises in order to monitor the cohort members' health, education, social and economic circumstances. These took place when respondents were aged 5 in 1975, 10 in 1980, 16 in 1986, 26 in 1996, 30 in 1999-2000, and 34 in 2004-2005. The data for the eighth data collection exercise which ended in spring 2009 was not ready by the time of the analysis. The first two sweeps (at 5 and 10 years) were carried out by the Department of Child Health at Bristol University. During these times, the survey was known as the Child Health and Education Study (CHES). The 16-year survey was carried out by the International Centre for Child Studies and named Youthscan. The 1999/2000 and 2004/2005 follow-ups were managed by the Centre for Longitudinal Studies (CLS), and fieldwork was carried out by the National Centre for Social Research. As well as BCS70, the CLS now also conducts the NCDS series.

With each successive attempt, the scope of BCS70 has broadened from a strictly medical focus at birth, to encompass physical and educational development at the age of five; physical, educational and social development at the ages of 10 and 16; and physical, educational, social and economic development at 26 years and beyond.

In 1999/2000, BCS70 combined with NCDS to undertake, for the first time, a joint survey in order to integrate the timing, design and analysis of future surveys of NCDS and BCS70. Data from both surveys are now lodged at the UK Data Archive, University of Essex. Access to the data is open, although intending users are asked to commit themselves to ensuring that confidentiality is observed, and to inform the Cohort Studies User Support Group at the CLS about their proposed use of the data and any resulting publications. Ferri *et al*. (2003) describe and compare the 1958 and 1970 cohorts. The use of the two datasets would enable comparisons between cohorts born at different times, or between different age groups at the same point in time.

2.2. Measures

2.2.1. Outcome measure

The response variable under consideration in this study is whether the study subject developed the particular chronic disease or not. The chronic disease condition was identified by self report questionnaire. At age 33 and 41-42 years in the NCDS and 29-30 years in the BCS70, participants were asked about their general health and about specific health problems. For this study, we used the measure of chronic disease collected in 2000/2001. This maximises the number of cohort members who have chronic disease, and has the further advantage that an identical methodology was used in both cohorts. We have focussed our attention on the subset of chronic health problems that were specifically asked during the follow-up interview, that are significant either in terms of severity or health service usage, and have occurred with sufficient frequency for meaningful statistical analysis. The diseases include cancer, Type 2 diabetes mellitus, and asthma.

For each disease, information was collected on whether the cohort member had ever had the disease, or been told that they had the condition, the age at which their condition first developed, whether they had it in the previous 12 months and if so whether they had seen a doctor about the problem.

2.2.2. Childhood psychological measures

The main explanatory variables in this study are the psychological measures which were collected at age 5, age 10 and age 16 years in the BCS70 and at ages 7, 11, and 16 years in the NCDS. These include behavioural maladjustments, hostility patterns, personality, and motivational assessment such as self esteem and locus of control. Both the parents and teachers independently rated the children's behaviour and emotional maladjustments at different age points using different measurement scales.

Bristol Social Adjustment Guide

Teachers completed a standardised instrument to provide a description of the child's behaviour in school using the Bristol Social Adjustment Guide–BSAG (Stott, 1963) at

ages 7 and 11 years in the NCDS. The BSAG is a validated measure of ‘maladjustments’, unsettledness or other emotional handicap in children of school age. It consists of a large number of 'phrases' which describe a child's behaviour (Table A1 in the appendix). These 'phrases' are grouped on the guide into 'paragraphs' under a heading. Teachers completed the guides for study members by underlining the 'items of behaviour' they thought described the child's behaviour or attitudes. Most of these phrases were allocated serial letters and a number, specially designed for the NCDS coding form. The numbered items were mostly in order of severity. For the NCDS, the behaviour items were grouped together into a number of ‘syndromes’ in accordance with a procedure agreed with Stott in 1965 but not necessarily the same as in the published manual or scoring form. It was assumed that the general behavioural pattern which underlies the individual items within a syndrome was the same. Table A2 (appendix) presents all the 12 syndromes and a sample list of the items under each syndrome.

Only the syndrome scores and not the scores on individual items were coded on the data tapes. The total syndrome scores were meant to give a quantitative assessment of the behaviour pattern in question and were derived by adding up the number of underlined phrases within that syndrome. The higher a child scores on each syndrome, the more ‘maladjusted’ they are. Finally, the syndrome sub-totals were added together to give a figure which indicated, fairly crudely, the total amount of behavioural deviance as measured by the guide.

As pointed out in the subsequent revisions of the BSAG manual (Stott, 1974), an over-all BSAG score is no longer recommended except for the broad epidemiological surveys, where the general incidence of behaviour disturbance has to be compared in different populations. This is because it is relatively uninformative in the individual case given that maladjustment takes such varied forms and thus will be too heterogeneous a variable for use in research. In its stead, the two main sub-scales representing the under- and over-reacting modes of maladjustment (Stott, 1974) can be used. The coefficients of reliability for the original scale were 0.74 for the under-reacting, and 0.77 for the overreacting components (Rutter *et al.*, 1970), showing a uniformly better correlation between the overreacting than the under-reacting scales. The authors attributed this to the unobtrusiveness of under-reaction, and the difficulty, so far as unforthcomingness, withdrawal and depression are concerned, in discriminating between different kinds of not-behaving. These two major dimensions of behaviour disturbance as measured by the

BSAG have also been confirmed through factor analytic studies. Ghodsian (1977), through a factor analysis using principal components factoring applied to the second follow-up of the NCDS revealed that the number of dimensions underlying the 12 syndromes can be reduced to two very stable factors. In his study, three components were extracted from the analysis under the conventional criteria of the minimum eigenvalue of unity. However, the two-factor solution provided better factor invariance across the six social class and sex categories plus a clearer interpretation of factors. It was thus suggested in his study, despite some theoretical and empirical limitations, that the two factors should be used to provide a simple and parsimonious description of behaviour at school as seen by the teacher. The two components identified explained just over 50 per cent of the variance.

The principal components factoring applied to the first follow-up data in this study revealed the same pattern as the second follow-up data (Table A3). Based on the acceptable theoretical interpretations given by Ghodsian (1977), the two components were chosen in this study. The first factor which has been labelled in this study as "conduct problems" represents what seems like over-reacting, aggressive, restless, outwardly expressed behaviour, while the second, which has been labelled as the "emotional problems", denotes under-reacting, withdrawn, inhibited behaviour. The syndromes that loaded on the first factor included anxiety for acceptance by adults, hostility towards adults, writing off adults, anxiety for acceptance by children, restlessness, and inconsequential behaviour (Table A3). The variables that loaded in the second component included unforthcomingness, withdrawal, depression, writing off adults and miscellaneous symptoms. The syndrome on 'writing off' adults loaded on both factors implying this syndrome is mixed. Only loadings equal to or greater than the arbitrary but conservative figure of 0.400 were considered significant. In all the groups the syndrome on miscellaneous nervous symptoms did not load appreciably on any factor and was considered separately. The factor scores were computed using simple summation of the major syndrome with the syndrome on 'writing off adults' excluded from both the factors. The scores were used in the analyses as continuous measures where higher scores represented severe behavioural problems. For preliminary analyses and graphical presentation, categorical measures of the score were used as in the previous studies (Ghodsian, 1983), where for each scale, a score in the top 13% defined a severe case of maladjustment, the lowest 50% were considered normal, and the remainder were considered mild case of maladjustment.

Rutter child scale

At various ages in childhood, parents and teachers of both the NCDS and BCS70 cohort members completed a set of questions which combine to give the Rutter scales, an index of behaviour difficulties in the child (Rutter, 1967; Rutter *et al.*, 1970). The scales consist of short questionnaires for collecting information from parents and teachers about the behaviour of children aged about nine to thirteen years, though the original scales have been adapted for use with younger children. They focus on emotional and conduct disorders and were designed as screening instruments for epidemiological research.

The parents' scale (Child Scale A) consists of 31 items divided into three sections concerning health problems (eight problems, from 'complains of headaches' to 'truants from school'), habits (five questions including eating difficulty etc.), and behaviours (eighteen brief descriptions concerning the child's behaviour- identical to those on the teacher's questionnaire), to which the respondent replies: "does not apply"-scored 0; "applies somewhat"-scored 1; and "certainly applies"-scored 2 by ticking one of the three boxes. The scale is scored by adding across all of the items to give a total score and across smaller groups of items to give scores for 'conduct disorder' (five items), 'emotional disorder' (four items), and 'hyperactivity' (three items) subscales (Elander and Rutter, 1996). In the original research describing the use of this scale (Rutter *et al.*, 1970), the individual item scores from the scale were summed to produce a total score with a range from 0-62. A cut-off score of 13+ was used to identify a significant level of maladjustment. Once a child was identified as showing some behavioural or emotional disorder the greater of the emotional (neurotic or internalised) and conduct disorder (antisocial, aggressive or externalised) sub-scales was used to describe the nature of the child's problems. Hyperactivity is scored separately, with a cut-off of three.

The power of the scale to discriminate between children with behavioural problems and normal children was tested by comparing questionnaire results with diagnoses made from the case notes of psychiatric clinic. As shown by Rutter and colleagues (1970, Table 10.2 pg 157), in their comparison of the normal children with those with psychiatric disorder on the basis of the child characteristics, very few variables distinguished the true and false positives, suggesting that the questionnaire score is indeed a valid indicator of psychiatric disturbance. A further indication of the validity of the original questionnaire was provided by an examination of the pattern of the antisocial and neurotic items of the

questionnaire in relation to the final psychiatric diagnosis made on the basis of the intensive investigations.

The teachers' scale or child scale B (Rutter, 1967) consists of 26 brief statements covering a variety of behavioural problems including subscales for neurotic and antisocial behaviour each of which is scored 0, 1, or 2, depending on whether the statement "doesn't apply", "applies somewhat" or "definitely applies" to the child in question, producing a total score within the range 0 to 52. A neurotic sub-score is obtained by summing the scores of items on "often worried, worries about many things"; "often appears miserable, unhappy, tearful or distressed"; " tends to be fearful or afraid of new things or new situations"; "has had tears on arrival at school or has refused to come into the building". An antisocial sub-score is based on the total score on items "often destroys own or others' belongings"; "frequently fights with other children"; "is often disobedient"; "often tells lies"; "has stolen things on one or more occasions"; and "bullies other children". A total score of nine or more indicates a behavioural problem. Of the children who show some disorder, those with neurotic score exceeding their antisocial score are designated "neurotic", while those with antisocial score exceeding their neurotic score are designated "antisocial".

At ages 7, 11 and 16 years in the NCDS, the parents (mostly mothers) were asked majority of the items from the child scale A. The versions of the scale used in the NCDS surveys and the method of scoring do not completely agree with the version that was subsequently published. At ages 7 and 11, a shortened version was used, the wording was sometimes different, and the metrics were not identical. The teacher component of the Rutter scale was also completed by teachers at the NCDS 16 years and BCS70 at 16 years. The teachers were asked to fill the forms based on the child's behaviour in the past 12 months. Table A4 (appendix) presents a list of the items asked during each sweep and the specific wording used in both the NCDS and the BCS70.

At ages 5, 10, and 16 years, parents (mostly mothers) in the BCS70 were also asked to complete items from the Rutter child scale A. At the 5-year assessment, the modified scale consisted of 29 items. Minor changes from the standard questionnaire were made to the "health problems" and "habits" sections. Additional items included separate questions on day-time and nocturnal enuresis. The wording of the item: "tears on arrival at school or resistance to enter school" was reduced to: "tears on arrival at school". The

item on “stealing” on the standard questionnaire was moved from the “habits” section to the main body of the questionnaire and was rephrased to “sometimes takes things belonging to others”. The items on stammering or stuttering and other speech problems in the standard questionnaire were not included in the modified questionnaire. Three response categories were used in the modified questionnaire: “does not apply” scored 1, “applies somewhat” scored 2, and “certainly applies” scored 3.

At the 10-year assessment, the modified Rutter A scale contained 32 items. Compared to the version used for the 5-year assessment, two items on “stammering/stuttering” and “speech difficulties” in the standard questionnaire were added to the “habits” section. A visual analogue scale was used to rate the 19 behavioural items in the main body of the questionnaire where a parent was given, for each description, a line with “certainly applies” at one end and “does not apply” on the other and was asked to make a vertical mark on the line scale alongside each statement to indicate the extent to which the statement applied to the child. A score was given for each item ranging from 0 (does not apply) to 100 (certainly applies). At age 16, mothers completed a modified version of the Rutter A scale consisting of 19 items.

For both the parent and teacher versions, a total score or scores for specifically defined problem clusters can be used. It is also possible to use total and subscale scores as continuous rather than categorical variables (Elander and Rutter, 1996), and in several studies scores have been derived from slightly different sub-groupings of items on the basis of factor analysis. For this study, both the total and the subscale scores were used. As thresholds indicative of likely disorder were not available for the modified instruments used in different sweeps of the data, we used the subscale scores in the continuous form rather than using the cut-off in the standard scale for all the analyses except the preliminary descriptive graphs where categorical scales were used. In categorising the variables, a score in the top 13% defined a severe case of maladjustment, the lowest 50% were considered normal, and the remainder were considered mild case of maladjustment (Ghodsian, 1983).

Another justification for using the continuous scale for the major analyses was based on the evidence from studies that have shown that the use of a data-derived ‘optimal’ cut-point rather than using continuous variable may lead to serious bias besides other problems, notably a considerable loss of information and power (Royston *et al.*, 2006). A

further reason for not adopting the standard cut-off was because for the BCS70, the use of an analogue rating scale at the 10-year assessment and categorical ratings at the 5-year assessment meant that absolute scores were not comparable across the two assessments. In addition, the 5-year assessment in the BCS70 lies outside the age-range of samples used to validate standard Rutter subscale cut-offs.

A common argument in favour of categorising the continuous variable is the perception that categorization makes it easier to report and interpret final results, especially its ability to allow investigation of a possible dose-response relation. For this reason, supplementary analysis based on categorised measures of childhood behavioural problems for the NCDS was performed and the results are presented in the appendix B.

There have been numerous publications concerning the behavioural dimensions of these scales as used in the two datasets, most of them describing the results of either exploratory or confirmatory factor analyses on the items in the scales. However, the results are varied ranging from one-factor to three-factor solution. The majority of the studies on the NCDS data (e.g. Elliott and Richards, 1991; Mcculloch *et al.*, 2000) have revealed two factors corresponding to the broad dimensions of externalising and internalising behaviour problems. However, some studies have found the highest internal consistency in single-factor solutions (Chase-Lansdale *et al.*, 1995), yet others have revealed a three-factor solution indicating traits of aggression, anxiety, and restlessness (Hobcraft, 1998). In the BCS70 Sigle-Rushton (2004) reported a three-factor solution similar to Hobcraft's; similarly, Thompson *et al.* (2003) found three factors corresponding to the subscales of conduct problems, hyperactivity and emotional problems at ages 5 and 10.

Because of lack of complete agreement on the dimensionality of the items used in the modified Rutter scale in the previous studies, we carried out exploratory factor analysis to identify the dimensionality of these items and then grouped those items which were fairly strongly correlated and made intuitive sense. A factor analysis appropriate for ordinal variables was performed on the items separately for each age using full information maximum likelihood (Joreskog and Moustaki, 2000; Jöreskog and Moustaki, 2006), as implemented in the program LISREL 8.8 (Jöreskog and Sörbom, 2004). Behavioural subscales were then derived based on the factor loadings. Since there were some differences among the individual items asked at each survey, we took those that

were asked in broadly similar form on each occasion to ensure comparability across the various data sweeps. This resulted into fourteen items in the NCDS, two of which (sucks thumb and bites nail) did not load on any factor. Table 2-1 presents the varimax-rotated factor loadings for the seven-year old follow-up in the NCDS. The 11- and 16-year follow-ups had the same pattern of factor loadings.

Factor analyses of each scale revealed three factors which are labelled in this study as conduct problems, hyperactivity and emotional problems. The items in the conduct problem broadly represented the outwardly expressed, aggressive, externalising behaviour and included: often destroys own or others belongings; is irritable, quick to fly off the handle; frequently fights with other children; and often disobedient. The emotional problem subscale contained items representing withdrawn, inhibited, internalising behaviours including: tends to do things on own– rather solitary; often appears miserable, unhappy, tearful or distressed; often worried, worries about many things; and tends to be fearful or afraid of new things or new situations. The third factor contained the items on the child being squirmy or fidgety, having twitches or mannerisms, and having difficulty settling or concentrating.

Table 2-1 : Varimax-rotated factor loadings for the shortened Rutter A scale at age 7 in the NCDS- Factor loadings more than 0.4 are shown in bold.

	Factor 1 Hyperactive	**Factor 2 Emotional Problems**	**Factor 3 Conduct Problems**
Difficulty concentrating	**0.57**	0.102	0.321
Prefers doing things alone	0.058	**0.404**	0.074
Bullied by other kids	0.231	**0.414**	0.139
Generally destructive	0.333	0.02	**0.503**
Miserable or tearful	0.198	**0.421**	0.345
Is squirmy or fidgety	**0.627**	0.176	0.319
Continually worried	0.146	**0.784**	-0.031
Irritable is quick to fly off the handle	0.196	0.272	**0.549**
Sucks thumb, finger	0.103	0.094	-0.001
Upset by new situation	0.104	**0.548**	-0.015
Has twitches, mannerisms or tics	**0.409**	0.227	0.108
Frequently fights with other children	0.093	-0.047	**0.566**
Bites nails	0.179	0.116	0.089
Is often disobedient	0.175	0.121	**0.689**

For the BCS70 a subset of 19 items similar to those used in the 16-year-old questionnaire was selected for each sweep. Factor analyses of each scale also revealed three factors of conduct problems, hyperactivity and emotional problems. The items that loaded on each factor were similar for the three sweeps and are summarised in Table 2-2.

Table 2-2: Factors extracted from the Rutter child scale in the BCS70.

Factors	**Items in each factor**
Hyperactive	Very restless, hardly ever still
	Is squirmy, fidgety
	Cannot settle to do anything for more than a few moments
Emotional Problems	Often worried about many things
	Tends to do things on own, rather solitary
	Tends to be fearful or afraid of new things or new situations
	Is fussy or over particular
	Often appears miserable, tearful or distressed
Conduct Problems	Often destroys own or other's belongings
	Frequently fights with other children
	Irritable, quick to fly off the handle
	Sometimes takes things belonging to others
	Is often disobedient
	Often tells lies
	Bullies other children

Malaise Inventory

At ages 23, 33, and 42, participants in the NCDS filled in a questionnaire for the Malaise Inventory. The Malaise Inventory is a commonly used self-completion scale for assessing the likelihood of a psychiatric morbidity. It consists of a 24-item list of symptoms of depression, anxiety and psychosomatic illness (Rutter *et al.*, 1970) taken from the Cornell Medical Index. The 24 items are summarised in Table A5 (appendix).

In its original form, each item in the Inventory requests a ``yes'' or ``no'' response. The items cover emotional disturbance and associated somatic symptoms. There is some evidence that the items may represent two separate psychological and somatic sub-scales rather than a single underlying factor of distress, 15 item subscales of psychological symptoms and an eight item subscale of somatic symptoms. Rodgers *et al.* (1999) studied

the psychometric properties of the scale in the NCDS. Even though there was evidence that the somatic component of the Inventory behaves differently from the psychological component owing to the observed gender differences, which were greater for the latter component, there was little justification for the separate summation of two corresponding dimensions since the full 24-item scale still indicated acceptable internal consistency and external validity. In this study, the Malaise Inventory items (scored ``1" for yes and ``0" for no) were summed to yield a total score. We used the full scale and adopted a cut-off score of 7 or more, which was recommended by the authors of the scale for identifying cases at an increased risk of psychiatric disorder (psychological plus somatic). A dichotomous variable derived to indicate scores above and below this cut-off was used in the analysis.

The Malaise Inventory was also completed by the BCS70 cohort members at ages 16, 26, and 29/30 years. At 26 and 29/30 years full versions of the scale were used, however, at age 16 the cohort members responded only to the first 22 items of the scale coded as most of the time (1), some of the time (2), and rarely or never (3), under the heading “feeling healthy” in the educational pack.

General Health Questionnaire- GHQ

The General Health Questionnaire (GHQ) is a self-administered screening test, designed to identify short-term changes in mental health (depression, anxiety, social dysfunction and somatic symptoms). It is a pure state measure, responding to how much a subject feels that their present state "over the past few weeks" is unlike their usual state. There are four different versions: GHQ12 - a quick screener for survey use, GHQ28 - Used to examine a profile of scores, GHQ30 - a screener with 'physical' element items removed, and GHQ60 - used to identify cases for more intensive examination. The twelve-item version, GHQ-12, was used as a screening instrument for psychiatric and psychological distress in the NCDS at 41/42 years and BCS70 at 16 years and 29/30 years. The items in the scale are summarised in Table A6 (appendix). In the GHQ-12, each item assesses the severity of a mental problem over the past few weeks using a 4-point scale (from 0 to 3- better than usual, same as usual, less than usual and much less than usual). The score was used to generate a total score ranging from 0 to 36, with higher scores indicating worse conditions (Goldberg *et al.*, 1988). Both the Malaise Inventory and the GHQ-12 cover

similar types of symptoms including depression, anxiety, and psychosocial dysfunction, but the GHQ-12 covers recent deviations from an individual-defined, usual state.

Child behavioural assessment at school

The child's developmental behaviour in the BCS70 was assessed using a 53-item Child Development Scale. The scale measures neurodevelopmental behaviour and was completed at 10 years by the child's teacher. Neurodevelopmental behaviour plays an important part in a school child's ability to interact with peers and to function successfully in society after leaving school. Assessment of such behaviour is difficult as it requires, in this case, teacher judgments on the basis of experience with the child. The items for the scale were taken mainly from various existing measures, but also included questions suggested by specialists in different fields. The Conners' teachers hyperactivity rating scale (Conners, 1969) and the Rutter teacher behavioural scale (Rutter, 1967) were the main sources. Items were carefully selected from these scales in order to avoid duplication and the wording was amended to relate it as much as possible to the present-day usage in Britain. A variety of other items from other topics of interest such as anxiety and neurosis were also added to the form. The 53 items of the scale are listed in Table A7. Initial analysis contained in the BCS70 ten-year follow-up first report (Butler *et al.*, 1982) used principal component analysis on the 53-item scale to identify nine meaningful behavioural dimensions. Even though under the conventional criteria of the minimum eigenvalue of unity only eight factors were identified, they settled for a nine-factor solution based on theoretical consideration with the ninth factor having an eigen value of 0.9. The subscales identified were indicative of the following types of behaviour: antisocial, disorganised activity, neurotic/anxious, clumsy, extroversion/ introversion, hyperkinetic, behavioural trauma, poor hand co-ordination and difficulty in getting dressed. We used the same components in our analysis.

Child motivational assessment: LAWSEQ and CARALOC pupil opinion questionnaire

Scales of self-esteem and one of locus of control were introduced in the BCS70 at 10 and 16 years in order to provide motivation-related scales aimed at eliciting some aspects of the children's self-esteem and motivation. These were specially selected to contribute to the explanation of educational performance. Self-esteem, a judgment of overall self-worth, is considered as one of the aspects of child's emotional state since a child's low

self-esteem may certainly depress her or his enthusiasm to carry out normal daily activities. An existing self-esteem scale, LAWSEQ (Lawrence Self Esteem Questionnaire) (Lawrence, 1973) validated for these age groups was used. The scale consists of a series of 16 questions (four of which are distractor questions and are not scored) aimed at identifying children with low self-esteem with higher score indicating higher self-esteem. The items of the scale are presented in Table A8.

Locus of control, the extent to which individuals believe that their life circumstances are a function of either their own actions or external factors beyond their control (Moorhead and Griffin, 1992), was also assessed using an existing questionnaire, the Children's Attribution of Responsibility and Locus of Control (CARALOC) scale (Gammage, 1975). The scale comprised 20 items (four of which are distractor questions and are not scored) selected from some well known tests of locus of control, to which several original research items were added. The items of the scale are presented in Table A9. People who believe that they are in control of their own lives and that effort and ability determine their futures have an internal locus of control. In contrast, individuals with an external locus of control believe that fate, luck, chance, or other people's behaviour determines what happens to them. The locus of control questionnaire identified children with a largely external locus of control, implying a fatalistic belief that there was little the child could do to alter his or her own level of attainment. Higher scores in the scale indicate greater internalization.

Child hyperactivity at home: Conners' hyperactivity scale

The Conners' Rating Scale (Conners, 1969) is a popular tool for the clinical assessment of childhood attention problems with separate parent and teacher checklists specific to home or school situations, respectively. Items from the Conner's parent's hyperactivity scale were included in the maternal self-completion form to the mothers of the BCS70 cohort members at age 10 years. The scale uses observer ratings and self-report ratings to help assess attention deficit/hyperactivity disorder (ADHD) and evaluate problem behaviour in children and adolescents. The items used in the scale had some departure in scoring from the original scales since an analogue scale with a wide range of possible scores (automated marking systems yielding 100 points on longer analogue scales) was used rather than the four categories measurement. A factor analysis on the 18 items

yielded four subscales representing impulsiveness, hyperactive/inattention, clumsiness and motor-coordination (Table A10).

Table 2-3 summarises the outcome and the childhood and mid-life psychological measures used in this study from the NCDS and BCS70.

Table 2-3: Summary of the outcome and psychological measures used in this study for the NCDS and BCS70.

Variable type	Variable Names	Ages	Database	Description
Outcome Measures	Cancer	42/30	NCDS/BCS	Ever been diagnosed with cancer?
	Diabetes	42/30	NCDS/BCS	Ever been diagnosed with diabetes?
	Asthma	16-42/16-30	NCDS/BCS	Ever been diagnosed with asthma?
Childhood psychological measures (Main predictors)	BSAG-Conduct problems‡	7,11	NCDS	Conduct problems assessed by teacher
	BSAG-Emotional problems‡			Emotional problems assessed by teacher
	Rutter-Hyperactive problems‡	7,11,16/5,10, 16	NCDS/BCS	Hyperactive problems assessed by mother
	Rutter-Conduct problems‡			Conduct problems assessed by mother
	Rutter-Emotional problems‡			Emotional problems assessed by mother
	Rutter B-Neurotic‡	16	NCDS	Neurotic behaviours assessed by teacher
	Rutter B-Antisocial‡	16		Antisocial problems assessed by teacher
	Child Development Scale‡	10	BCS	Factors derived from a 53-items child development behavioural scale at school
	Antisocial Behaviour			
	Disorganised activity			
	Neuroticism/Anxiety			
	Clumsiness			
	Poor hand-Eye Coordination			
	Hyper/Kinesis			
	Introversion/Extroversion			
	Behavioural Trauma			
	Dressing			
	Locus of control†	10	BCS	To identify children with largely external locus of control
	Self esteem*	10	BCS	To identify children with low self-esteem
	Conners' Hyperactivity Scale	10	BCS	For the clinical assessment of childhood attention problems
	Impulsive			
	Hyperactive/Inattention			
	Clumsy			
	Poor Motor Coordination			
Psychological factors in mid life	Malaise inventory: psychologically distressed?	23,33,42/26, 30	NCDS/BCS	For assessing the likelihood of psychiatric morbidity: dichotomous variable used.
	GHQ12+	42/30	NCDS/BCS	Short-term changes in mental health

‡ : Higher scores indicate more severe behavioural problems or worse conditions of psychological distress

*Higher score indicate higher self-esteem.

†Higher scores in the scale indicate greater internalization

2.2.3. Other measures

A fairly wide range of control variables which are considered aetiologically important for each disease type were adjusted for. The choice of the variables to adjust for was based on the literature review for each disease group for all the putative risk factors.

Confounding factors

Several confounding factors, that is, factors measured prior to, or at the same time as the childhood psychological factors were adjusted for to ensure that any associations are not due to confounding. These included demographic, social, childhood health, and mid-teenage health behaviour.

Demographic and social environment: Demographic variables included the sex of the cohort member. Social environment variables in the NCDS included the parent's social class at age 7 years and educational level of the parents (the age at which the mother and father left full time-education). Childhood social class was based on father's occupation at age 7 classified according to the 1960 registrar general's classification, ranging from class I (professional) to V (unskilled manual). Households with no male head of household were put in a separate group. In the BCS70, the fathers' social class was based on the father's occupation when the cohort members were aged 10. Social class categories were based on the 1980 census classification. Households were classified into one of six categories ranging from Class I to Class V, with Class III being divided into two subcategories Class III – non-manual, and Class III – manual.

In the NCDS, parental education was assessed by whether the father had stayed in school past the minimum school leaving age (16); a similar variable was used to assess mother's education. In the BCS70, the highest educational qualification was sought through the mother's home interview at 5-year follow-up. For analysis, the qualifications were re-coded as a three-category variable: mothers with no education; mothers with 'O level' or equivalent or other vocational trainings (shorthand and/or typing, trade apprenticeships, State Enrolled Nurse (SEN) or Enrolled Nurse (Scotland), hairdressing diploma, etc); and mothers with 'A levels' or their vocational equivalent, or anything higher than that. A similar variable was used to assess father's education.

Family size was also considered since it might influence the parental behavioural ratings. This is because the parent's standards in judging the behaviour of children are likely to be largely based on the observations of their own family. Rutter *et al.* (1970) in their assessment of the validity of the Rutter scale A found out that interviews with parents suggested that when there were several deviant children in a large family, parents often regarded as abnormal only the child thought to be most deviant.

Childhood health in the NCDS: These included antenatal and perinatal factors (parity, maternal age, pre-eclampsia, birth weight, foetal distress (Thomas, 1990)), and paediatric growth (height, weight and body mass index at age 7, breastfeeding history). Others included pregnancy conditions accompanied by high blood pressure including pregnancy related hypertension, eclampsia, toxaemia and proteinuria, which were dichotomised as those with or without such condition.

Birth weight in the NCDS was recorded in pounds and ounces and converted into kilograms for analysis. Duration of gestation was estimated from the date of the last menstrual period reported by the mother and checked against general practitioner records. The z-scores of birth weight for gestational age were calculated by sex for each week of gestation. Small for gestational age was defined as birth weight below the 10^{th} percentile; appropriate weight for gestational age (AGA) as 10^{th} – 90^{th} percentile, and large for gestational age (LGA) as birthweight above 90^{th} percentile, with reference to population-based percentiles, separately for boys and girls and for singletons and twins. In the BCS70 birth weight was measured in grams; gestational age was based on the day of the last normal menstrual period (in completed weeks); parity (number of previous pregnancies resulting in a stillbirth or live birth) was categorised into no previous child, one previous child, two previous and three or more previous children; maternal age (mother's age at last birthday) was expressed in completed years but re-categorised into four age groups (<21, 22-25, 26-30, and 31+) for analysis based on the variation of the variable by each disease group.

At the 7 and 11 year follow up in the NCDS, and 5 and 10 year follow up in the BCS70, a history of various childhood diseases including eczema, whooping cough, measles, pneumonia, and hay fever or recurrent sneezing attacks since birth was recorded. In the subsequent sweeps respondents were asked about these conditions occurring in the past 12 months.

The childhood cognitive ability at age seven in the NCDS was measured by arithmetic and reading test scores. The arithmetic test was devised specifically for NCDS by the National Foundation for Educational Research (NFER) and has a possible range of scores from 0 to 10, with the scores being the number of correctly answered questions in a 10-question set. The reading test used was the Southgate Group Reading Test- SGRT (Southgate, 1962). This is a standardized test of word recognition and sentence completion, and has a possible range of 0 to 30. A higher score indicates greater ability in both the tests.

In the BCS70, the cognitive ability was assessed at age 10 by four indicators including one measure of ability, the British Ability Scale (BAS) and three performance measures (Reading, Maths and Languages Tests). The BAS (Elliott, 1983) consisted of two verbal and two non-verbal subscales. Verbal sub-scales comprised 37 items of word definitions and 42 items of word similarities. Non-verbal sub-scales comprised 34 items of recall of digits and 28 items of matrices. Administration of the test was adapted so that it could be done by teachers. The scoring was carried out when the completed forms were returned to survey headquarters. Both scores were standardized to have means equal to zero and standard deviations equal to one within the full 10-year sample.

Mediating factors

These are factors that might help to explain why childhood psychological factors are linked with chronic disease, and are measured after the childhood psychological factors but before the chronic disease. They are classified according to Cohen and Rodriguez's (1995) pathway model-health behaviour, social and cognitive.

Health behaviours: The health behaviours variables included smoking, alcohol consumption, drinking problem determined by the CAGE questionnaire, participation in physical exercises, diet, and obesity as determined by the body mass index (BMI). Information on smoking behaviour was collected age 16, 26 and 42 years in the NCDS. Information was also collected on participation in physical exercises, measures of obesity (BMI), and diet at 33 and 42 years, and illegal substance use at 42 years.

Data on alcohol consumption for early adults was collected at age 23 in the NCDS and 26 in the BCS70. Respondents reported their frequency of drinking any kind of alcohol

and how much of the specific kind they had consumed in the preceding week. The amount of the specific kind of alcohol consumed were converted into standard units (1 unit = ½ a pint of beer, 1 glass of wine, one measure of spirit, etc). In line with the previous studies (Wilson, 1980; Ghodsian and Power, 1987), the distribution of units of alcohol consumed within the preceding week in the 1958 cohort were divided into categories of consumption (0-10 for men, 0-5 for women; 1l-50 men, 6-35 women; over 50 for men, over 35 for women) as either light, medium or heavy drinkers. Since there were considerably more non-drinkers and light drinkers among the 1970 cohort at the age of 26 as compared to the 1958 cohort when they were 23, we used a different categorization where heavy drinking was defined as the top-fifth of the alcohol consumption distribution (24 or more units of alcohol consumption per week), the same categorization used in the 26-year follow-up report (Bynner *et al.*, 1997). The non-drinkers category included those who did not drink or only drank on special occasions while the 'light' category also included those who had not drunk in the previous week.

The study participants were also asked about the questions developed for the detection of alcoholism, the CAGE questionnaire (Mayfield *et al.*, 1974; Ewing, 1984) at age 42 in the NCDS. The CAGE is comprised of four non-threatening questions about drinking, which loosely correspond to the acronym, "CAGE." The questions include: Have you ever... felt you ought to *cut* down on your drinking? ; felt *annoyed* by people criticizing your drinking?; felt bad or *guilty* about drinking?; and had a drink first thing in the morning (*eye-opener*)?. Yes responses are coded 1; No responses are coded 0. Responses to the four items are summed to derive a total score with values ranging from 0-4. A higher score indicates greater risk for alcoholism. Mayfield and colleagues (1974) used two or more positive responses as indicative of alcoholism or problem drinking and this is the same cut-off used in this study.

Cohort members were also asked about their consumption of fresh fruit in summer and their consumption of salads/raw vegetables in winter at age 33 and age 42 years as part of dietary questions. The dietary variables were recorded on a six category frequency scale of "never", "less than once a week", "1 or 2 days a week", "3-6 days a week", "once a day" and "more than once a day".

Social and cognitive: These included marital status and satisfaction with relationship at 33 and 42 years in the NCDS, emotional and social support from friends and families at

42 years, psychosocial job strain, emotional expression, participation in organised religion, education attainment, and social class.

Education level of cohort member at age 23 in the NCDS and ate age 26 in the BCS70 was measured by a six-category ordinal measure of increasing academic and vocational qualification ranging from no qualification to degree level or higher/ national vocational qualifications 5 or 6. Social class of the NCDS cohort members was determined when they were 33 years old using the 1991 registrar general's classification of occupations ranging from class I (professional) to V (unskilled manual). Women were classified according to their own occupation and not that of their partner. A similar measure was used in the BCS70 when cohort members were 30 years old.

Moderating factors

These are factors that might alter the magnitude of the association (either synergistically or antagonistically). Such factors can come from either the list of confounding variables or the list of mediating factors.

Table 2-4 summarises all the possible confounding and mediating variables used in the NCDS and BCS70.

2.2.4. Measures in the biomedical survey

The elements in the computer-assisted personal interviewing (CAPI) used in the main survey included: Prescription drugs- all prescribed drugs taken, by name and BNF code; and anthropometric measures- standing height, sitting height, weight, waist circumference, and hip circumference were measured by a research nurse using a standardized protocol and equipment (scales and a stadiometer). Height and weight measures were taken without shoes and in light clothing. Waist circumference was measured by a nurse midway between the costal margin and iliac crest. Adiposity was assessed by BMI, calculated as kilograms per meter squared, and waist circumference in centimetres World Health Organization recommendations for BMI (≥30 kg/m2) and sex-specific waist circumference (≥102 cm for men and ≥88 cm for women) were used to indicate total and central obesity (World Health Organization, 2000).

Table 2-4: Summary of the potential confounding and mediating variables

Type	Variable Names	Ages	Database	Description
Possible	Sex		NCDS/BCS	Sex of the cohort member
Confounding	Parent's social class	7,10	NCDS/BCS	Social class of mother's husband
	Parent's education	5,7	NCDS/BCS	Age at which parents left full-time educ.
	Family size	5,7	NCDS/BCS	Number of people in the household
	Mother's age at delivery	5,7	NCDS/BCS	Age of mother at birth of cohort member
	Maternal smoking	5,7	NCDS/BCS	Whether mother smoking during pregnancy
	Parity	5,7	NCDS/BCS	Number of previous pregnancies
	Birthweight	5,7	NCDS/BCS	Birthwieght in Kg.
	Breastfed	7	NCDS	Whether the child was breastfed
	HBP/proteinuria/eclampsia	7	NCDS	HBP/proteinuria or eclampsia at birth
	Weight for gestational age	7	NCDS	Birthweight for gestational age
	Arithmetic score	7	NCDS	Arithmetic score
	Reading score	7	NCDS	Reading score
	BAS	10	BCS	British ability scale
	Smoking (No of packets)	16	NCDS	Cohort member smoking status
	Family history of diabetes	7	NCDS	History of diabetes in parents/siblings
	Pneumonia	7,11	NCDS	Attack by pneumonia
	Eczema	7,11	NCDS	Attack by eczema
	Whooping cough	7,11	NCDS	Attack by whooping cough
	Hayfever	7,11	NCDS	Attack by hayfever
	Abdominal pain	7,11	NCDS	Childhood abdominal pain
	Family history of atopy	10	BCS	Family history of eczema and hayfever
Possible	Educational level at age 23	23/26	NCDS/BCS	Educational attainment
mediating	Social class	33/30	NCDS/BCS	Social class of cohort member
factors	Alcohol consumption	23/26	NCDS/BCS	Amount of alcohol consumed
	Drinking problems-CAGE		NCDS	For the detection of alcoholism
	Physical exercise a		NCDS/BCS	Participation in physical exercise
	BMI		NCDS/BCS	BMI calculated from height & weight
	Fruit Consumption	33/42	NCDS	Consumption of fresh fruits in summer
	Salads/ raw vegetables	33/43	NCDS	Consumption of salads in winter
	Waist circumference	45	NCDS	Measure of sex-specific waist
	Atopy	45	NCDS	Whether the cohort member was atopic
	Total IgE (kU/L)	45	NCDS	Total IgE taken at age 45
	Forced vital capacity (log_{10})	45	NCDS	Forced vital capacity taken at age 45
	Forced expiratory vol in 1s	45	NCDS	Forced expiratory vol in 1s

Lung function: Spirometry was done in the standing position without nose clips, using a Vitalograph hand-held spirometer. Three measures (from up to five attempts) of forced vital capacity (FVC), forced expiratory volume (FEV_1) and peak expiratory flow rate (PEFR) ; and non-fasting blood sample- four tubes filled and sent by nurses to laboratories in London, Newcastle and Bristol. In addition, respondents completed a CASI (computer-assisted self-administered interview) section, covering smoking and drinking habits; and adverse childhood experiences.

Chapter 3

Analytical Methods

Analysing the complex interrelationships between the psychological factors measured during the childhood, other risk factors measured during the life course, and the development of chronic diseases over time using longitudinal data spanning broad periods of life raises several analytical problems. One of such problems is that the temporal, and possibly causal, hierarchies among the exposures need to be taken into account. This is because the risk factors for most chronic diseases operate at a number of stages in the life course and may also influence each other. Furthermore, such longitudinal data involve more than one point exposure and numerous potential confounding variables.

Another unavoidable problem is that of the missing data, which if not adjusted for, may greatly affect the estimates since the number of subjects for whom data are complete on any subset of the variables of interest may be reduced. Another common problem with the longitudinal data is that of the measurement errors. This results from the fact that, for delicate measurements, even immediate replication will not be able to avoid a certain level of variation, which if not accounted for properly may lead to misleading conclusions based on falsely detected statistical significance (Carroll, 2000). This chapter discusses the analytical approaches used in this study to address these difficulties. The analytical approaches are discussed first, followed by an elaborate discussion on handling missing data. More than one analytical approach has been adopted to gain more insight into the underlying mechanisms by comparing the results and investigating any inconsistencies.

All the analyses were carried out using Stata 10 (Statacorp., 2007) except for the structural equation modelling and factor analyses where Mplus (Muthén and Muthén, 1998-2007) and LISREL (Jöreskog and Sörbom, 2004) were used. All the statistical tests were done at 5% significance level. However, due to a large number of statistical tests carried out, emphasis was placed on p-values under 1%, and on clusters of significance that gave similar measures. This was to reduce the risk of type I error. Given the number of significance tests, this study may also play an important role in generating hypotheses to be tested in other studies.

The two cohorts were analysed separately. Where identical psychological measures were taken in both cohorts (as in Rutter scale A) the statistical models derived from the NCDS cohort (where chronic disease were more frequent due to longer follow-up) were directly tested in the BCS70 cohort. In this way, a significant association of the risk factors and the chronic disease in both the cohorts give more evidence that the association is unlikely to be a chance finding.

Statistical power and effect size

Given that we are using secondary datasets for analyses, nothing much can be done to decide on the appropriate sample size for the study. However, it is worth knowing whether the study will have enough power to detect a difference in the average psychological measures scores between those who developed and those who did not develop the disease. Assuming a simple case of comparing the mean Rutter score at age 7 between those who developed cancer (n= 263) and those who did not (n= 11,156), we will be able to detect an effect size of 0.20 with a power of 90% at 5% significance level. Figure 3-1 shows the variation in the effect size if the sample size is reduced from the original 11,419 to about 5,000 at different power levels maintaining the same ratio between those with and without cancer. The figure shows that even if the sample reduces to about 5,000 participants, it will still have a 90% power to detect an effect size of 0.31. Since all the three disease groups had varying prevalence, we can also vary the frequency of those who had the disease and see if there is substantial variation in the effect size at different power levels. Table 3-1 shows a number of frequencies of those who developed the disease and the associated effect sizes with 90% and 80% power. The table shows that the study has the power to detect medium to large effect sizes for diseases with low prevalence and to detect small effect sizes on more common chronic diseases.

Table 3-1: Effect sizes that can be detected at different frequencies of the disease and at different power levels, assuming the original sample of 11,419 participants in the year 2000.

Frequencies of disease	**50**	**100**	**150**	**200**	**300**	**500**	**1000**	**2000**
Effect size with 90% power	0.46	0.33	0.27	0.23	0.19	0.15	0.11	0.08
Effect size with 80% power	0.34	0.28	0.23	0.20	0.16	0.13	0.09	0.07

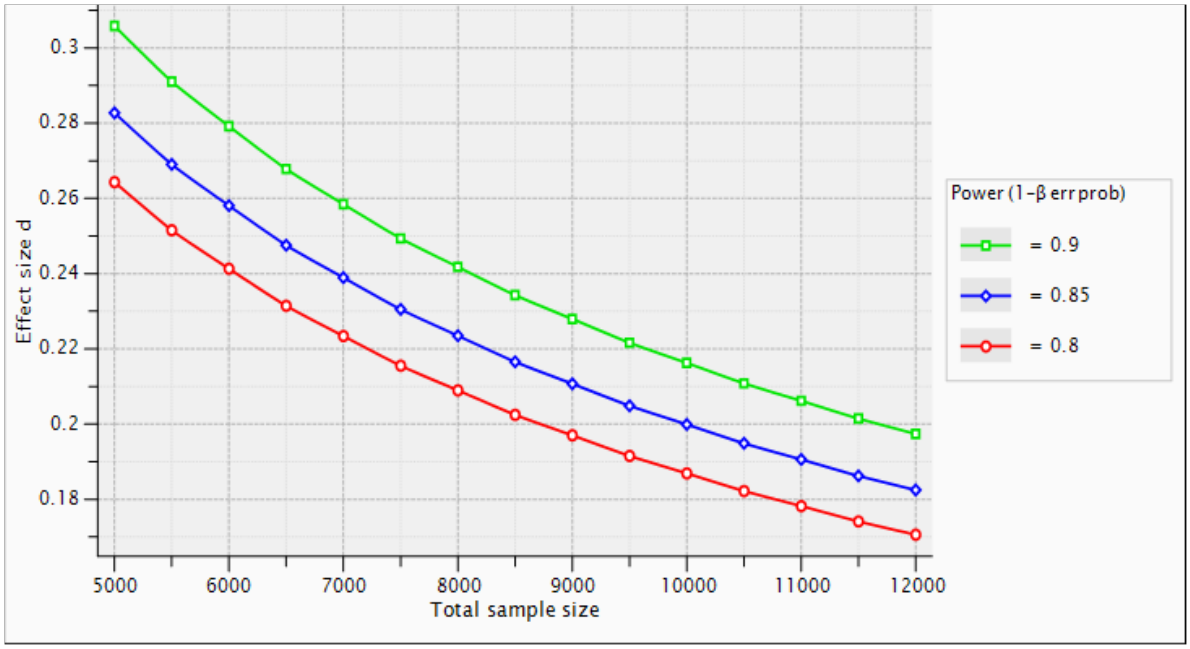


Figure 3-1: Effect of sample size and power on effect size for comparing the mean total Rutter score at age 7 years among those who developed cancer and those who did not.

3.1. Data Management and Univariable Analysis

There are usually rigorous data cleaning and quality checks by the CLS staff before the datasets are deposited for access by researchers. Despite the already high quality of the data, we carried out a few other consistency checks and data management tasks. The accuracy of the data on chronic disease was checked both internally within the follow-up and then cross-checking with data from previous follow-ups. In order to ensure the temporal sequence of psychological measurement preceding development of chronic disease, for each condition we only included those who were free of that condition at 16 years old. This excluded relatively few cases from the analysis and ensured that all the 7, 11, and 16 year psychological measures were made before the development of the chronic disease in the NCDS. Similarly, for the BCS70 the exclusion of those with the condition before age 16 ensured that the 5, 10 and 16 year measures were made before the development of chronic disease. Since a history of some chronic diseases was recorded from review of medical records at 16 year and 10 years in NCDS and BCS70, respectively, those who had any of the chronic condition by age 16 years in NCDS or 10 years in BCS70 were also excluded from the analysis of the specific condition.

Another data management task was the derivation and creation of new variables for analysis as already described in Section 2.2 . Due to the inter-disciplinary background to

the two cohort studies, their rich set of variables appears in a wide variety of forms and has, over time, been transformed into a selection of diverse variable types. Another complication with the datasets is the fact that each wave of the survey introduced subtle variations in data format even when the intention was to replicate the previous wave. Therefore, to try to eliminate the variations and minor inconsistencies within the data, extensive data recoding and transformation were necessary. This involved the creation of behavioural subscales from the factor analyses solutions as well as recoding other variables to appropriate categories. For instance, the Rutter Child Scales for parents and teachers which had a different coding from the one in the published manual was transformed to have the same coding of 0, 1 and 2 (instead of 1, 2, and 3), so as to allow for a distinction of children with behavioural disorder according to the criteria from the manual.

As an initial step before the multivariable analyses, an exploratory analysis was conducted to check for the presence of unusual features in the data, and to discover the percentages and patterns of missing observations for the variables considered. Initial hypothesis testing was performed using univariable models. The results from these analyses helped us to direct the focus of more sophisticated analyses, with emphasis placed on those associations that were not easily explained by chance.

3.2. Time to Event Models

Since the year of disease diagnosis was known as reported by the cohort members who had had or had been told they had the disease, it is imperative to take the duration to the event of interest (time to first disease diagnosis) into account rather than homogenizing the probability of contracting the chronic disease for all years. We therefore applied the survival (event history) analysis techniques to model the time-to-event (chronic disease onset).

A key analytical difficulty that occurs with time-to-event data is the presence of censored observations. Censored data arise when an individual has been followed up only to a certain time point before the event has taken place. For example, at age 30 and 42 in the BCS70 and NCDS, respectively, there were individuals who had not been diagnosed with any of the chronic diseases and so the only information available is that the individual has not experienced the event at the maximum follow-up time. This type of censoring is

known as right censoring. Thus, the event of interest is only observed if it happens prior to some censoring time, otherwise the time is censored in that we know the event has not occurred up to this time. Censored data can also result when an individual is lost to follow-up or withdraws from the study before the event occurs. Another complication with time-to-event data is that values of covariates may change as time elapses and the effects of covariates may change over time. Therefore, it is essential to apply the survival models to adequately deal with these features in the data.

Though the event of interest, time to disease onset, is continuous in the sense that it may occur literally at any time, it was recorded in discrete time since we know only the age (in years) at which an individual was first diagnosed with the disease not the exact month or day. Another feature of the data is that it has many tied events, that is, many study subjects being diagnosed with the disease in the same year. Due to these characteristics of the data, we applied the discrete-time models to reflect the nature of the data available. Discrete-time models have the strength that they can easily accommodate time-varying covariates. In addition, they do not require a hazard-related proportionality assumption that is commonly used in continuous time survival analysis. Those who were not diagnosed with the disease at the final sweep of data collection (in the year 2000) were considered to be censored.

Our goal is to estimate a regression model in which the probability of a person having the chronic disease is dependent upon many explanatory variables. The two approaches which have been used are through the effect of the variables on the hazard function- the hazard model- or their effect on event time- accelerated failure time model- (Kay and Kinnersley, 2002); we only focused on the hazard model in this study in order to gain an insight on how the risk depends on the covariate values. The key concept in this model is the hazard rate, which in discrete time, is the probability that an event will occur at a particular time to particular individual, given that an individual is at risk at that time. In this study, it is the probability of being diagnosed with a particular chronic disease within a particular year for those who do not have the disease yet. It is assumed that the hazard rate varies by year but is the same for each individual within each year. In the hazard model, the hazard is expressed as a product of some baseline hazard and a function that explains how the risk depends on the covariate values. In this study, some of these variables are baseline measures at childhood and are assumed to be constant over time.

Other variable were measured across subsequent sweeps, thus, we have both constant and time varying covariates.

As shown by Allison (1984), a convenient feature of the discrete-time hazard survival models is that they become models for dichotomous response when the data have been expanded to so-called person-period data with one observation for each year the person is at risk. Models appropriate for dichotomous responses such as logit, probit or complementary log-log models can then be used in the estimation of the discrete-time logistic model. For each person-year, the dependent variable is coded 1 if a person experienced the event in that year, otherwise it is coded 0. The explanatory variables are assigned the values they took in each person-year. In this way, the two problems of censoring and time-varying explanatory variables are solved. The estimation of the model parameters for the dichotomous response variable is then done by maximum likelihood (ML) method. The discrete-time survival analysis can now be formulated as a generalized latent class analysis of event history indicators (Muthén and Masyn, 2005) and is incorporated in the Mplus program. In this study, we obtained the estimated hazards as predicted probabilities by using logistic regression adjusted for the rare outcome events.

Logistic regression and adjustment for rare outcomes

It is recognised that for some sets of analyses such as diabetes and cancer the number with chronic disease were quite few and this inevitably limits the degree to which sophisticated multivariable analysis can be carried out for these diseases. As a result, there is a need to control for the problem of rare events data- binary dependent variables with dozens to thousands of times fewer disease cases- when estimating the hazards (using logistic regression models). Without the correction, the probability of the rare events can be sharply underestimated by the regression models. One of the methods that have been used to control for such imbalances is the propensity score, the conditional probability of exposure to a treatment given observed covariates (Joffe and Rosenbaum, 1999). The propensity scores are used to create matched pairs or matched sets or strata that balance many observed covariates; however, unlike random assignment of treatments, the propensity score may not also balance unobserved covariates. King and Zeng (2001) have developed an alternative method of computing probability estimates that correct the problems due to the rare events. The authors discuss the remedies for the problems

associated with rare events and develop corrections for the biases in logistic regression that occur when predicting or explaining rare outcomes. Their results show that, for rare-events data, the probability of an event of interest, Pr(Y = 1), is underestimated, and hence the probability of the other event, Pr(Y = 0), is overestimated. We applied their correction in our analysis as implemented in the ReLogit package for Stata developed by Tomz *et al.* (2003).

3.3. Structural Equation Modeling

In order to use an existing theoretical model of the link between psychological factors and disease to test whether associations are mediated by biological, behavioural, social, and/or cognitive pathways, we need joint models that deal with several outcomes simultaneously. In this way, we would be able to explicitly define a presumed process underlying intermediate and distal outcomes (chronic disease measure), and to estimate both the indirect and direct effects of psychological factors on chronic disease. One of the statistical approaches to allow this is the use of structural equation modeling (SEM) techniques.

SEM is a statistical technique consisting of sets of linear equations used for testing and estimating "causal" relationships using a combination of statistical data and qualitative causal assumptions. SEM encourages confirmatory rather than exploratory modelling (Jöreskog *et al.*, 1979; Bentler and Lee, 1983; Bollen, 1989) and is considered as a second generation statistical tool; thus, it is suited to theory testing rather than theory development. However, Asparouhov and Muthén (2008) have recently proposed an exploratory structural equation modelling (ESEM) approach, where in addition to or instead of confirmatory factor analysis (CFA) measurement model parts, exploratory factor analysis (EFA) measurement model parts with factor loading matrix rotations can be used. Historically, SEM was derived from the hybrid of two separate statistical traditions. The first tradition is factor analysis developed in the disciplines of psychology and psychometrics. The second tradition is simultaneous equation modelling developed mainly in econometrics, and introduced to the field of sociology under the name path analysis.

Unlike first generation regression tools, SEM not only assesses the structural model – the assumed causation among a set of dependent and independent constructs – but, in the

same analysis, also evaluates the measurement model – loadings of observed items (measurements, indicators or manifest variables) on their expected latent variables (unobserved variables, constructs or factors). The combined analysis of the measurement and the structural model enables the measurement errors of the observed variables to be analyzed as an integral part of the model, and factor analysis to be combined in one operation with the hypotheses testing. SEM techniques provide fuller information about the extent to which the research model is supported by the data than in regression techniques, thus they offer great potential for furthering theory development.

As with all statistical methodologies, SEM requires that certain underlying assumptions be satisfied in order to ensure accurate inferences. The major assumptions associated with SEM include: multivariate normality, no systematic missing data, sufficiently large sample size, and correct model specification. This requires that the data to be continuous in order for the normality assumption to be met, yet in social and behavioural science data are rarely continuous. Rather, we tend to encounter categorical data and often, we find mixtures of scale types within a specific analysis. A significant development has been made to enhance the facility for modeling under these more realistic conditions by providing a unified approach for estimating models containing mixtures of measurement scales and to incorporate latent continuous and categorical variables (Muthén, 1984, 2001; Skrondal and Rabe-Hesketh, 2004). The basic idea of Muthén's (1984) method is that underlying each of the categorical variables is a latent continuous and normally distributed variable. The statistics for estimating the model are correlations among these latent variables. Since most indicator variables under consideration in this study were categorical, Muthén's method as implemented in Mplus (Muthén and Muthén, 1998-2007) was applied in our analysis.

3.3.1. Standardized coefficients in logistic regression and SEM

To compare the effects of quantitative predictors having different units, it can be helpful to report standardized coefficients. Menard (2004) discusses six alternative approaches to constructing standardized logistic regression coefficients. We only discuss the two approaches presented in this study. One approach, commonly referred to as the X-standardization, fits the model to standardized predictors, replacing each predictor, x_j , by $(x_j - \bar{x_j})/s_{x_j}$ where s_{x_j} is the standard deviation of x_j (Agresti, 2002). Then each regression coefficient represents the effect of a standard deviation change in a predictor,

controlling for the other variables. Equivalently, for each j one can multiply unstandardized estimate $\widehat{\beta_j}$ by s_{x_j}. This is an example of a partially standardized coefficient because it incorporates the variance in the predictor, but not the empirical variation in the dependent variable.

Another approach is to have a fully standardized logistic regression coefficient, commonly referred to as *XY*-standardization. For the case of the linear regression, both the *X* and the *Y* variables are standardized to have a mean of 0 and a standard deviation of 1. However, this is not as straight forward in logistic regression since it is not the value of *Y*, but the probability that *Y* has one or the other of its possible values. The dependent variable is logit(*Y*) not *Y* in logistic regression, so the calculation of means or direct calculation of standard deviations is not possible. Standard deviations are calculated using the predicted values of logit(*Y*), $logit\,\widehat{Y}$, and the explained variance, R^2. As suggested by Menard (2004), the estimated standardized logistic regression coefficients can thus be obtained by $\widehat{\beta_j}$ (s_{x_j})(R)/$s_{logit\,\hat{Y}}$. In the SEM models, the coefficients are standardized using the variance of the background and/or outcome variables, in addition to the variance of continuous latent variables.

Standardized regression coefficients are frequently reported for many purposes. The main reason is for determining the relative importance of explanatory variables since the predictors are placed on a common scale so that each has the same mean and standard deviation, thus variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors in the equation.

The use of standardized coefficients, however, remains controversial with several researchers objecting to their use. Such objections have been raised for many reasons. King (1986) argued first that standardized coefficients are very difficult to interpret; secondly, that they do not add any information that may help to compare effects from different explanatory variables; and thirdly that they are a mixture of two important concepts, the estimated effect ($\hat{\beta}$) and the standard deviation, which should be analyzed separately. Another common objection is that standardized coefficients are thought to be sample specific and not stable across different samples because of changes in the variance of the variables (Hanushek and Jackson, 1977). Another heavy criticism was from Greenland *et al*. (1986) who concluded that standardized regression coefficients, correlations, and path coefficients have no meaningful biologic or public health

interpretation as measures of effect. They recommended that their use be avoided in epidemiologic analysis. Therefore, following the advantages and the disadvantages of standardization, the decision about whether each variable is to be standardized should be made and justified on an individual basis.

In this study, the unstandardized estimates (odds ratios) have been presented as measures of effects for all the models estimated by logistic regression. However, supplementary results with standardized estimates of the continuous childhood psychological measures are presented in appendix B. Since in SEMs, each path consists of a different model estimated by a different statistical technique (logistic regression, linear regression, ordinal logistic regression, and so forth) depending on the response, the presentation of the standardized estimates was preferred as a way of presenting uniform estimates across the pathways.

3.4. Treatment of Missing Data

Missing data is a pervasive problem in many studies including sample surveys, longitudinal or repeated measurement studies and clinical trials. The causes of missingness are often numerous, some due to design, and some to chance. The standard approach of handling missing data, which is the default in majority of the statistical software, is to restrict the analysis to subjects with complete data on the variables involved in the analysis and discard any cases that involve missing values. Estimates from such analysis can be biased, especially if the subjects who are included in the analysis are systematically different from those who were excluded in terms of one or more key variables. Moreover there is a substantial loss of information in the discarded cases leading to an unacceptable loss of power.

If covariate values are collected by a questionnaire or interview as was the case for most variables in the NCDS and BCS70, nonresponse is a typical source of missing data. Nonresponse in sample surveys occurs when a sampled unit does not respond to the request to be surveyed or to particular questions. Reasons for nonresponse may include total nonresponse (unit nonresponse), which occurs when no information is collected from a sampled individual because of non-contact, refusal or some other reason from the outset of the study; and item nonresponse that occurs when some but not all the required information is collected from a sampled individual. As a convention, weighting

adjustments are used for the former and imputation for the latter. In longitudinal surveys, like the data used in this study, there is the additional complication of wave nonresponse and attrition. By wave nonresponse, we mean the individual cohort members who respond to some but not all waves of data collection, while attrition or dropout refers to the unintended and permanent loss of cohort members from the longitudinal target sample as the cohort ages.

3.4.1. Non-response in the NCDS and BCS70

In common with all longitudinal studies, the sizes of the NCDS and BCS70 samples decline as the cohorts' age. Figure 3-2 sets out the differences between the target and observed samples at each sweep in the NCDS as well as the reason for not being in the sweep.

Sweep (Age)	0 (0)	1 (7)	2 (11)	3 (16)	4 (23)	5 (33)	6 (42)
Observed sample (x-sec)*	17,415 (98.8%)	15,425 (92.2%)	15,337 (91.5%)	14,647 (86.7%)	12,537 (76.1%)	11,407 (70.3%)	11,419 (70.3%)
Observed sample (long)+	17,415 (98.8%)	15,051 (91.2%)	14,757 (90.8%)	13,917 (86.6%)	12,044 (75.8%)	10,979 (70.6%)	10,979 (71.1%)
Non-response: refusal	0	80 (0.5%)	783 (4.8%)	1,114 (6.9%)	1,130 (7.1%)	1,735 (11.1%)	2,043 (13.2%)
Non-response: other‡	219 (1.2%)	1,178 (7.1%)	491 (3.0%)	708 (4.4%)	1,705 (10.7%)	1,100 (7.1%)	308 (2.0%)
Eligibility unknown†	0	191 (1.2%)	222 (1.4%)	329 (2.0%)	1,006 (6.3%)	1,746 (11.2%)	2,121 (13.7%)
Target sample	17,634 (100%)	16,500 (100%)	16,253 (100%)	16,068 (100%)	15,885 (100%)	15,567 (100%)	15,451 (100%)

*** :** Observed cross-sectional sample; +: Observed longitudinal sample

‡ : These are cases for which (a) there is no data (either a response or a refusal) for the current sweep but some data at a later sweep, and (b) temporary emigrants who were known to be abroad at the current sweep but who returned to GB later.

†: Includes cases of participants for whom eligibility is unknown because there are no data both in this sweep and in any future sweep. Comprise those who were not traced and also cases who had in fact died or permanently emigrated.

Figure 3-2: NCDS longitudinal target and observed samples, sweep 0 to 6. Taken from Table 1 of Hawkes and Plewis (2006).

The NCDS longitudinal target sample consist of all children born (alive or dead) in Great Britain (GB) in a week in March 1958, until they die or permanently emigrate from GB.

The observed longitudinal sample consists of cohort members with at least some data at that sweep, while observed cross-sectional sample are all children born anywhere in a specific week in March 1958 and living in GB at that sweep. A total of 18,563 cases have been involved in NCDS at least once. This comprises a cohort of 17,634 babies born in GB, and an additional 929 children possibly born outside GB who were added to the survey between sweeps 1 and 3 as immigrants.

The target population changes over time, for instance, of the 17,634 target sample at birth in the NCDS, only a target sample of 15,451 (87.6%) adults were remaining by sweep six at age 42 (Hawkes and Plewis, 2006). However, the observed sample was much lower at each sweep of data collection. For example, of the 17,415 children with at least some data at birth in the NCDS, only 11,419 adults had some data at sweep six in the year 2000. The sharp drop between sweeps three and four could be explained by a change in respondent from a parent or carer to the cohort member themselves as adults. The longitudinal target sample for BCS70 consisted of 17,287 babies and then declined (monotonically by definition) to 15,503 adults by sweep 5 at target age of 30 (Figure 3-3).

Sweep (Age)	**0 (0)**	**1 (5)**	**2 (10)**	**3 (16)**	**4 (26)**	**5 (30)**
Cross-sectional Observed sample	16,571 (95.9%)	13,071 (79.8%)	14,874 (89.7%)	11,621 (69.4%)	9,003 (55.3%)	11,261 (70.1%)
Longitudinal Observed sample	16,571 (95.9%)	12,981 (78.9%)	14,350 (88.7%)	11,206 (70.0%)	8,654 (55.0%)	10,833 (69.9%)
Non-response	716 (4.1%)	2,812 (17.0%)	1,108 (6.9%)	3,293 (20.6%)	4,765 (30.3%)	1,833 (11.8%)
Uncertain eligibility	0	668 (4.1%)	723 (4.5%)	1,500 (9.4%)	2,307 (14.7%)	2,837 (18.3%)
Target sample (estimated)	17,287 (100%)	16,461 (100%)	16,181 (100%)	15,999 (100%)	15,726 (100%)	15,503 (100%)

Figure 3-3: BCS70 estimated longitudinal target sample and observed sample, sweep 0 to 5 available data. Taken from Table 6.3 of Plewis *et al.*(2004).

Nathan (1999) gave a comprehensive review on the extent and effect of non-representativeness or attrition in the two birth surveys. Findings and analysis in his review indicated an overall high survey quality for these surveys. As expected, the cumulative attrition was found to be high, but the evidence on its effect did not show serious biases, except with respect to certain small sub-groups of the population. Thus,

based on his review, representativeness can be considered as being attained, to a high degree, and attrition does not seem to seriously impinge on the usefulness of the surveys.

Questions about the correlates of sample loss and non-response, and the effects that these losses might have on substantive analyses in the NCDS are answered by Hawkes and Plewis (2006). Their findings revealed systematic differences between respondents and non-respondents at every sweep with a tendency for male cohort members, cases with lower educational attainments, less stable employment patterns and living in more disadvantaged circumstances to be more likely to be lost from the study. However, despite greater loss from more disadvantaged groups, they found the cohorts to be largely representative, thus the problem of wave nonresponse may not be serious in the two datasets. For that reason, our adjustment for missing data in this study has mainly focused on item-nonresponse. A few studies have evaluated the problem of item nonresponse in the NCDS. Wiggins *et al.* (2000) through the use of 10% of the NCDS data to evaluate a range of currently available software remedies to handle missingness, concluded that analyses based on fully observed data (using case-wise deletion) may miss, under- or overstate substantive relationships that occur post imputation**.** The authors recommended the exploitation of multiple imputation to understand the nature of any potential response bias prior to analysis.

3.4.2. Problems of missing data and mechanisms that lead to missing data

Missing data can affect properties of estimators (e.g. means, variances, regression parameters etc.). The effects include biases in point estimators, inflation of the variance of the point estimators, and biases in customary estimators of precision. Missing data can also affect inferences, i.e. the properties of tests and confidence intervals. A critical determinant of these effects is the way in which the probability of an observation being missing (the missingness mechanism) depends on other variables (measured or not) and on its own value. Missing-data mechanisms are crucial since the properties of missing-data methods depend very strongly on the nature of the dependencies in these mechanisms. Little and Rubin (1987) make important distinctions between different missing values processes and the formal and mathematical definitions can be found in this text. Data are considered to be missing completely at random (MCAR) if the missingness is independent of both unobserved and observed data, that is, missingness is not related to any factor, known or unknown, in the study, a strong assumption that is

usually not met. A more plausible assumption is that missingness is missing at random (MAR), that is, conditional on the observed data, the missingness is independent of the unobserved measurement. Finally, when neither MCAR nor MAR hold, missing data are considered to be nonignorable (NINR- nonignorable nonresponse) or missing not at random (MNAR), that is, it depends on unobserved quantities, for example, the probability of missing data on a certain variable may be dependent on the values the variable is taking.

3.4.3. Missing data methods

Much has been written about statistical methods for handling incomplete data. Allison (2001), Schafer (1997), and Little and Rubin (2002) are some of the texts that have given a comprehensive review of the available methods. These methods include procedures based on completely recorded units; weighting procedures; imputation based procedures where missing values are filled in and the resultant completed data analysed by standard methods; and model based procedures which involves defining a model for the observed data and basing inferences on the likelihood or posterior distribution under that model, with parameters estimated by procedures such as maximum likelihood. These methods can be broadly categorised as *principled* and *unprincipled* methods. Principled methods are based on statistical models for the data, and the methods of model fitting, analysis and inference are based on formal statistical paradigms, principally frequentist and Bayesian (Kenward and Carpenter, 2007). Unprincipled methods are characterized by ad-hoc procedures – typically manipulating the data so that the analysis originally intended for fully observed data can be run.

Several authors (e.g. Little and Rubin, 1987; Verbeke and Molenberghs, 2000; Little and Rubin, 2002), have described several ad-hoc methods and their limitations. These methods include complete case analysis, which restricts the analysis to subjects with complete data on the variables involved in the analysis and discards any cases that involve missing values; available case methods, where the cases with complete data for the variables in the fitted model are analysed utilising the largest possible dataset; and simple forms of imputation such as last observation carried forward for longitudinal data, hot deck imputation where recorded units in the sample are used to substitute values, mean imputation where means from sets of recorded values are substituted, and regression imputation where the missing variables for a unit are estimated by predicted

values from the regression on the known variables for that unit. Imputation method has the advantage that observed values in the incomplete cases are retained. Another advantage is that it allows for the standard complete-data methods of analysis to be used. A problem of simple imputation procedures is that they may yield inconsistent point estimates unless the missing cases are MCAR. Imputing a single value treats that value as known, and thus without special adjustments, simple imputation cannot reflect sampling variability under one model for nonresponse or uncertainty about the correct model for nonresponse.

Another widely used ad-hoc method for handling missing data is the indicator method recommended by Cohen and Cohen (1975) in the earlier edition of their book. This approach for continuous variables involves recoding missing values to some common value, creation of an indicator of missingness as a new variable, and including both these variables along with their interaction in the regression model. A similar approach for categorical variables involves the creation of an additional category for missing values. Research has shown that this "missing indicator" method will result in biased effect estimates under most conditions and are not advisable in general (Vach and Blettner, 1991; Greenland and Finkle, 1995; Jones, 1996; Horton and Kleinman, 2007). In particular, this method can exhibit severe bias even when the data are MCAR (Greenland and Finkle, 1995).

Although unprincipled methods may give valid inference in certain settings, such settings are typically narrow and often both unrealistic and difficult to establish in practice (Kenward and Carpenter, 2007). Therefore, unless the proportion of missing data is too small as to be unlikely to affect inferences, these simple ad-hoc methods are regarded as inadequate and should be avoided. A multitude of alternative missing-data techniques have been devised. These include maximum-likelihood (ML) methods (e.g., EM algorithm, full information maximum likelihood in structural equations, or mixed models) based on all the available data; weighting methods (Robins *et al.*, 1995; Carpenter *et al.*, 2006), where a model for the probability of missingness is fit, and the inverse of these probabilities are used as weights for the complete cases; and multiple imputation (MI) methods whose comprehensive treatment is given by Rubin (1987). In fully parametric models, maximum-likelihood estimates can often be calculated directly from the incomplete data by specialized numerical methods, such as the EM algorithm (Dempster *et al.*, 1977). The estimates obtained through such procedures may be

somewhat more efficient than those from MI, because they involve no simulation. However, MI is more general than likelihood based methods and has therefore emerged as a flexible alternative to likelihood methods for a wide variety of missing-data problems. Due to this and other advantages pointed out in the subsequent sections, we used MI to adjust for missing data in this study; therefore we give a brief overview of the method.

3.4.4. Multiple imputation

MI refers to the procedure in which each missing value is replaced with $m > 1$ simulated values prior to analysis. Instead of filling in a single value for each missing value, MI replaces each missing value with *m* sets of plausible values that represent the uncertainty about the right value to impute. The multiply imputed data sets are then analyzed separately by using standard procedures for complete data and results from these analyses, which may vary, are then combined by simple arithmetic, the Rubin's (1987) rules, to obtain overall estimates and standard errors that reflect missing-data uncertainty as well as finite sample variation. The primary advantage of MI besides the advantages of single imputation is that it leads to valid statistical inferences in the presence of nonresponse since the inference based on the combined results of *m* complete-data validly reflects sampling variability because of the missing values. This is a very attractive feature since the goal of MI, like any other statistical procedure, is to make valid and efficient inferences about a population of interest but not to estimate, predict, or recover missing observations nor to obtain the same results that we would have seen with complete data. Since MI is principled, and likelihood based, it also has the advantage of efficiency as it incorporates information from subjects with incomplete sets of observations. The key assumption with the MI, as with most approaches to missing data problems, is that the missing data are MAR.

Another attractive feature of MI is that we do not need a very large number of imputed datasets for precise estimates. Rubin (1987) showed that the efficiency of an estimate based on *m* imputations, relative to one based on an infinite number, is $(1+\lambda/m)^{-1}$, where λ is the rate of missing information, that is, a measure of the increase in the large-sample variance of a parameter estimate due to missing values. For example, with 50% missing information, *m* = 10 imputations will be 95% efficient; additional imputations do little to remove noise from the estimate itself. However, with the great

increase in available computing power, it has become practicable to do MI with many more imputations in routine problems and examine the consequences of this. In many practical applications Schafer and Graham (2002) found that increasing the number of imputation to m=20 can effectively remove noise from the other statistical summaries (e.g., significance levels or probability values).

The key practical issue with MI concerns the appropriate specification of the imputation model, since if this is misspecified, then there is the potential for bias. It is crucial that imputation model be general enough to preserve effects of interest in later analyses. In general, the imputation model should contain variables known to be predictive of missingness and accommodate structure, for example, interactions or hierarchical structure, in the substantive model since failure to do this can cause bias in the resulting analysis. In addition, when imputing covariates, the outcome variable must be included as an explanatory variable in the imputation model. Since the imputation model and substantive model are kept separate, additional covariates can be included in the imputation model which we do not want to adjust for/condition on in the substantive model to maximize the plausibility of the missing data being MAR. Such over-fitting, given the Bayesian nature of the imputation step may be expected to reduce the precision of the final estimates to some extent. Though, Schafer (2003), has found out that with real data, the increase in standard errors that arises when the imputation model is more general than analysis model is often barely noticeable. In contrast, omission of important predictors of missingness would be expected to produce bias. Therefore, it may be better in the imputation model to err on the side of over- rather than under-fitting (Kenward and Carpenter, 2007) .

There are a variety of imputation models that have been used. In most general applications, the model for the missing data given the observed is a fully specified joint model. Often a multivariate normal model has been used, as it is computationally tractable (since only the mean vector and variance-covariance matrix needs to be estimated). This is difficult to specify for a mixture of continuous and categorical data. This model has been used even when some of the variables are not Gaussian. Many authors (e.g., Schafer, 1997) have recommended rounding the imputed values so that imputed values greater than or equal to .5 are set to 1 and anything less is set to 0. However, it has been shown that such rounding can produce biased estimates of proportions, especially when the true proportion is near 0 or 1 (Horton *et al.*, 2003;

Allison, 2005). Many techniques for MI for incomplete categorical data have been developed, for example, the use of saturated multinomial model (Schafer, 1997). In situations with multivariate data involving non-linear relationships particularly when multiple categorical and continuous variables have missing values, the joint distribution may be complicated. Little and Rubin (2002, P 214`-217) give a review of other methods for creating multiple imputations. One of the methods useful with real multivariate data is the one drawing from pragmatic conditional distributions (Van Buuren and Oudshoorn, 1999; Raghunathan *et al.*, 2001). A number of practical implementation of this idea have been devised and one of them is the multivariate imputation by chained equations- MICE (Van Buuren and Oudshoorn, 1999; Raghunathan *et al.*, 2001). Under this method, no joint distribution is set up, rather, a set of conditional distributions relating each variable to a set of other variables is formulated.

The MICE assumes that, for each incomplete variable, the user specifies a conditional distribution for the missing data given the other data. Thus the algorithm imputes an incomplete column (the target column) by generating appropriate imputation values given other columns in the data. A separate univariate imputation model can be specified for each column. For example, logistic regression could be used for incomplete binary variables, polytomous regression for categorical data, and linear regression for numerical data. Under the assumption that a multivariate distribution exists from which these conditional distributions can be derived, MICE constructs a Gibbs sampler from the specified conditionals. This sampler is used to generate multiple imputations. More information about this method can be found in Van Buuren and Oudshoorn (1999).

Roughly, depending on the implementation, MICE proceeds as follows: First, each incomplete variable is initialized by filling in a random draw from the marginal distribution of the observed values to ensure that no relevant values are missing. The 'filled-in' values in the first variable, Y_1 , are discarded leaving the original missing values. Then Y_1 is imputed using regression imputation conditional on all other data (observed and imputed combined). The 'filled-in' values in the second variable, Y_2, are discarded. Then Y_2 is imputed using regression imputation conditional on all other data (using the most recent imputations for Y_1). This process is repeated for each variable in turn. Once each variable has been imputed using the regression method we have completed one cycle or pass. Subsequently, a second pass is started through the data,

using all imputations created during the first pass, and so on. This step is repeated according to the number of cycles desired, replacing the imputed values with updated values at the end of each cycle. Van Buuren and Oudshoorn (1999) recommend about 20 cycles. The set of imputations that are created after the 20^{th} pass are used to derive the first complete data matrix. This whole procedure is executed *m* times in parallel, thus producing *m* completed data sets. This method is called regression switching.

The MICE algorithm is computationally simple to implement, flexible and a practical way available in several software to generate multivariate MIs. The theoretical weakness of this approach is that the specified conditional densities can be incompatible, and therefore the stationary distribution to which the Gibbs sampler attempts to converge may not exist. However, simulation studies (Van Buuren *et al.*, 2006) have indicated that the method often works quite well. Another practical problem, common to all other MI procedures, is that the specification of imputation models from large databases containing hundreds of variables may involve a lot of work and may be marred by problems of multicollinearity and other instability problems if too many predictors are thoughtlessly added to the imputation model. Therefore, it is useful to select a suitable subset of data to avoid this problem.

Implementation in the NCDS and BCS70

To account for missing data in the NCDS and BCS70, missing values were imputed by MICE technique using the imputation by chained equations (ICE) program implemented in Stata by Royston (2004). Our imputation model was sufficiently general for our models of interest so that all the associations potentially of interest were included in the imputation model. All the variables that appeared in the complete-data model as well as those for which the distributions differed between the response and nonresponse groups were included in the imputation model. These were identified by examining the important predictors of the response indicator of each target variable to be imputed. By using the longitudinal datasets, we had an advantage of allowing the utilisation of data from the previous waves to impute missing wave data since in most cases the best predictors of response at any sweep were variables measured at the previous sweep. This improved the validity of the imputation model under the MAR assumption. Continuous variables which were highly skewed were transformed to approximate normality before imputation, and back transformed after imputation for the analysis of interest. Based on

the recommendation by van Buuren, Boshuizen, and Knook (1999) the logarithm of the time to disease onset (survival time) and the censoring indicator were used as potential predictors in the imputation model so that multiplicative relations between survival time and the covariates could be modelled by additive models. The final dataset used was based on 10 imputations with 20 cycles each. The Stata programs MICOMBINE (Royston, 2004) and mim (Carlin *et al.*, 2008) were used to calculate the average regression estimates over the set of replicates, adjusting the standard errors according to Rubin's rule (Rubin, 1987) and refinements thereof (Li *et al.*, 1991). Sensitivity analysis of the results was done at the most basic level by comparing the result with those of complete-case analysis.

SECTION II

CANCER

Chapter 4

Literature Review for Cancer Risk Factors

4.1. Introduction

Cancer, also known as malignant neoplasms, describes a range of diseases in which abnormal cells proliferate, spread out of control beyond their boundaries, and can invade adjoining tissues and spread to other organs via lymph or blood (metastasis). The vast catalogue of cancer cells acquire certain capacities to be self-sufficient in growth signals, insensitive to antigrowth signals, have limitless replicative potential, evade apoptosis (programmed cell death), have sustained angiogenesis and lead to tissue invasion and metastasis (Hanahan and Weinberg, 2000). The potential aetiologies include external causes such as chemicals, radiation and viruses, and internal causes such as, hormones, immune system abnormalities and inherited mutations (Fife *et al.*, 1996). These potential causes do not necessarily act in isolation but more than one can be present at any one time, thus there are a highly complex set of causal factors rather than a single cause. There are approximately 200 different types of cancer and all organs of the body can become cancerous. Although some cancers can now be cured, and treatment can significantly increase the prognosis for many others, the diagnosis and treatments are often stressful and their side effects can have adverse effects on the quality of life.

With more than 10 million new cases every year (Stewart and Kleihues, 2003), cancer has become one of the most devastating diseases worldwide. By the year 2005, it was estimated that cancer was only second to the cardiovascular diseases, as a leading cause of chronic disease deaths, contributing to about 13% of the nearly 58 million deaths from all causes worldwide (World Health Organization, 2005). Based on projections by the WHO (2005), cancer deaths will continue to rise with an estimated 9 million people dying from cancer in 2015, and 11.4 million dying in 2030 if the major risk factors are not eliminated. The World Cancer Report (Stewart and Kleihues, 2003) provides a global view of cancer by giving the frequency of cancer in different countries, trends in cancer incidence and mortality and describes the known causes of human cancer. From the report, IARC-WHO estimates that cancer rates are set to increase at an alarming rate, from 10 million new cases globally in 2000, to 15 million in 2020. However, there is an

opportunity to stem the predicted sharp increase in new cancer cases by taking action now, especially through planning effective cancer control strategies.

Europe has an estimated cancer prevalence of about 3%, increasing to 15% at old age and almost 50% of deaths at middle age is caused by cancer, partly resulting from lowering mortality from other causes of death (Karim-Kos *et al.*, 2008). In the UK, it is estimated that approximately 1.2 million people (2% of the population), 1.5% of males and 2.5% of females at the end of 1992 were living with a diagnosis of cancer (Forman *et al.*, 2003). The single cancer that contributed most to this total in females was breast cancer, with an estimated 172,000 women alive who had had a diagnosis of breast cancer. According to their figure, cancer prevalence increased steeply with age, reaching values of 7.3% and 7.8% in males and females, respectively, in the 65 years age group. In this group, the most prevalent cancers were those of the prostate, lung, colon and rectum in males, and of the breast, colon and uterus in females. The pattern was similar among the middle aged population (45–64 years), although the absolute prevalence estimates were substantially lower, especially for prostate cancer in males.

This chapter presents a literature review on the risk factors for cancer including the well-known and established risk factors, the psychological risk factors, and perinatal and childhood risk factors. Medline and PsychINFO were the major databases checked up to the year 2009, using the keywords neoplasms-aetiology or neoplasms-epidemiology or neoplasms and risk or psycho-oncology in combination with psychological factors or stress or personality or depression or affective states or depressed mood. Relevant articles were judged on the basis of a reading of the abstracts. Additional references including relevant books were obtained from the citations in these articles and review articles. Other sources were the reports such as World Cancer Report and WHO reports.

4.2. Known Risk Factors

In order to assess the predictive value of psychological risk factors, it is important to have an accurate assessment of physical risk factors as well. The majority of the risk factors for cancer are well established and well known. The most important modifiable risk factors are tobacco use, unhealthy diet and excessive energy intake, and physical inactivity (World Health Organization, 2005). Many more risk factors have been identified but account for a smaller proportion of cancer risk. They include harmful

alcohol use, occupational factors, environmental factors, infectious agents, psychosocial factors, and genetic and hormonal factors. Since these factors do not necessarily act in isolation, it is not possible to give a precise estimate of the proportion of the cancers directly attributable to the individual risk factor. At times the extent to which cancer in general, or specific cancers, may be modified by any factor, are calculated and reported by many researchers. However, these estimates should be treated with some caution since they are estimates, and cannot be exact, and so are best given as ranges. In addition, individual causes of cancer often interact with one another to increase or decrease risk, or are modifiers or precursors of others; and some act together to produce a multiplicative effect.

Despite the difficulty in estimating the proportion of the cancers directly attributable to the individual risk factor, several reports have quantified the effects of risk factors on cancer incidence and mortality, as summarised in the World Cancer Report (Stewart and Kleihues, 2003). Most of these studies, however, are restricted to one risk factor, one site of cancer, or one population (Doll and Peto, 1981; Mezzetti *et al.*, 1998; Engel *et al.*, 2003; Danaei *et al.*, 2005; Sprague *et al.*, 2008). A few others have quantified the risk factors for the disease in the absence of the residual confounding and interaction; however, such confounding cannot be completely eliminated. Fioretti *et al.* (1999) for example, investigated the aetiology of oral and pharyngeal cancer in never smokers using a case-control study and found alcohol consumption as a major risk factor with an odds about three-fold higher in drinkers than non-drinkers; though these figures were in the presence of other dietary indicators.

4.2.1. Tobacco consumption

Tobacco consumption remains the most important avoidable cancer risk. The World Cancer Report (Stewart and Kleihues, 2003) shows that in the 20th century, approximately 100 million people died world-wide from tobacco-associated diseases (cancer, chronic lung disease, cardiovascular disease and stroke). It is estimated that between 25 and 30% of all cancer deaths in developed countries are tobacco-related (Boyle *et al.*, 2003). Tobacco smoking is accepted as a major risk factor for cancers of the lung, larynx, oral cavity and pharynx, and oesophagus (Franceschi *et al.*, 1990; Parkin *et al.*, 1994; Peto, 1994; Peto *et al.;* Boyle *et al.*, 2003). In the developed world, between 87 and 91% of lung cancers in men, and between 57 and 86% of lung cancers in

women, are attributable to cigarette smoking (Boyle *et al.*, 2003). The interaction between smoking and other harmful exposures can result in a much greater risk in people exposed to both. For both sexes combined, the proportion of cancers arising in the oesophagus, larynx and oral cavity attributable to the effect of tobacco, either acting singly or jointly with the consumption of alcohol, is between 43 and 60% (Boyle *et al.*, 2003). In addition, a significant proportion of cancers of the urinary bladder and pancreas, and a smaller proportion of cancers of the kidney, stomach, cervix and nose, as well as myeloid leukaemia, are also causally related to tobacco consumption (Boyle *et al.*, 2003).

Cigarette smoking has been linked to a two- to fivefold increase in cervical cancer risk in women who are infected with oncogenic human papillomavirus (HPV) in a number of studies (Castle *et al.*, 2002; Mcintyre-Seltman *et al.*, 2005; Gunnell *et al.*, 2006). In a meta analysis, Haverkos *et al.* (2003) pooled 72 case-control studies evaluating cigarette smoking among women with and without cervical disease, and found an evidence supporting the role of cigarette smoking as a risk factor for cervical cancer (summary OR for all cervical disease for current smokers versus non smokers = 2.13, 95% CI=2.02 to 2.25). However, the molecular mechanisms by which smoking increases the risk of cervical pre-cancer and cancer remain unclear. A number of such mechanisms have been suggested. One is that smoking inhibits the immune response to HPV (Poppe *et al.*, 1995). Another one is that carcinogenic HPV-infected cells are exposed to smoking carcinogens that cause DNA damage (Ali *et al.*, 1994).

Cigarette smoke contains at least 80 known mutagenic carcinogens, including arsenic, cadmium, ammonia, formaldehyde, and benzopyrene (World Cancer Research Fund and American Institute for Cancer Research, 2007), each of which has a separate mechanism for causing cancer. Despite the knowledge of smoking as a major risk factor for cancer, smoking prevalence in the UK still remains high especially among the young adults with around one in four British adults smoking by 2002 (Rickards and Office for National Statistics, 2004).

4.2.2. Unhealthy diet and excessive energy intake

Dietary factors have been thought to account for approximately 30% of cancers in Western countries (Doll and Peto, 1981), making diet second only to tobacco as a

preventable major risk factor for cancer. Most of the research has focused on identifying the associations with particular components of diet including the intake of fruits and vegetables, intake of fat in the diet particularly from animal sources, intake of salt and nitrites, dietary fibre intake, and intake of red and processed meat.

Daily intake of a variety of vegetables and fruits

A number of epidemiological studies have indicated a protective effect of higher intakes of vegetables and fruit on the risk of a wide variety of cancers. Recent studies have shown that daily consumption of about 80-100 grams of fruits and vegetables is associated with almost half reduction in the risk of oral cancer (Pavia *et al.*, 2006); a reduced risk of squamous cell carcinoma of the oesophagus by about 20% (HR: 0.78, 95% CI: 0.67-0.91) (Freedman *et al.*, 2007); a substantial evidence of reduced risk of stomach cancer by about 30% and of lung cancer (World Cancer Research Fund and American Institute for Cancer Research, 2007); and a reduced risk of laryngeal cancer (Bosetti *et al.*, 2002a). In a review of the scientific literature on the relationship between vegetable and fruit consumption and risk of cancer, Steinmetz and Potter (1996), using the results from 206 human epidemiologic cohort and case control studies, found a consistent evidence for a protective effect of greater vegetable and fruit consumption for cancers of the stomach, oesophagus, lung, oral cavity and pharynx, endometrium, pancreas, and colon. The types of vegetables or fruit that were often found to appear to be protective against cancer were raw vegetables, followed by allium vegetables, carrots, green vegetables, cruciferous vegetables, and tomatoes.

In order to understand the possible mechanisms by which vegetable and fruit intake might alter risk of cancer, a myriad of substances in vegetables and fruit have been shown or postulated to have anticarcinogenic properties. These include carotenoids, vitamins C and E, selenium, dietary fibre, dithiolthiones, glucosinolates and indoles, isothiocyanates, flavonoids, phenols, protease inhibitors, plant sterols, allium compounds, and limonene (Steinmetz and Potter, 1996). These agents have both complementary and overlapping mechanisms of action, including the induction of detoxification enzymes, inhibition of nitrosamine formation, provision of substrate for formation of antineoplastic agents, dilution and binding of carcinogens in the digestive tract, alteration of hormone metabolism, antioxidant effects, and others. Recent developments in new DNA chip technology and functional proteomics may shed new

light on the complex nutrient-gene interactions. This may provide pathophysiologic mechanisms of cancer causation and prevention and improve the ability to conduct the cancer surveillance that is crucial in identifying at-risk populations (Go *et al.*, 2001).

Dietary fibre intake

Cereals with high fibre content and whole-grain cereals have been associated with lower risk of colorectal cancer and other digestive tract tumours in a few European studies. Results from the European Prospective Investigation into cancer and nutrition (Bingham *et al.*, 2003) showed that dietary fibre in foods (average of 27g/day) was inversely related to incidence of large bowel cancer (about 20% reduction) as compared to low fibre intake (average of 17g/day), the protective effect being greatest for the left side of the colon, and least for the rectum. Despite the challenges of such a finding by recent prospective and intervention studies, the panel of the World Cancer Research Fund and American Institute for Cancer Research (2007), after a review of several prospective and case-control studies, concluded that foods containing dietary fibre probably protect against colorectal cancer; and that there is limited evidence suggesting that such foods protect against oesophageal cancer. The Panel also judged that the evidence that foods contaminated with aflatoxins (cereals and peanuts are the foods most commonly infested by these fungal toxins) as a risk factor for liver cancer is convincing. Foods high in dietary fibre may have a protective effect because of being bulky and relatively low in energy density. Other mechanisms of protective nature of fibre include the fermentation of fibre (non-starch polysaccharides, NSP) in the bowel that produces short-chain fatty acids, which have known anti-cancer properties.

Red and processed meat, fish and poultry

The evidence that red meats and processed meats increase the risk for colorectal cancer is convincing (Larsson and Wolk, 2006; World Cancer Research Fund and American Institute for Cancer Research, 2007). Larsson and Wolk (2006), through a meta-analysis, found that consumption of red meat and processed meat was positively associated with risk of both colon and rectal cancer, although the association with red meat appeared to be stronger for rectal cancer; risk estimates for an intake of 120 g of red meat (generally including processed red meat) per day were around 25–35% while the risk estimates for processed meat varied more widely, from 9–36% for a daily intake of 30 g.

There is some degree of evidence suggesting that fish, and foods containing vitamin D, protect against colorectal cancer (>80 g/day versus <10 g/day, HR = 0.69, 95 % CI = 0.54 - 0.88) (Norat *et al.*, 2005). There is also limited evidence that red meat is a risk factor for cancers of the oesophagus, lung, pancreas and endometrium; that processed meat increases the risk for cancers of the oesophagus, lung, stomach and prostate; and that foods containing iron increase the risk for colorectal cancer, though these evidences are generally insubstantial (World Cancer Research Fund and American Institute for Cancer Research, 2007).

While the mechanisms remain unclear, processed meat is relatively high in nitrosamines, which are linked to some cancers, and it is thought that consumption of red meat causes the body to increase its own production of nitrosamines.

Milk and dairy products

Milk probably protects against colorectal cancer. A pooled analysis of 10 cohort studies in five different countries found out that an increased consumption of milk and calcium were related to a lower risk of colorectal cancer (Cho *et al.*, 2004). Their result showed that compared with participants who consumed less than 70 g/day of milk, the pooled multivariate relative risks for colorectal cancer were 0.94 (95% CI = 0.86 to 1.02) for those who consumed 70–174 g/day, 0.88 (95% CI = 0.81 to 0.96) for those who consumed 175–249 g/day, and 0.85 (95% CI = 0.78 to 0.94) for those who consumed 250 g/day or more. There is also limited evidence suggesting that milk protects against bladder cancer; that cheese increases the risk for colorectal cancer; that diets high in calcium are a probable risk for prostate cancer; and that high consumption of milk and dairy products increase the risk for prostate cancer (World Cancer Research Fund and American Institute for Cancer Research, 2007).

Salt and nitrites

A high dietary salt intake is a significant risk factor for gastric cancer with the people eating more than 16 g/day of salt having two–three times the risk than people eating 10 g/day or less (Shikata *et al.*, 2006). Salt-preserved foods have also been found to be a probable risk factor for stomach cancer. Salt may increase cancer risk by increasing

sensitivity of the lining of the stomach to carcinogens such as nitrates, or by directly causing mucosal damage and inflammation.

Fat

There is some evidence suggesting that total fat is a risk factor for lung cancer, and of postmenopausal breast cancer. Cho *et al.* (2003) in their prospective analysis of the relation between dietary fat intake and breast cancer risk among premenopausal women found out that relative to women in the lowest quintile of fat intake, women in the highest quintile of intake had a slight increased risk of breast cancer (RR = 1.25, 95% CI = 0.98 to 1.59). There is also limited evidence that animal fat increases the risk for colorectal cancer; and that consumption of butter increases the risk for lung cancer based on the evidence from a review of many studies by the World Cancer Research Fund and American Institute for Cancer Research (2007).

As a result of the growing evidence of the importance of healthy diet, most of the Western governments have recommended, in line with the WHO recommendation, a "five-a-day" regimen of fruits and vegetables, high-fibre whole-grain cereals, olive oil and fish for adults and children over five (World Health Organization, 1990; Boyle *et al.*, 2003; World Cancer Research Fund and American Institute for Cancer Research, 2007). Conversely, excessive use of saturated fats, added sugar and salt and trans-fatty acids should be avoided.

4.2.3. Physical activity, overweight and obesity

Physical activity

Based on comprehensive reviews on weight control and physical activity, the evidence that physical activity protects against colon cancer is convincing (Boyle *et al.*, 2003; World Cancer Research Fund and American Institute for Cancer Research, 2007). One of the largest cohort studies (Friedenreich *et al.*, 2006) found that physical activity reduced colon cancer risk by about 20% for the most active people; there was even more reduction for the right-sided tumours (HR: 0.65 , 95% CI, 0.43-1.00) and for lean participants.

There are a number of mechanisms by which physical activity may protect against colorectal cancer, including the reduction of faecal transit time, reduction in insulin resistance, the beneficial effect of physical activity on body fatness, and modifying the endogenous steroid hormone metabolism (World Cancer Research Fund and American Institute for Cancer Research, 2007).

Physical activity also probably protects against postmenopausal breast cancer with risk reductions ranging from 20% to 80% (Monninkhof *et al.*, 2007); the evidence suggesting that it protects against premenopausal breast cancer is limited. Physical activity may also protect against cancer of the endometrium with the most active women having a 20% reduced risk of endometrial cancer compared to the least active women, according to a meta-analysis of seven cohort studies (Voskuil *et al.*, 2007). The evidence suggesting that physical activity protects against cancers of the lung and pancreas is limited (Steindorf *et al.*, 2006; Nöthlings *et al.*, 2007).

Since physical activity protects against overweight, weight gain, and obesity, it also protects against cancers for which the risk is increased by these factors. However, in some cases, the preventive effect of regular exercise for some cancers seems to act independently of weight control (Boyle *et al.*, 2003).

Obesity

Obesity is an established major cause of morbidity and mortality and is the largest risk factor for chronic disease in Western countries after smoking, particularly increasing the risk of diabetes, cardiovascular disease and cancer (Boyle *et al.*, 2003). The best evidence for a relationship between cancer and excess bodyweight is for cancers of the endometrium, kidney, oesophagus and colon and for breast cancer in post-menopausal women (Bianchini *et al.*, 2002). Estimates based on a review of the epidemiological literature and quantitative summary by meta-analysis on the relationship between excess weight and the risk of developing cancer at the above listed sites suggest that overall, excess body mass accounts for 5% of all cancers in the European Union, 3% in men and 6% in women (Bergstrom *et al.*, 2001), and in the UK, more than 4% of all cases could be avoided if no-one exceeded a body mass index (BMI) of 25.

4.2.4. Alcohol use

There is convincing epidemiological evidence that the consumption of alcoholic beverages increases the risk of cancers of the oral cavity, liver, colon, pharynx and larynx, and of squamous cell carcinoma of the oesophagus (Boyle *et al.*, 2003; Corrao *et al.*, 2004). Estimates based on relative risks of cancers of the oral cavity, pharynx, oesophagus, liver, colon, rectum, larynx and female breast obtained from a meta- and pooled analyses suggest that up to 9% of cancer incidence in Europe is attributable to alcohol intake (Boffetta *et al.*, 2006).

There are various possible mechanisms for the carcinogenic effect of alcohol consumption at these cancer sites. Acetaldehyde, the primary metabolite of alcohol, has been shown to alter DNA and cause cell proliferation. Alcohol may act as a solvent for other carcinogens (for example tobacco smoke) thus facilitating their carcinogenic effect; may produce reactive oxygen species and nitrogen species; and may interfere with metabolism of folate or other micronutrients (Boffetta *et al.*, 2006).

4.2.5. Occupational and environmental factors

Occupational factors

The prevention of exposure to occupational and environmental carcinogens has followed the identification of a substantial number of natural and man-made carcinogens, and has led to significant reductions in cancer occurrence (Boyle *et al.*, 2003). The more common occupational exposures are solar radiation, passive smoking, crystalline silica, diesel exhaust, radon, wood dust, benzene, asbestos, formaldehyde, polycyclic aromatic hydrocarbons, chromium VI, and cadmium and nickel compounds. The cancers that have most frequently been associated with occupational exposures are those of the lung, urinary bladder, mesothelioma, larynx, leukaemia, angiosarcoma of the liver, nose and nasal cavity and skin (non-melanoma); several other neoplasms including cancers of the oral cavity, nasopharynx, oesophagus, stomach, colon and rectum, pancreas, breast, testis, kidney, prostate, brain, bones, soft-tissue sarcoma, lymphomas and multiple myeloma have also been associated with occupational exposures but the evidence is less strong (Boyle *et al.*, 2003).

In the British population, a study of the occupational exposures and cancer (cancer of the bladder, lung, non-melanoma skin, and sinonasal cancers, leukaemia and mesothelioma) was carried out in 2004 (Rushton *et al.*, 2008). The study estimated that 8% of cancer deaths in men and 1.5% of cancer deaths in women were attributable to work-related carcinogens for the 6 cancers assessed. Incidence estimates were 6.7% for women and 1.2% for men. The study also estimated that almost 5,000 skin cancer cases were as a result of occupational exposure to solar radiation, mineral oils and polycyclic aromatic hydrocarbons.

Extensive preventive measures in the workplace in recent decades have resulted in the prevention of many cancers related to workplace exposures. In the UK, most known occupational carcinogens are either banned or well regulated and the majority of occupation related cancers diagnosed in the UK today are the result of people being exposed more than ten years ago.

Environmental factors

Environmental exposures usually refer to exposures of the general population that cannot be directly controlled by the individual. They include air-pollution, drinking water contaminants, passive smoking, radon in buildings, exposure to solar radiation, food contaminants such as pesticide residues, dioxins or environmental estrogens, chemicals from industrial emissions, and others. These exposures have been associated with a variety of neoplasms, including cancers of the lung, urinary bladder, leukaemia and skin (Boyle *et al.*, 2003).

4.2.6. Genetic syndromes

All cancer types exhibit familial clustering, suggestive of a significant inherited component (Easton, 1994). The inherited basis of certain families with a high risk of common cancers has been confirmed with the identification of predisposing mutations, or the localisation of susceptibility genes by linkage analysis. Amongst the important known susceptibility genes are those dominant genes conferring a high risk of breast and ovarian cancer (BRCA1), colon cancer (hMSH2 and hMLH1), and melanoma (MLM). The identification of genes that are associated with high risk of breast, ovarian, and colorectal cancer has advanced our understanding of cancer predisposition (Struewing *et*

al., 1997; Lynch and De La Chapelle, 1999; Bingham *et al.*, 2003). These studies show that, for example, women who are born with a mutation in one of their BRCA genes have a much greater chance of developing breast and ovarian cancer than women who do not. A study involving twins (Ahlbom *et al.*, 1997) also found out a profound familial effects for all cancer sites presented as well as for total cancer. All these genes confer a high lifetime risk of the disease concerned, but are rare and only account for a small minority (less than 5%) of cases (Easton, 1994).

4.2.7. Exogenous hormones

Hormone levels may explain differences in risk for some of the most commonly diagnosed female cancers. The benefits and drawbacks of hormone replacement therapy and the use of oral contraception (OC) have been under serious review (Hulka and Brinton, 1995). Oral contraceptives have been shown to reduce the risk of endometrial cancer (Vessey and Painter, 2006), and ovarian cancer by almost 50% (Bosetti *et al.*, 2002b), but possibly increase the risk of other cancers, notably breast (Boyle *et al.*, 2003). Women taking oestrogen-only replacement therapy are at an increased risk of endometrial and ovarian cancers (Lacey *et al.*, 2002).

4.2.8. Infectious agents

Despite cancer not being an infectious disease, a small number of infectious agents, especially certain viruses, appear to play a key role in causing particular types of cancer. These oncogenic infectious agents include the human papillomaviruses (cervical carcinoma); human polyomaviruses (mesotheliomas, brain tumours); Epstein-Barr virus (B-cell lymphoproliferative diseases and nasopharyngeal carcinoma); Kaposi's Sarcoma Herpesvirus (Kaposi's Sarcoma and primary effusion lymphomas); hepatitis B and hepatitis C viruses (hepatocellular carcinoma- a type of liver cancer); Human T-cell Leukaemia Virus-1 (T-cell leukaemia); and helicobacter pylori (gastric carcinoma). From a universal perspective infectious agents especially viruses account for several of the most common malignancies– up to 20% of all cancers (Pagano *et al.*, 2004). In developed countries, cancers caused by chronic infections only amount to approximately 8% of all malignancies. This discrepancy is particularly evident for cervical cancer. In developed countries with an excellent public health infrastructure and a high compliance of women,

early cytological detection of cervical cancer (PAP smear) has led to an impressive reduction of mortality.

4.3. Psychological Factors and Cancer

The relationship between cancer and psychological factors can be considered as a reciprocal one: psychological factors might affect cancer incidence or progression; conversely, cancer might affect the incidence of stress and other psychological changes, as well as any physical or psychological events that may accompany it. In this thesis we are concerned with the former.

4.3.1. How might psychological factors influence cancer onset and progression?

The idea that psychological factors and stress play a role in the onset or progression of cancer continues to excite considerable interest and heated debate in the scientific literature and in the media. The notion that disease is multi-factorial in origin and a result of interrelationships between genetic, endocrine, nervous and immune systems is not new either, therefore, it would be important to know about the physical implications of the psychological responses identified and whether the identified physical responses contribute in any way to cancer aetiology. The psychobiological model has a long history, but more recent progress in the development of the psychoneuroimmunology model has brought this topic out from the speculative and into scientific domain.

A possible role of psychoneuroimmunology

Psychoneuroimmunology (PNI), the study of behaviourally associated immunological changes and immunologically associated behavioural changes that result from reciprocal interactions among the nervous, endocrine, and immune systems (Cohen *et al.*, 2007), may elucidate some of the questions regarding the possible influence of psychological factors on cancer. The field of human PNI emerged as interdisciplinary effort to understand the links between brain, behaviour, and the immune system, as epidemiologic evidence demonstrate the influence of psychological stress and depression on chronic disease and health. Research examining the mind–body interactions and health has shown many reciprocal links among the central nervous system (CNS), which recognizes

and records experiences; the autonomic and neuroendocrine system, which produces neurotransmitters, and hormones that govern many bodily functions; and the immune system, which organizes responses to infections and other challenges (Irwin, 2008).

Research in PNI has been greatly encouraged by the brain-behaviour-immune system interaction and evidence has converged over time to establish these connections. Many authors have described in detail the pathways of interactions of the nervous, endocrine and immune systems (Rabin, 2005; Ader, 2007; Cohen *et al.*, 2007; Ziemssen and Kern, 2007; Byrne-Davis and Vedhara, 2008; Irwin, 2008; Tausk *et al.*, 2008). All these evidences converge to the fact that the immune function is influenced by autonomic nervous systems activity and by the release of neuroendocrine substances from the pituitary. Conversely, cytokines (including interleukin (IL)-6, IL-1, and tumour necrosis factor (TNF)-α) and hormones released by an activated immune system influence neural and endocrine processes.

Mind-body connections

An understanding of the immune, endocrine, and the nervous systems enables study into their potential for mediating observed connections between mind and body. Earlier experiments linking psychological events with physiological responses led to the identification of two important systems responsible for coping with stressors: the active (fight/flight) system and the passive (conservation/withdrawal) system (Byrne-Davis and Vedhara, 2008). The pathways for these systems are important in understanding health and disease as they both culminate in the release of hormones that can and do influence immune functioning. The sympathetic adrenal medullary system (SAM) provides the pathway for the active system and involves activation of the sympathetic nervous system and then the adrenal medulla, which results in the release of adrenaline and noradrenaline. In general, activation of the SAM axis has been associated with an up-regulation of the immune system (Byrne-Davis and Vedhara, 2008). The hypothalamic pituitary adrenocortical axis (HPA) corresponds to the passive system, where stress activates the hypothalamus that secretes corticotrophin-releasing factor, stimulating the pituitary. This activates the adrenal cortex and culminates in the release of cortisol. In general, the activation of the HPA axis has been associated with a down-regulation of the immune system (Byrne-Davis and Vedhara, 2008). Other important lines of compelling evidence for the powerful relationships between mind and body include the CNS

interventions, including anterior hypothalamic lesions studies (Cross, 1980); the evidence that changes in hormone or transmitter levels produce changes in immune function and vice versa; and the fact that lymphoid cells express receptors for a variety of hormones and transmitters (Tausk *et al.*, 2008).

4.3.2. Psychological factors and cancer risk

There is mounting evidence that psychosocial variables and chronic stress have immunosuppressive effects in humans as well as in animal studies (Rabin *et al.*, 1989; Ader and Cohen, 1993; Herbert and Cohen, 1993; Glaser *et al.*, 1998; Kiecolt-Glaser *et al.*, 1998; Cohen *et al.*, 1999), and that an impaired immune system predisposes to malignant growth (Penninx, 1998; Spiegel and Giese-Davis, 2003; Reiche *et al.*, 2004), especially the types of cancer mainly associated with a DNA tumour virus, retrovirus insertion near a cellular oncogene, and other viruses such as Epstein-Barr virus (EBV)(Reiche *et al.*, 2004).

Despite the accumulating evidence indicating that the CNS may regulate the activity of the immune system, the overall significance of the immune system in cancer remains controversial and some researchers have questioned whether stress-related immune changes are of either the type or the magnitude to influence tumour growth and metastases (Bovbjerg, 1991; Cohen and Rabin, 1998). Cancer differs in several respects from most diseases and pathogens that interact with the immune system, providing special challenges for both tumour immunologists and PNI researchers.

For psychoneuroimmunological perspective of cancer to be valid, it is necessary to demonstrate that tumour development can be regulated by immune defences and that psychosocial factors are capable of altering the immune mechanism involved in cancer regulation (Turner-Cobb *et al.*, 2001). Those cancers that are induced by chemical carcinogens (e.g. lung cancer) may be less influenced by psychological, behavioural and immunological factors than cancers that are associated with a virus, which are immunogenic (Kiecolt-Glaser *et al.*, 2002b).

Another methodological problem regarding the link between psychological factors and cancer is the fact that cancer is comprised of a heterogeneous group of diseases with multiple aetiologies, and immunological involvement may vary across different cancers

(Kiecolt-Glaser *et al.*, 2002b). Therefore, what holds true for one type of cancer may not hold true for other types of cancer, or stages of disease. Besides, it is usually difficult to determine with any precision the actual date of cancer onset, particularly in the case of slower growing tumours. Thus, the assessment of psychological factors might take place in the presence of as yet undetected cancer which may exert an influence on the CNS or psychological state and thus bias the assessment (Walker *et al.*, 2005).

Parameters likely to be influenced by psychological factors

Three processes identified as particularly important in cancer prevention are immune system dysregulation, DNA repair, and apoptosis.

Immune system dysregulation

PNI, through numerous publications, has showcased observations of stress effects on cancer and on immune processes. The immune system is a complex mixture of a variety of interactive cells and soluble molecules whose function is to patrol the blood and tissues looking for antigens in order to protect the host from infection. In the context of cancer, the tumour is derived from the host cells and therefore cannot be considered as foreign in the same way as bacterium or virus. However, as a consequence of mutations that have occurred during the process of cell becoming a cancer, these cells possess subtle variations that can be used to distinguish them from their normal counterparts and it is these variations that enable components of immune system to identify and target cancerous cells (Walker *et al.*, 2005).

The principal components of the immune system which are known to have anticancer properties are the natural killer (NK) cells, T-lymphocytes, dendritic cells, and to a lesser extent antibodies (Walker *et al.*, 2005). Psychological factors are thought to affect at least three components of anticancer immune function (Fife *et al.*, 1996): cytokine production, NK cell activity, and lymphocyte mitosis. The NK cells, which are a subset of a large granular lymphocytes, play an important role in a variety of immune functions, including defence against viral infections (Welsh, 1986), and surveillance of tumour cells (Andoniou *et al.*, 2006; Moretta, 2007). In general, both stress and depression are associated with the decreased cytotoxic T-cell and NK cell, including depressing the stimulatory response of NK cell to cytokines (Reiche *et al.*, 2004).

Numerous studies have shown that an elevation of stress hormones alters production of cytokines (Kiecolt-Glaser, 1999; Rabin, 1999). Since cytokines are important for activation of many components of the immune response, this may be one of the most important ways that stress alters the defence against infectious diseases (Rabin, 2005). The hormonal response to stress can also alter the acute inflammatory response by altering the production of proinflammatory cytokines that mediate the inflammatory response (Glaser *et al.*, 1999).

DNA repair

Stress may also have a direct effect on the initiation and/or production of abnormal cells independent of the immune system. Most carcinogens appear to induce tumours by damaging cellular DNA, thus producing abnormal cells (Setlow, 1978). In a study designed to explore mechanisms that would account in part for the relationship between stress and tumour development at the level of DNA repair, stress was found to be associated with low concentrations of O6-methyl-transferase, an important DNA repair enzyme induced in response to carcinogen damage, in the spleen lymphocytes of rats subjected to rotational stress (Glaser *et al.*, 1985).

Impaired apoptosis

Apoptosis, a process of genetically programmed alterations of cell structure that lead to failure of proliferation and differentiation, and eventual cell death (Tomei *et al.*, 1990), is another important defence against the development of malignant cells. This is because the ability of tumour cell populations to expand in number is determined both by the rate of cell proliferation and the rate of cell attrition, majorly represented by the programmed cell death-apoptosis. Stress has been shown to enhance the inhibition of apoptosis, which could result in suppression of immune function. The results of analysis by Tomei *et al.* (1990) suggested that psychological stress may induce physiological changes that regulate the ability of immune cells to initiate apoptosis.

4.3.3. Evidence for an association between psychological factors and cancer onset and progression

Despite the evidence that several psychological factors lead to impairment of endocrine and immune function, which may in turn predispose to the development of some types of

cancer, the question of whether psychological factors have an influence on cancer initiation and progression still remains unanswered. Very early studies suggested links between personality types and cancer aetiology; however, interpretation of these findings has been significantly hampered by methodological problems in many of these studies. A few recent studies suggest a relationship between stress and the onset of cancer; however, overall, the relationship between stressor exposure and the aetiology of cancer in humans is weak (Reiche *et al.*, 2004).

Recent reviews in this area have failed to find a convincing evidence to support the influence of psychological factors in cancer development (Dalton *et al.*, 2002; Garssen, 2004). However, some factors such as helplessness and repression have emerged as 'most promising' factors to contribute to an unfavourable prognosis, while denial/minimizing seemed to be associated with a favourable prognosis (Garssen, 2004). Most of the psychological factors that have been examined in the psychological research include personality and locus of control, stressful life events, bereavement and other loss events, depression, social relations, negative emotions, repression of emotions, coping and adjustment to illness, hopelessness and other related factors.

Personality or personality traits

Most of the studies on personality have been inspired by the notion of a 'cancer-prone personality' as well as the effect of repression or expression of emotions, and locus of control. The role of personality in the causation of cancer has been controversial. Earlier studies have shown an association between cancer development or progression with a type C personality, characterised with suppression of emotional reactions (Dattore, 1980; Temoshok and Fox, 1984; Greer and Watson, 1985). However, other studies of robust design, because of their access to large, random samples of the population, or prospective cohort studies (Nakaya *et al.*, 2003; Hansen *et al.*, 2005), in accordance with the overall conclusions of recent reviews (Dalton *et al.*, 2002; Garssen, 2004), have failed to demonstrate a relationship between personality and cancer.

Locus of control is examined in cancer studies more often than any other personality factor. Experiencing control over a stressful situation strongly influences the impact of the situation, and one may expect that the negative consequences of cancer are dampened in people with an internal locus of control (those who believe that they have control over

their destinies). As Garssen (2004) points out in his comprehensive review of the psychological factors and cancer development, only one out of the five studies investigating the role of locus of control found some indication for a relationship (Garssen, 2004). In that study, three variables (expressive activities at home, extroversion, low anger) were significant prognostic factors in women with breast cancer for overall survival independent of clinical and other psychosocial factors.

The role of repression in cancer progression seems a promising factor. In a review by Garssen (2004), this was demonstrated by five out of eight studies. With respect to cancer initiation, only a few studies have found that more repression is related to higher chance of developing cancer (Dattore, 1980), while other studies have failed to confirm this finding with respect to breast cancer (Hahn and Petitti, 1988) and overall risk of cancer (Persky *et al.*, 1987).

Emotional suppression has been associated with the onset or progression of cancer. After a review of 18 relevant studies, Gross (1989) found out that emotional expression may be directly involved in cancer onset and progression. This may be explained by the fact that a repressive personality style is significantly associated with poorer natural killer cell activity (Levy, 1985).

Major life events

The effect of life events is negligible, if studied in isolation. Jacobs and Bovasso (2000) examined the role of parental death and chronic depression with severe episodes in affecting risk of breast cancer for 1,213 women in Baltimore, USA. Their results showed an increased risk for breast cancer of 2.56 (95% confidence interval (CI) 1.59–4.35) in adjusted analyses for women whose mother had died during their childhood (only 6 cases), whereas recent life events were not associated with an increased risk (no risk estimates given). The authors suggested that meta-analysis of other prospective studies were needed to create larger groups of individuals with these stresses to confidently establish these variables as risk factors. Petticrew *et al.* (1999) summarized 15 studies about the role of adverse life events as a risk factor in a meta-analysis which was restricted to breast cancer studies and dealing with the role of life events in the initiation of cancer. They found that breast cancer patients reported adverse life events more than twice as often as control subjects. However, the methodological quality of most studies

was low, according to the authors as most of the studies had questionable group-comparison or semi-prospective design.

4.3.4. Summary

A large number of studies on psychoneuroimmunological aspects of cancer have shown that there is substantial biological plausibility of the association between psychological factors and the onset of cancer, primarily via alteration of the endocrine and the immune systems. However, whether the psychological factors can exert an influence on the development of cancer remains an intriguing question. This has been occasioned by the generally weak associations found in most of the studies; the inconsistency of the results across studies; and the unresolved underlying biological mechanism. Methodological problems may be a major obstacle in clarifying the true impact of these factors. Investigation of the association between psychological factors and cancer requires prospective designs and large study population to provide sufficient statistical power for detecting small increases or decreases in the risk of cancer at individual sites associated. Moreover, the confounding factors should be considered in these studies so that the possibility that psychological factors, which do not have any predictive power if studied in isolation, may have an effect in interaction with demographic and medical factors.

4.4. Effects of Psychological Factors on the Physical Risk Factors

The evidence from the review in the previous sections has revealed that two separate categories of risk factors, physical and psychological, are responsible for the majority of cancer cases. It is therefore impractical to separate the psychological factors from the physical factors when examining cancer risk; instead, a postulation of a proper model of interaction is vital. Indeed, studies have found that physical and psychosocial risk factors interact synergistically (i.e. their effects multiply) to predict cancer mortality (Grossarth-Maticek *et al.*, 2000). Thus, psychological factors such as stress may affect health not only through its direct biological effects on neuroendocrine or immune functioning, but also indirectly, by influencing risk behaviours such as smoking, physical activities and diet which themselves have an impact on health. We briefly discuss the impact of the psychological factors on these major physical risk factors.

Impact of psychological factors on smoking

A host of factors have been investigated in numerous attempts to determine the antecedents of cigarette smoking among adolescents. Peer and family smoking behaviour have been consistently implicated (Miller and Slap, 1989), but the roles of psychological factors too cannot be disregarded. The relationship between psychological factors and smoking can be thought of as reciprocal. Psychological factors such as stress and associated distress or depression have been shown to play an important role in the initiation of smoking and with maintenance of the behaviour (Bonaguro and Bonaguro, 1987; Covey and Tam, 1990; Byrne *et al.*, 1995). Other psychological factors that have been consistently associated with smoking are self-esteem, whether overall or with regard to specific contexts such as home or school (Bonaguro and Bonaguro, 1987; Smith *et al.*, 2004), and locus of control (Eiser *et al.*, 1989).

Conversely, the use of smoking for dealing with stress is not unexpected since nicotine, which is a stimulant drug, may have direct pharmacological effects that moderate stress (Leventhal and Cleary, 1980). Despite the characteristics of nicotine which would suggest that it should act as a pharmacological stressor, smokers frequently report that they want to smoke most when stressed and that smoking calms them down. In fact, smoking has been cited as a means of dealing with stress among smokers (Mates and Allison, 1992).

Psychological factors and diet

There is now a scientific consensus that diet is a major risk factor for cancer, and specific recommendations have been published. Psychological factors such as stress could increase the risk of cancer by inducing adverse changes in diet that are opposite to these recommendations. In addition, stress and related psychological factors may promote the development of cancer to greater extent in the presence of a diet that raises the risk factors for cancer. However, the diet, mediated behaviourally by food choice, is under the influence of many other factors which might influence the people's choice of food. These include the cost, availability, taste, convenience, perceived health promoting features, and social, cultural, religious, or psychological considerations (Shepherd, 1990; Blanck *et al.*, 2009). Furthermore, dietary habits and preferences are modified through a lifetime of learning about the consequences of eating, and through reacting to the

influence of parents, family, and friends as well as persuasion from the food industry (Wardle and Gibson, 2002). Therefore, the influence of stress on diet is mediated by any of these factors.

The dominant and longstanding physiological concept on the effects of stress on eating behaviour is that stress will inhibit appetite and food intake, through a combination of suppression of upper gastrointestinal motility and stimulation of energy substrate mobilisation, although research continues into the underlying mechanisms and impact of different stressors (Friedman, 1995; Wardle and Gibson, 2002).

Psychological factors and physical activity

A growing body of literature has focused on the inter-relationship between physical activity and psychological variables such as stress and anxiety. Psychosocial influences such as social support for physical activity, health beliefs in regards to the outcome of physical activity, and self-efficacy (perceived confidence individuals have in their ability to execute physical activity) for physical activity have all been considered as possible influences on behaviours including intention for, and the level of physical activity, while depression has been found to be negatively correlated with adolescent physical activity (Sallis *et al.*, 2000). Psychological variables found to have no association based on a review by Sallis *et al.* (2000) were talks loudly, external locus of control, self-esteem, self-motivation, enjoys exercise, and perceived stress.

The study of exercise and mental health is not new either. Many studies have looked into the impact of physical activity on depression, anxiety and stress, emotion, mood and well-being, self-esteem and self-perceptions, sleep quality, and the negative effects of exercise. Reviews and Meta analyses that have focused on the effect of exercise on clinical depression (Craft and Landers, 1998; Fox, 1999; Biddle *et al.*, 2000) have concluded that physical activity is associated with decreased risk of developing clinical depression. However, the relation of physical activity to depression is complex owing to the number of psychosocial predictors of depression that might confound the relation. Camacho *et al.* (1991) in their prospective epidemiological study found that in a non-depressed population sample, the odds ratio of getting depressed over a period of nine years for those who remained low in activity was 1.22 and for those who became inactive was 1.61 against a baseline of high activity on both occasions. This association persisted

but became insignificant with adjustment for associated variables including physical health, socioeconomic status, social supports, life events, and other health habits.

Additionally, exercise has a moderate reducing effect on state and trait anxiety and can improve physical self-perceptions and in some cases global self-esteem; aerobic and resistance exercise enhances mood states; and there is a weaker evidence that exercise can improve cognitive function (primarily assessed by reaction time) in older adults (Fox, 1999).

4.5. Childhood and Perinatal Risk Factors

There is now extensive evidence from many countries that conditions before birth and in early childhood influence health in adult life. Factors could be part of a chain of biologically linked events (the chain risk model) that result in the development of cancer; or there could be cumulative effects of a set of independent risk factors that culminate in disease development (accumulation model) (Potischman *et al.*, 2004). The pace of the reports in this subject was accelerated after Trichopoulos and colleagues (1990) had postulated that in-utero exposure to high amounts of endogenous oestrogen might contribute to the development of breast cancer, and that perinatal factors might be surrogate measures of intrauterine oestrogen exposure. The major hormone-related perinatal and infant risk variables that have been considered in many studies include preeclampsia; birthweight and other measures of birth size; and twinship. Most of these perinatal factors are associated with altered concentrations of maternal endogenous oestrogen (Ekbom *et al.*, 1992).

Largely, the studies on the perinatal risk factors have focussed on breast cancer but a few have considered other sites such as prostrate and testicular cancers. The evidence from most of the studies suggests that preeclampsia is associated with reduced risk but being a twin or having had a high birthweight is associated with increased cancer risk. However, the effects of placental weight, gestational age, maternal age, birth order and having been breastfed have inconsistent results across studies. The following sections review the literature for individual perinatal and childhood risk factors with particular emphasis given to breast cancer.

4.5.1. Maternal preeclampsia

Pregnancy conditions accompanied by high blood pressure, such as preeclampsia or eclampsia and pregnancy-related hypertension, which are also associated with reduced maternal urinary oestrial excretion, have been hypothesized to be associated with a lower risk of breast cancer in female offspring born of these pregnancies in several epidemiologic studies. Two Swedish studies (Ekbom *et al.*, 1992; Ekbom *et al.*, 1997) have provided a strong support for an inverse association between pre-eclampsia and risk of breast cancer. In these studies with partially overlapping populations, the birth records for all deliveries at five different hospitals in Sweden during the period from 1874 through 1961 were used to define a large cohort of women. The investigators used the cancer registry data to ascertain the incident case patients with breast cancer in this cohort; in a case-control study nested in the cohort, abstracted data from birth records on women with incident breast cancer and on control subjects individually matched to the case patients on date of birth was used. A markedly reduced risk of breast cancer among daughters born to the preeclamptic mothers was noted in the first analysis of 458 cases and 1,197 matched controls from one hospital (odds ratio (OR) = 0·24, 95% CI 0·09-0·70, p = 0·01) after adjusting for other maternal and pregnancy factors (Ekbom *et al.*, 1992). Similar results were obtained when the other four hospitals were included (1,068 cases, 2727 control, OR = 0.41; 95% CI = 0.22-0.79) (Ekbom *et al.*, 1997). However, the associated confidence intervals (CIs) for these studies were generally wide, indicating considerable variability in the data. Besides, data were unavailable, to allow evaluation of confounding and effect modification by the daughter's adult breast cancer risk factors.

Pooling together the data in form of a Meta analysis can provide a sound overview and a valuable assessment of existing evidence. In a recent review and meta-analysis of the intrauterine factors and risk of breast cancer (Xue and Michels, 2007), maternal pre-eclampsia or eclampsia during pregnancy was found to have a protective effect of breast cancer regardless of menopausal status (summary rate ratio- RR 0·48, 95% CI 0·30–0·78), but findings from studies that analysed premenopausal breast cancer separately suggested no overall association (summary RR 1·00, 95% CI 0·61–1·65).

The possible mechanism for the protective effect of preeclampsia on female offspring's breast cancer risk still remains unclear. Ekbom and colleagues (1997) suggested that preeclampsia could be accompanied by lower intrauterine oestrogen and that this could

explain the lower breast cancer risk in the female offspring. However, many physiologic changes occur in preeclamptic pregnancies besides alteration in oestrogen metabolism. The intrauterine effects are probably mediated through endocrine factors, but long latency until the manifestation of clinical breast cancer in adulthood renders the direct study of any association of intrauterine exposures with the disease almost impossible (Lagiou, 2007). Instead, researchers have studied perinatal characteristics that are correlated with the intrauterine endocrine environment, and placed emphasis on birth size, pregnancy toxaemia, and twin membership (Ekbom *et al.*, 1992). Because preeclamptic babies tend to be smaller for gestational age than other babies, this condition may also affect breast cancer risk through an alteration of established breast cancer risk factors such as pubertal development and adult size (Potischman *et al.*, 2004).

4.5.2. Birthweight

Various studies have reported on the relationship between birthweight, taken as a marker of prenatal environment, and breast cancer, but with differing results. Birthweight has been positively associated with the risk of breast cancer in a number of studies (Sanderson *et al.*, 1996; De Stavola *et al.*, 2000; Lahmann *et al.*, 2004; Vatten *et al.*, 2005), whereas other studies have found no significant association (Ekbom *et al.*, 1992; Ekbom *et al.*, 1997; Titus-Ernstoff *et al.*, 2002). Links between birthweight and breast cancer have been found mostly among premenopausal women, whereas studies focusing on breast cancer diagnosed after age 50 years fairly consistently reported a lack of association with birthweight (Michels *et al.*, 2006). The role of adult variables, possible effect modifiers and cancer characteristics has remained unclear.

Despite the inconsistent results, the collective evidence, summarised by Xue and Michels (2006; 2007) strongly suggests that the birthweight affects risk of breast cancer in offspring. In their review, the relative risk estimate for breast cancer comparing women with high birthweight to women with low birthweight combining all studies including both pre- and postmenopausal breast cancer was 1.23 (95% CI=1.13-1.34) (Michels and Xue, 2006). An updated meta-analysis after integrating the newly published studies that they omitted in their first review generated a summary RR associated with higher birthweight of 1·15 (95% CI 1·09–1·21, p for heterogeneity= 0·05, degrees of freedom (df) = 18) for breast cancer regardless of menopausal status (Xue and Michels, 2007).

Ideally, to investigate the relationship between birthweight and breast cancer, we need cohort studies with lifetime information including the birthweight rather than the self-reported birthweight. Studies using birthweight information from mothers of adult participants are therefore considered to have higher validity than studies using birthweight from daughter's self report. De Stavola and colleagues (2000) examined the relationship between birthweight and breast cancer in a UK national cohort of 2,221 women who had been followed since their birth in 1946 up to 1997 and confirmed the results of other studies that there was greater risk of breast cancer with greater birthweight, with women who weighed 4 kg or more at birth nearly six times more likely to develop breast cancer prior to menopause than those who weighed less than 3 kg. Despite the cohort being relatively young implying a relatively small number of breast cancer cases (37 cases), this study had a major strength that the information on birthweight was obtained prospectively from routinely completed birth records and therefore was not affected by recall bias besides being able to examine whether the effect of birthweight on breast cancer was confounded or modified by other markers of childhood growth and adult-life risk factors for breast cancer.

4.5.3. Gestational age

Gestational age or preterm delivery and the risk of breast cancer later in life has been investigated in several studies but majority of them have given inconsistent results and very few have shown statistical significance. Two Swedish studies investigating the effect of extreme pre-maturity found that female babies born prematurely (before the 33rd gestational week) had an increased risk for breast cancer (Ekbom *et al.*, 1997; Ekbom *et al.*, 2000). A twofold to fourfold increased risk was observed among women born in the 31st or 32nd gestational week but the relative risk of breast cancer declined with longer gestational time. However, since women born before the 33rd gestational week constituted a very small fraction, the cases of breast cancer patients in the two studies were very few. In contrast, another Swedish study of female twins found a positive association of gestational age and breast cancer and no increase in risk with preterm birth (Lichtenstein *et al.*, 2001). The study found out that compared with twins with gestational age less than 33 weeks, twins with gestational age of more than 40 weeks were at increased risk of breast cancer (OR = 8.4; 95% CI 1.3-54.4). However, the small number of participants in this study and small number of cancer cases (only one twin) would limit the interpretation of findings from this study. The summary RR for cohort

studies in a meta analysis by Xue and Michels (2007) also suggested no association between gestational age and risk of breast cancer (RR= 0·95 [0·71–1·26], p for heterogeneity = 0·53, df = 2), and findings from case–control studies were significantly heterogeneous (p for heterogeneity = 0·01, df = 7).

4.5.4. Placental weight

The placenta is the main regulator of the intrauterine hormonal environment in pregnancy, making it reasonable to evaluate its size and function in relation to future breast cancer risk of female offspring. There is a positive correlation between placental weight and birth weight and the hormonal influence of a large placenta is likely to stimulate a larger birth size (Potischman *et al.*, 2004). However, findings for placental weight have been inconsistent. While Ekbom and colleagues (1992) found that placental weight was significantly related to breast cancer risk in the offspring, another study in Norway (Vatten *et al.*, 2002) found no such association.

4.5.5. Twins

The rationale for evaluating twins is that pregnancies involving two placentas, that is, dizygotic twin pregnancies would be producing more estrogens and other factors than single-placenta pregnancies. A number of investigators have found that overall, breast cancer risk appears to be increased in twins and risk has been hypothesized to vary by the zygosity of the twin pair.

Majority (Hsieh *et al.*, 1992; Braun *et al.*, 1995; Ekbom *et al.*, 1997) but not all (Sanderson *et al.*, 1996) studies have found an elevated risk of breast cancer among twins compared with singletons. Evidence from the Swedish twin registry indicates that compared with the risk for breast cancer in the singleton, the risk for breast cancer in dizygotic twins was increased, although this increase was not statistically significant (OR = 1.72; 95% CI = 0.92-3.20) (Ekbom *et al.*, 1997). Another evidence from the Swedish twin registry (Braun *et al.*, 1995) found testicular cancer excess among dizygotic twins (observed/expected[O/E ratio = 2.3, CI = 1.1-4.2) compared with older men (O/E ratio = 1.2, CI = 0.5-2.4). In addition, a substantially elevated incidence of breast cancer was observed in dizygotic twin women aged 20 to 29 years (O/E = 6.7, CI = 2.9-13.1) but not in other age groups. The summary RR estimate in a meta analysis by Xue and Michels

(2007) suggested that twin membership was associated with a decreased risk of breast cancer that was of marginal statistical significance (summary RR 0·93 [0·87–1·00], p for heterogeneity = 0·09, df = 4) regardless of menopausal status at diagnosis of breast cancer.

4.5.6. Parental age at delivery

The association between maternal age at delivery and risk of breast cancer has been inconsistent. Modest increased risk in breast cancer has been observed in older mothers in some (Le Marchand *et al.*, 1988; Janerich *et al.*, 1989; Thompson and Janerich, 1990) but not all studies (Ekbom *et al.*, 1992; Sanderson *et al.*, 1996; Ekbom *et al.*, 1997).

The inconclusive evidence by many studies regarding the effect of parental age at delivery on breast cancer risk among daughters is perhaps because few large prospective studies have been available to examine this association and few existing studies have properly controlled for other early life exposure, adult risk factors and age of the other parent. One of the recent large prospective studies (Xue *et al.*, 2007) used 109,773 women in the Nurses' Health Study who were followed from 1976 to 2002 and found a modest positive association between maternal age and daughter's risk of breast cancer, possibly mediated by hormonal factors. Using 6,827 incident cases of invasive breast in this cohort and adjusting for other early life exposures and family history of breast cancer, the hazard ratio for breast cancer in women born to mothers aged 21–25, 26–30, 31–35, and ≥ 36 years was, respectively, 1.08 (95% CI: 0.99–1.18), 1.12 (95% CI: 1.03–1.23), 1.17 (95% CI: 1.06–1.29), and 1.12 (95% CI: 1.01–1.25), compared to women born to mothers aged ≤ 20 years (p for trend = 0.008). Similarly, advanced paternal age was associated with increased incidence of breast cancer (p for trend = 0.03), but the association disappeared when conditioning on maternal age.

The most plausible mechanism underlying a positive association between maternal age and risk of breast cancer in the daughter is high intrauterine exposure to endogenous oestrogens. Concentrations of oestrogen in maternal blood during pregnancy have been shown to be higher in older women (Panagiotopoulou *et al.*, 1990) .

4.5.7. Other factors

A number of other pregnancy and neonatal-related factors have been evaluated in several studies, including maternal smoking, pregnancy weight gain, number of previous pregnancies, birth length, breastfeeding, exposure to diethylstilboestrol and neonatal jaundice. Most of these studies have shown generally little or no association. Besides, the small number of cases in these studies has generally limited the interpretation of findings.

An effect of maternal smoking might be mediated through changes in circulating estrogens or in birthweight. However, there is either very little or no evidence at all that smoking during pregnancy is related to increased or decreased risk of breast cancer (Sanderson *et al.*, 1996; Weiss *et al.*, 1997), but there are a few exceptions. A study by Sandler and colleagues (1985) based on all cancer sites but basal cell cancer of the skin found an increase in cancer risk by almost 50% among offspring of men who smoked. This increased risk was not explained by demographic factors, social class, or individual smoking habits, and was not limited to known smoking related sites. Their study also showed a small difference between cases and controls in reported exposure to maternal smoking (estimated relative risk (RR) = 1.1, 95% CI =0.7, 1.6).

Studies on effect of breastfeeding have shown a potentially protective effect of having been breastfed (Brinton *et al.*, 1983; Freudenheim *et al.*, 1994; Weiss *et al.*, 1997). However, using record linkage data, Ekbom and colleagues (1993) did not find such an association; compared to women who at discharge were wholly or partly breastfed, women who as newborn were not breastfed had a relative risk of breast cancer of 0.97 with 95% CI of 0.44-2.17 (p = 0.95). Neonatal jaundice has also been associated with a higher risk of breast cancer (OR= 2·16, 95% CI=1·27–3·67) (Ekbom *et al.*, 1997).

Overall, the reviews strongly suggest that perinatal factors are involved in the development of cancer, predominantly breast cancer, in the offspring, and in particular, the hypothesis that pregnancy estrogens may be directly or indirectly implicated is strongly supported. Even though the results from epidemiologic studies assessing prenatal exposures are consistent with the hypothesis concerning oestrogen exposure, the specific biologic mechanisms remain largely unknown.

4.6. Choice of Cancer Sites for Analysis in the NCDS and BCS70

The analysis for individual cancer sites in most cohort studies with lifetime information may pose a number of challenges. First, large studies followed over a long period of time are needed because cancers are relatively rare compared with other chronic diseases. Secondly, even for large cohorts, these studies generally tend to have limited number of cases for any particular cancer. Another barrier to the application of the life course approach to cancer is the lack of intermediate end-points, thereby limiting the study in young cohorts.

In the NCDS and the BCS70, a number of cancer sites were considered including leukaemia, Hodgkin's disease, lymphoma, skin cancer, bone cancer, breast cancer, cancer of the uterus, cancer of the cervix, cancer of the testes, and cancer of the colon. The NCDS cohort of 11,419 participants followed from 1958 to 2000 yielded only 263 cases of cancer for analysis. Out of these, 38 were for breast cancer, 42 for skin cancer and 89 for cervical cancer. The other cancer sites had very few cases ranging from four for leukaemia and 14 for cancer of the testes. The same pattern was reported in the BCS70 where out of the 11,261 cohort members followed from 1970 until 2000, only 136 cancer cases were reported. Of these, there were 57, 16, and 15 for the cervical, testes, and skin cancers, respectively, with the remaining cancer sites having very few cases reported. Thus, the two British cohort studies used in this study are still relatively young in respect to cancer risk and the number of cancer cases are relatively small to allow for investigation of risk factors for individual cancer sites. In consequence, the study lacks power for cancers that have a low incidence. We therefore chose the cancer sites that have occurred with sufficient frequency for meaningful statistical analysis; in this case only cervical cancer in both the NCDS and BCS70. The virally induced cancers, such as cancer of the cervix may be preferred in this field of study, because they are sensitive to hormonal and immunological factors, and may be influenced via a neuro–hormonal–immunological pathway by psychological factors.

Apart from cervical cancer, we also analysed the total incident cancer. One frequently made criticism about this approach is that different cancers may have very different origins, follow a different course, and respond differentially to treatment. Hence, it may seem meaningless to throw together a random collection of cancers into a general cancer category. The reason for doing so is obvious; even in a large cohort such as the two

British cohorts considered in this study; very few will develop a particular kind of cancer as has been demonstrated, and so will lack the statistical power for meaningful interpretation. As demonstrated in most of Grossarth-Maticek's work (Grossarth-Maticek *et al.*, 1997; Grossarth-Maticek *et al.*, 2000), it may be argued that the success of predicting cancer from psychosocial factors suggests that the criticism is probably invalid (Grossarth-Maticek *et al.*, 2000). This is because the psychological factors are thought to have a common pathway of suppressed immunity linking them to cancer, irrespective of the cancer site.

4.7. Analytical Strategy

The present study uses information on 11,376 participants from the NCDS for whom data on cancer were available at age 42, and 11,261 participants from BCS70 for whom data on cancer were recorded at age 30. In order to perform the discrete time-to-event analysis, person-time at risk was computed for each study subject from when the cohort members were aged 17 years up to the year of cancer diagnosis, the year of loss during follow-up (due to death, emigration, etc.) or the year of the final sweep for which the information on cancer was available (year 2000), whichever came first. The estimation of the hazard rate was done through logistic regression models adjusted for the rare outcome event.

Univariable analyses provided age-adjusted odds ratios and 95% confidence intervals (CIs) for the psychological variables and other potential risk factors. These were to examine the association between each risk factor and the outcome. The associations were re-examined after adjusting for the effects of other social, cognitive and health behaviour factors.

Adjusting for potential confounders

The relation between childhood psychological factors and cancer may not be a simple one, but may be a result of complex causal chains. Thus, the effect of any of the childhood psychological factors cannot be fully understood except in the context of all the other potential risks. One possibility is that the perinatal, social and other childhood factors may lead to both childhood psychological problems and to the onset of cancer, so that ignoring the confounding variables may lead to incorrect inference about the relation

between childhood psychological factors and the disease outcome. Such adjustment was accomplished through a series of discrete-time survival models, estimated by multiple logistic regressions, to estimate the adjusted odds ratios (with 95% CIs) for the association between the disease outcome and each psychological risk factor, with a simultaneous control for age and other background variables.

Based on the literature, a large number of background variables were selected to be tested as potential confounders. The method used to select the significant confounders to control for in a multivariable model involved two steps. The first step involved the test of each confounder-disease association. In this case the alpha-level for rejecting the null hypothesis of no confounding was raised to 0.20 instead of using the traditional 0.05 level (Hosmer *et al.*, 2008) in order to insure adequate power. Since it is expected that some of the potential confounders would be strongly correlated among themselves, and including all of them in the model would inflate the variance of the parameter estimates, a test of multicollinearity was performed. This was done by first examining the correlations (continuous) and associations (categorical) between the independent variables. Given that several independent variables may be involved in interdependencies even if there are no strong pair-wise associations, the multicollinearity diagnostic statistics for linear regression analyses (variance inflation factor) was used to check for the existence of multicollinearity when several potential confounders were adjusted for simultaneously. If multicollinearity existed, one of the correlated variables was dropped from the model; the choice of the variable to be included in the model was based on how strong it was related to the response. The second step involved simultaneous adjustment for age and all the significant potential confounders, followed by deletion in sequence of the least significant variables. The significance of each variable in the model was examined and if a variable appeared non-significant it was removed from the model and the model was refitted. The reduced model was compared with the complex model using the likelihood-ratio (LR) test, Akaike information criterion (AIC), and the Bayesian information criterion (BIC). The LR compares the log likelihoods of the two models and tests whether this difference is statistically significant. If the difference is statistically significant, then the less restrictive model (the one with more variables) is said to fit the data significantly better than the more restrictive model (the reduced model). The LR test statistics equals twice the difference in the maximised log-likelihoods of the complex and the reduced model. The two criteria (AIC and BIC) judge a model by how close its fitted values tend to be to the true values, in terms of a certain expected value. The smaller the

criteria value the better a particular model fits. Akaike (1973) showed that the AIC selects the model that minimizes

AIC= - 2 (maximized log likelihood — number of parameters in the model).

This penalizes a model for having many parameters. The BIC additionally takes sample size into account.

Possible effect modifiers

Baron and Kenny (1986) define a moderator as a qualitative or quantitative variable that affects the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable, and are often tested as interaction effects. The moderator hypothesis is supported if the interaction is significant suggesting that the coefficient of the focal predictor variable differs across levels of the moderator. There may also be significant main effects for the predictor and the moderator, but these are not directly relevant conceptually to testing the moderator hypothesis. The way to measure and test the differential effects depends in part on the level of measurement of the independent variable and the moderator variable. In case of categorical moderators, when a moderating risk factor is identified, the population can be split into subpopulations of the moderator variable and subsequent analysis would check for risk factors separately in these subpopulations. Unlike the mediator-predictor relation where the predictor is causally antecedent to the mediator, moderators and predictors are at the same level in regard to their role as causal variables antecedent or exogenous to certain criterion effects.

In this study, the test for the moderation effect was assessed by the interaction terms between the childhood psychological measures and the other early life independent variables. Effect modification was assessed via maximum likelihood ratio tests for the significance of the interaction terms.

Assessing mediation effect

In general, a given variable may be said to function as a mediator to the extent that it accounts for the relation between the predictor and the criterion (Baron and Kenny, 1986). In an intervening variable model, the focal independent variable *X* is postulated to

exert an effect on an outcome variable *Y* through one or more intervening variables, sometimes called mediators. Thus, the independent variable achieves all or part of its effect on the dependent variable by first changing the intermediate construct.

The theoretical model to test the mediation effect in this study was broadly stimulated by the conceptual model (Figure 1-1) that links psychological and physical disorder (Cohen and Rodriguez, 1995), and the life course perspective (Kuh and Ben-Shlomo, 1997). According to Cohen and Rodriguez's model, the primary pathways from psychological disturbances to physical disorder are biological and behavioural. The cognitive and social pathways are more likely to influence illness behaviour as well as the elements of the behavioural pathway. Based on this conceptual framework, variables were grouped according to the stage in life course at which they occurred in order to reflect the temporal ordering among the different life course measures as depicted in Figure 4-1. The paths identified in the model are moving in only one direction from the perinatal factors to the adult disease. The reciprocal relationships are not considered. The absence of alternative paths is not intended to imply that they do not exist, but we have relied a great deal on the literature to identify the relevant factors that are likely to influence the relationship, as confounders or mediators, between childhood psychological problems and physical illness.

In the proposed model, the childhood psychological factors are theorized to have both direct and indirect effect (denoted by single arrows) on physical illness. The direct effect depicts the biological pathway, whereby childhood psychological disturbance could lead directly to neuroendocrine perturbations that may influence the disease risk later in life. The indirect effect is depicted majorly by the behavioural pathways, whereby childhood psychological problems could foster unhealthy behaviour- cigarette smoking, alcohol consumption, physical inactivity- (either directly or indirectly through education attainment and socioeconomic status), which may in turn increase the risk for the disease onset. Another indirect pathway is through the mid life psychological distress, whereby childhood psychological problems continue into adulthood and their cumulative effect over the life course increases the risk of cancer. This pathway represents both the biological pathway and the cumulative model of the life course perspective.

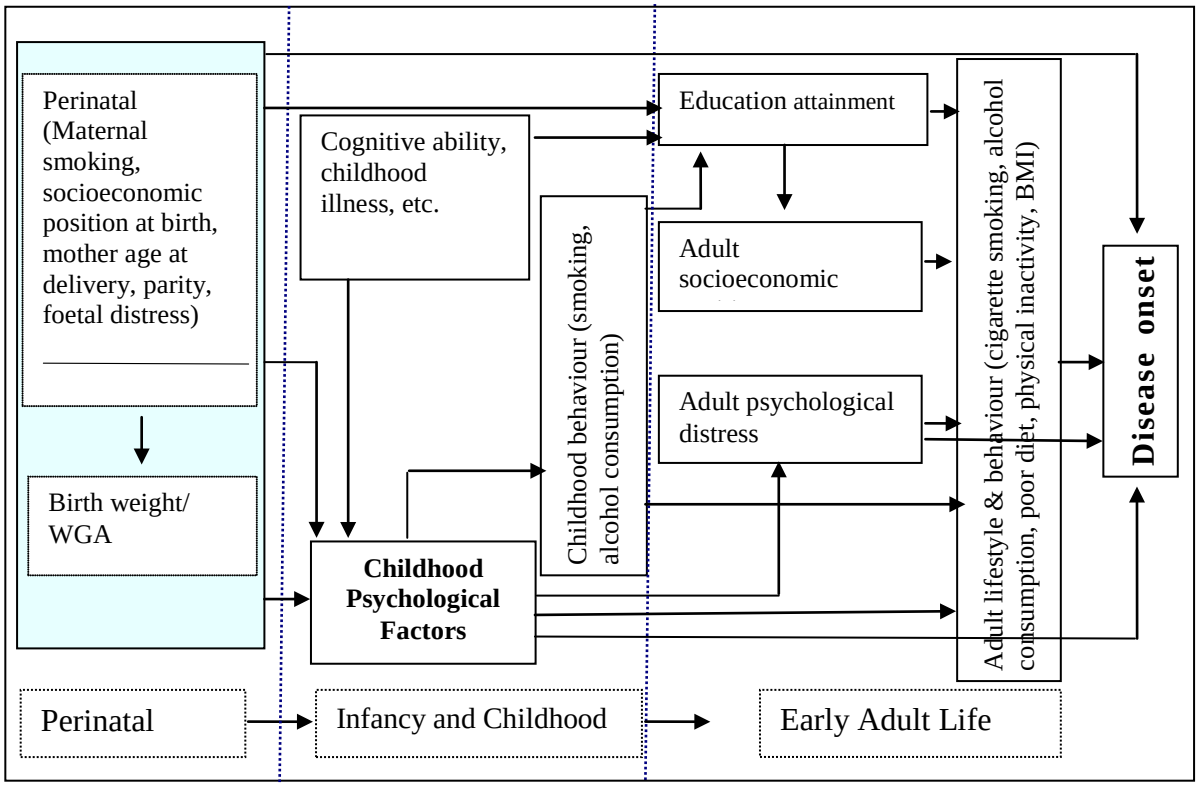


Figure 4-1: Conceptual framework for the influence of foetal, infant, childhood, and adult factors on risk of cancer from age 17 onwards.
The arrows show the possible pathways between each group of variables and disease onset. Both direct and indirect effects of each stage of life course are shown. The indirect effects are those that are mediated through later stages of life course.

Many studies have painted a comprehensively poor picture of adult life for adolescents with behavioural problems, and these form the basis for the pathways we have chosen in our model. Adolescents with either mild or severe externalising behaviour have been found to be more likely to leave school with no qualifications than other adolescents and are also more likely to be in manual social classes in adulthood even after adjusting for sex, father's social class, and cognitive ability (Colman *et al.*, 2009). Conduct problems in adolescence have also been linked to alcohol abuse in adulthood in many studies (Moffitt *et al.*, 2002; Farrington *et al.*, 2006; Odgers *et al.*, 2007). A wide range of other adverse psychosocial outcomes including, substance use, mental health, sexual/partner relationships have also been linked to conduct problems in middle childhood even after control for other confounding factors (David *et al.*, 2005). Psychological factors are also associated with adverse behaviours such as smoking, poor diets, and physical inactivity as already discussed in Section 4.4.

Studies have also identified perinatal and early childhood factors that might increase the risk for behavioral problems in mid childhood. Since these factors are also known to be risk factors for most physical illnesses later in life, they may serve as potential confounders. A number of studies have suggested an effect of low birth weight on development of subsequent conduct problems, though the mediating factors of this effect are not clear (Datar and Jacknowitz, 2009; Mankuta *et al.*, 2010). Children with emotional and conduct disorders have also been found to be more likely to live: with lone parents, in lower income households, in social sector housing, in reconstituted families, and with parents with no educational qualification (Meltzer *et al.*, 2000). Child's cognitive performance has also been implicated in maladjusted behaviours. Using a UK cohort data, Emerson and Einfeld (2010) found that higher rates of emotional and behavioural difficulties among children may be partially attributed to greater risk of exposure to cognitive performance and adverse socio-economic circumstances. Emotional and conduct problems have also been found to be more prevalent in children who reported at least one of the physical complaints and infection in childhood (Meltzer *et al.*, 2000).

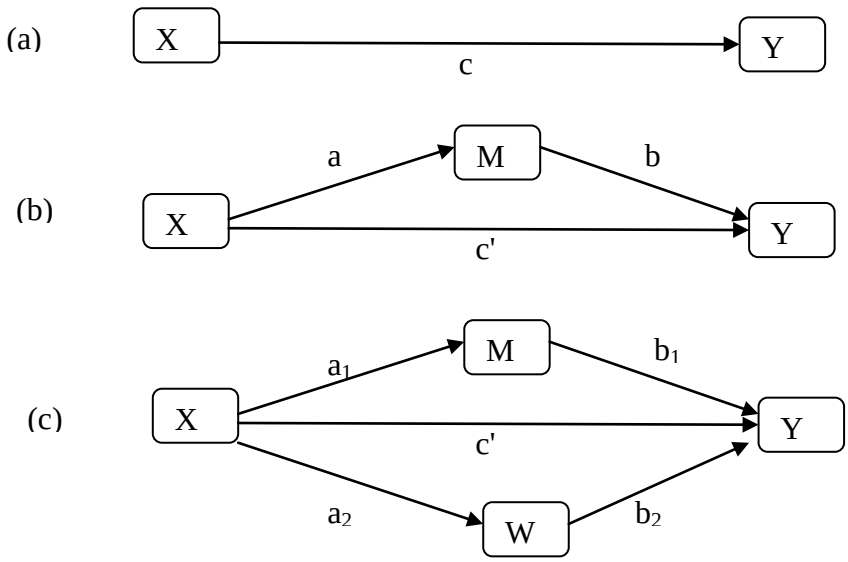


Figure 4-2: The total effect of *X* on *Y* (a), a simple mediation model (b), and a single-step multiple mediator model (c).

Statistical approaches for assessing mediation

Several approaches exist for assessing mediation effects. Mackinnon *et al.* (2007) have grouped these methods into three broad categories. All of these methods use information from a series of three regression equations. Considering a simple mediation model in

Figure 4-2 (b), the first equation regresses the dependent variable Y on the independent variable X. The second equation regresses Y on both X and the mediator variable M. The third equation regresses the mediator M on the independent variable X. The most widely used method to assess mediation is the causal steps approach. To establish mediation using this approach, the following conditions must hold: (1) a significant relation of the independent variable to the dependent variable is required in the first equation, (2) a significant relation of the independent variable to the hypothesized mediating variable is required in the third equation, (3) the mediating variable must be significantly related to the dependent variable when both the independent variable and mediating variable are predictors of the dependent variable in the second equation, and (4) the effect of X on Y shrinks upon the addition of the mediator to the model.

The second approach to assessing mediation effects is the difference in coefficients where two regression or correlation coefficients are compared- that for the relationship between X and Y ignoring M and that for the relationship between X and Y after removing the effect of M. The third approach is the product of coefficients. In this approach, one can compute a coefficient for the indirect effect of X on Y through M by multiplying the coefficient for path $X\ M$ by the coefficient for path $M\ Y$.

MacKinnon *et al.* (2007), among other authors, are rather critical of the first two approaches. They note that the causal steps approach has low power and also opine that one should not require that X be correlated with Y- it could be that X has both a direct effect on Y and an indirect effect on Y (through M), with these two effects being equal in magnitude but opposite in sign- in this case, mediation would exist even though X would not be correlated with Y. This is an example of inconsistent models (Davis, 1985). Another criticism of the causal steps approach is that it is not based on a quantification of the very thing it is attempting to test- the intervening effect (Hayes, 2009). Rather, the existence of an indirect effect is inferred logically by the outcome of a set of hypothesis tests. Brown (1997) also discusses various limitations of using the two independent approaches of using multiple independent models to assess components of the overall structure in a piecemeal manner, and proposes the use of SEMs as an alternative. Based on the criticisms on the first two approaches, we used the product of coefficients method in the SEMs in order to assess the mediation effect. Extension to these approaches have been developed to incorporate complicated models including multiple independent variables, multiple mediators, multiple outcomes, situations where mediation requires

temporal precedence from *X* to *M* to *Y*, and longitudinal mediation (Mackinnon *et al.*, 2007).

Total, direct, and indirect effects

In path analysis, the effects of one variable on another can be decomposed into direct, indirect and total effects (Bollen, 1989). Direct effects are the influences of one variable on another that are not mediated by any other variable. Indirect effects are the ones that are mediated by at least one other variable and the total effects are the sum of the direct and indirect effects. Figure 4-2 (a) presents a primary relationship to be explained where the predictor, *X*, influences the outcome, *Y*. This relationship, represented as *c*, is termed the "total effect" of *X* on *Y*. The coefficient *c* is obtained from a simple regression of *Y* on *X*, and is represented in standardized or unstandardized form or as a path coefficient from a maximum likelihood-based method such as SEMs.

Panel (b) is the simplest of all intervening variable models, the simple mediation model, with *a* being the coefficient for *X* in a model predicting *M* from *X*, and *b* and *c′* are the coefficients in a model predicting *Y* from both *M* and *X*, respectively. In this model, the predictor, *X*, influences the outcome, *Y*, in two ways: directly represented by *c*' and called the "direct effect"; and indirectly through the mediator, *M*. According to Baron and Kenny (1986), if *M* accounts for the relationship between *X* and *Y*, at least in part, then it is a mediator of the *X*-*Y* relationship. This effect of *X* on *Y* through *M* is the mediation effect, also called the "indirect effect", and, mathematically, it is the product of the coefficients for the two paths involved, *a* and *b*. The "total effect" of *X* on *Y*, *c*, is obtained by summing the direct and indirect effects, $ab + c$ (Mackinnon *et al.*, 1995).

The same rules of obtaining the indirect and direct effects apply for the two mediator model in panel (c) and even more complex mediation models. In (c), the total effect is equal to the direct effect of *X* on *Y* plus the sum of the indirect effect through *M* and the indirect effect through *W* (that is, $c = c' + (a_1b_1 + a_2b_2)$. In a model with two or more intervening variables, the indirect effect through particular intervening variable(s) is called a "specific indirect effect" and the sum of the specific indirect effects is called the "total indirect effect" of *X*. Thus, in models with multiple mediators, it is possible that the indirect effect is attributable more to one mediator than the other. A comprehensive mathematical definition of these effects for general SEMs is presented in Bollen (1989).

Inference about intervening variable effects

For the simple mediation model, the point estimate of the mediated effect is the product of $\hat{a}$ and $\hat{b}$ and can be tested for significance by dividing $\widehat{ab}$ by its standard error and comparing the result to the standard normal distribution. This is the standard *z* method for testing mediation. The most commonly used standard error for the product method was given by Sobel (1982), who used the multivariate delta method based on a Taylor series approximation and is computed as $\sqrt{\hat{a}^2\hat{\sigma}_b^2 + \hat{b}^2\hat{\sigma}_a^2}$, where $\hat{\sigma}_{\hat{a}}^2$ is the variance of the regression coefficient $\hat{a}$ and $\hat{\sigma}_{\hat{b}}^2$ is the variance of the regression coefficient $\hat{b}$. Confidence limits for the mediated effect can then be formed using the point estimate and standard error. One a major flaw of this standard error is that it requires the assumption that the sampling distribution of the indirect effect be normal which is not attainable in most cases. Improvements to significance testing and confidence limit formation for indirect effects have been proposed (Mackinnon *et al.*, 1995; Mackinnon *et al.*, 2002), and the one using resampling methods, in particular, two types of percentile bootstrap, has been found to overcome some of the problems that arise from the assumption of normality inherent in the *z* test for indirect effects and tend to have highest power and the best Type I error control (Williams and Mackinnon, 2008). Bootstrapping is already implemented in some SEM software (most extensively in Mplus) as is the method used in this study.

The SEM models were used to estimate both the direct and indirect effect of the childhood psychological factors in the development of cancer. Latent variables were used to represent each of the subscales of the psychological measures rather than using the separately calculated subscale scores in regression analyses. This reduces the measurement error. In addition, SEMs have an advantage of modelling more than one pathway simultaneously, taking into account the temporal ordering of the variables. To assess the model fit, root mean square error of approximation (RMSEA) and comparative fit index (CFI) were used. An RMSEA value below 0.05 and a CFI value close to 1 indicate a good fitting model. The analyses were carried out using Mplus (Muthén and Muthén, 1998-2007). Mplus provides maximum likelihood estimation to handling missing data under MCAR and MAR assumptions. Special features in Mplus also allow multiple-imputed data to be analyzed. We compared the results from these two approaches.

Chapter 5

Cancer: Results

5.1. Descriptive Statistics

Of the original 18,558 cohort members with at least some data since birth in the NCDS, 11,419 (61.5%) were observed at age 42 in the year 2000. The lost cases were attributable to deaths (5.9%), temporary emigrants (0.1%), permanent emigrants (7.0%), refusals (11.4%), later contacts (1.6%), and no later contacts (12.5%). Only 263 cases of cancer (61 men and 202 women) were reported representing 2.3% of the population. The distribution of the cancer cases according to the sites is summarised in Table 5-1. The median age at first cancer was 34 years. Women reported mostly cervix (n= 89), breast (n= 38) and skin (n= 26) cancers; for men the most common cancers were those of the skin (n= 16) and testes (n= 14). Eleven men and 38 women reported having cancer in the past 12 months; all but 3 had seen their doctors about it. Sixteen reported more than one cancer, and 257 cancer cases occurred for the first time after the age of 16 years and are the ones that have been used in the analysis.

Table 5-1: Self reported cancer cases by the cancer sites in the year 2000 for the 1958 NCDS and the BCS70 cohorts.

	NCDS (42 Years old)						BCS70 (30 Years old)					
	Males		Females		Both		Males		Females		Both	
Cancer Sites	#	%	#	%	#	%	#	%	#	%	#	%
All sites	61	1.08	202	3.49	263	2.30	38	0.70	98	1.73	136	1.21
Leukaemia	1	0.02	3	0.05	4	0.04	2	0.04	0	0.00	2	0.02
Hodgkins disease	7	0.12	6	0.10	13	0.11	1	0.02	6	0.11	7	0.06
Lymphoma	1	0.02	4	0.07	5	0.04	2	0.04	1	0.02	3	0.03
Skin cancer	16	0.28	26	0.45	42	0.37	7	0.13	8	0.14	15	0.13
Bone cancer	1	0.02	1	0.02	2	0.02	1	0.02	1	0.02	2	0.02
Breast cancer	-	-	38	0.66	-	-	-	-	5	0.09	-	-
Cancer of the uterus	-	-	13	0.22	-	-	-	-	-	-	-	-
Cancer of the cervix	-	-	89	1.54	-	-	-	-	57	1.01	-	-
Cancer of the testes	14	0.25	-	-	-	-	16	0.30	0	0.00	16	0.14
Cancer of the colon	5	0.09	1	0.02	6	0.05	0	0.00	1	0.02	1	0.01
Lung cancer	-	-	-	-	-	-	1	0.02	0	0.00	1	0.01
Other	16	0.28	28	0.48	44	0.39	8	0.15	19	0.34	27	0.24
Suffered in past 12 months	11	18.03	38	18.81	49	18.6	4	10.5	10	10.2	14	10.3
Median age first had cancer					34						25	
No. with cancer before 16					6						10	
No. of the cohort members	5,626	49.3	5,793	50.7	11,419		5,404	48.80	5,670	51.20	11,210	

Similarly, in the BCS70, of the original 19,101 cohort members with at least some data since birth, 11,261 (59%) survived up to the sixth sweep of data collection in the year 2000 when the cohort members were aged 30 years. Out of these, 11,210 had information on cancer. About 3.9% were lost due to deaths, 7% due to refusals, 1.6% permanent emigrants, and 18% could not be contacted. Only 136 cancer cases were reported at a median age of 25 years. Most of the cancer sites had very few cases except the cervical cancer which had 57 cases (Table 5-1). The age at which the first cancer was reported in both the NCDS and BCS70 is summarised in Table 5-2.

Table 5-2 : The age at cancer diagnosis in the NCDS and BCS70: age intervals between survey sweeps.

NCDS		BCS70	
Age group	Cancer Cases	Age group	Cancer Cases
0-16	6	0-16	11
17-23	26	17-26	74
24-33	97	27-30	51
34-42	134		
Total	263		136

Table 5-3 presents the mean and range of the scores for each of the continuous psychological measures for both boys and girls in the NCDS. Each variable has a different range of scores depending on how many items of the behaviour were in the subscale and how they were scored. Higher scores for each measure correspond to higher levels of the reported problem behaviours.

The percentages of missing values for each variable considered in the analysis are included in Tables 5-4 to 5-8 for the NCDS and Tables 5-18 to 5-21 for the BCS70 that also show the main body of results. The frequency of non-response differed across each variable. Missing observations were generally higher for the BCS70 for almost all the variables. Data on childhood psychological measures in the NCDS were missing for between 11 and 26 percent of the cohort members with the highest number of missing data at age 16 (Table 5-4). The adulthood measures in the final sweep of data collection had the least amount of missing data for both cohorts. However, the percentages of missing data increased considerably when several variables were analyzed together when considering only the complete cases.

Table 5-3: Mean score (together with standard deviation and range) for the derived continuous psychological measures in the NCDS.

		Males				Females			
		N†	M*	SD‡	Range	N†	M*	SD‡	Range
Age 7- Child Behaviour at Home (Rutter A)	Total Score	4879	6.4	3.5	0 - 24	5069	6.0	3.6	0 - 25
	Hyperactive	4873	1.1	1.2	0 - 6	5067	0.9	1.2	0 - 6
	Emotional problems	4879	2.2	1.6	0 - 8	5068	2.3	1.6	0 - 8
	Conduct problems	4877	2.3	1.5	0 - 8	5068	1.8	1.5	0 - 8
Age 7- Child Behaviour at School (BSAG)	Emotional problems	4962	3.9	4.5	0 - 34	5155	3.1	4.2	0 - 29
	Conduct problems	4962	4.3	5.4	0 - 39	5155	3.1	4.4	0 - 42
	Misc. nervous syndrome	4962	0.2	0.5	0 - 4	5154	0.1	0.3	0 - 4
Age 11- Child Behaviour at Home (Rutter A)	Total score	4766	6.5	3.5	0 - 25	4895	5.9	3.4	0 - 23
	Hyperactive	4766	1.1	1.3	0 - 6	4894	0.9	1.2	0 - 6
	Emotional problems	4765	2.5	1.6	0 - 8	4895	2.6	1.6	0 - 8
	Conduct problem	4764	2.0	1.5	0 - 8	4894	1.6	1.4	0 - 8
Age 11- Child Behaviour at School (BSAG)	Emotional problems	4826	3.7	4.2	0 - 30	4952	3.1	4.0	0 - 27
	Conduct problems	4826	4.2	5.5	0 - 40	4952	2.7	4.4	0 - 45
	Misc. nervous syndrome	4826	0.1	0.4	0 - 4	4952	0.1	0.3	0 - 4
Age 16-Child Behaviour at Home (Rutter A)	Total score	4135	3.9	3.5	0 - 30	4275	4.2	3.6	0 - 25
	Hyperactive	4132	0.4	0.9	0 - 6	4270	0.3	0.7	0 - 6
	Emotional problems	4135	1.3	1.4	0 - 8	4273	1.5	1.5	0 - 8
	Conduct problem	4134	0.8	1.2	0 - 8	4272	0.9	1.2	0 - 8
Age16-Child Behaviour at School (Rutter B)	Neurotic	4311	0.7	1.1	0 - 8	4520	0.9	1.2	0 - 8
	Antisocial	4315	0.8	1.9	0 - 12	4521	0.5	1.3	0 - 12
Malaise score at age 23	Total score	4651	1.9	2.4	0 - 16	4960	3.3	3.1	0 - 20
Malaise score at age 41	Total score	5532	3.1	3.4	0 - 24	5740	4.1	3.8	0 - 24
GHQ at age 41	Total score	5534	10.6	4.5	0 - 34	5740	11.5	4.9	0 - 36

† Number of complete observations; * Mean score; ‡ Standard deviation

5.2. The NCDS Results

Results based on complete cases and on ten multiply-imputed data to allow all the eligible subjects in every analysis, assuming that missing data had occurred at random (MAR), are presented for all the models. Generally, the effects estimated using the imputed data are slightly smaller than those obtained from complete cases. However, the conclusions remained unchanged for most of the variables. Since MAR is a less restrictive assumption than that of MCAR assumption in the complete records analyses, the MI results are to be preferred.

5.2.1. All cancer sites

The results presented in this section are for all the cancer sites analysed together in order to establish whether there is a link between early life psychological factors and cancer development. Preliminary analyses involved the plots of Nelson-Aalen cumulative hazard function to visualise whether the cumulative probability of being diagnosed with cancer differs across the three categories of the behavioural scores (severe, mild or normal) and how such relationship changes with age. A formal test of the univariable relationship between childhood psychological factors and cancer was done through a series of discrete-time survival models estimated by logistic regression for each of the psychological measure. Robust estimation methods to adjust for the rare outcome events were used.

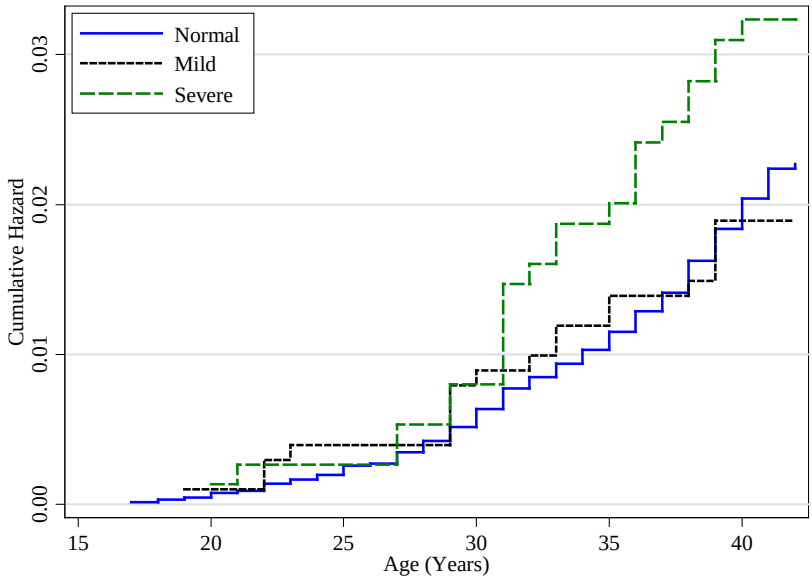
Bivariate models

Childhood psychological measures

Figures 5-1 presents sample plots for the hyperactive, conduct, and emotional problems sub-scales of the Rutter child scale as assessed by the mother at age 16 years. The rest of the plots have not been shown, but the discrete-time survival models results for the age-adjusted univariable relationship are presented for all the childhood psychological measures. The cumulative risk of being diagnosed with cancer increased with age but clear differences in the risk between the categories of the behavioural problems were only evidenced for most of the variables after age 30. For the age 16 measures, those with severe hyperactive and conduct problems had constantly higher risk for cancer later in life, especially after age 30, though there were no clear difference in cancer risk for the categories of emotional problem (Figure 5-1). All the plots showed that the risk of developing cancer increases with age, and as a result all the analyses were adjusted for the effect of age.

The discrete-time survival models results, estimated by logistic regression, are presented as the unstandardized odds ratios and 95% confidence intervals (CIs). The odds ratios reflect the magnitude of the association between each measure and the disease.

a)



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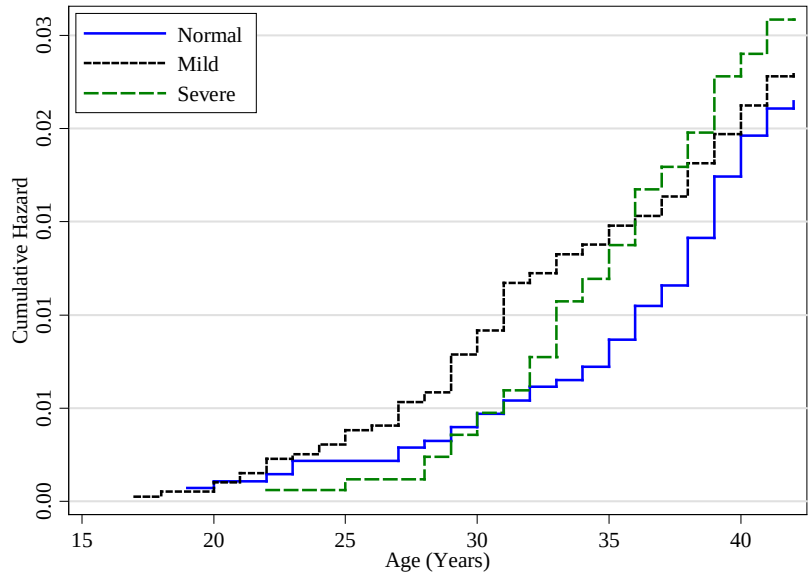


c)

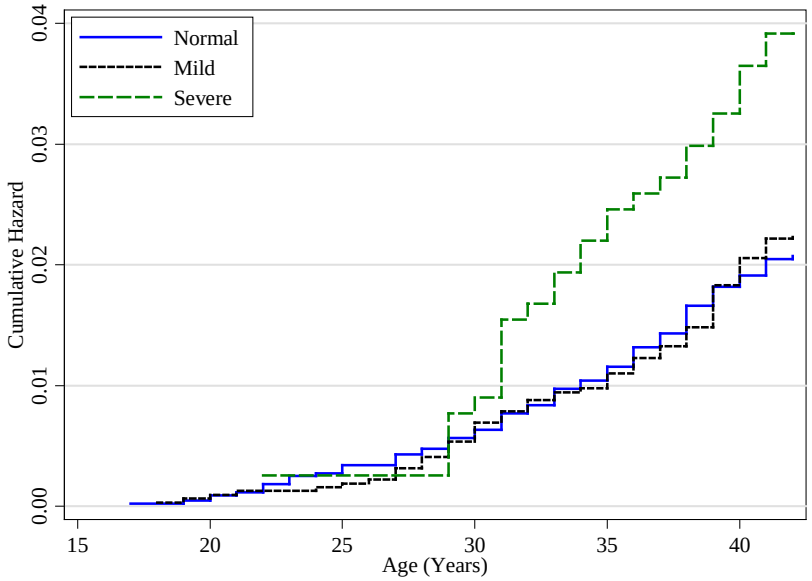


Figure 5-1: Sample cumulative hazard function for all cancer risk, by categories of Rutter A scale at 16 years: (a) hyperactive (b) emotional and (c) conduct problems.

For the measures presented on continuous scale, the unstandardized estimates reflect the change in the odds of being diagnosed with cancer for every unit increase in the behavioural score. Since the scaling of the childhood psychological measures are different for each measure (Table 5-3), it is not possible to compare the odds ratios as presented to find out which factor has the highest impact. For this purpose, standardised coefficients would be required, and these have been presented for all the childhood psychological measures in Tables B1-B4 (appendix B).

The age-adjusted odds ratios and 95% CIs for the effect of childhood psychological factors on cancer development between age 17 and 42 years old in the NCDS are shown in Table 5-4. No significant associations were found between cancer and most of the age seven and age eleven years psychological factors except for the teacher assessed conduct problems or overreaction behaviours as measured by BSAG at eleven years (OR=1.04, 95% CI= 1.01-1.06) and the Rutter A total score at age 11 years (OR=1.05, 95% CI=1.01-1.08). However, significant associations were found for almost all the sixteen-year psychological factors for both the teacher and the mother scales, with children showing worse conditions of behavioural maladjustment having higher risk for developing cancer.

Perinatal and childhood health behaviour, social, and cognitive measures

Relying on the literature and the available data, a number of perinatal and early-life social, health behaviour, social, and cognitive measures were considered, to test whether they had any effect on cancer risk (Table 5-5), so that they could be adjusted for as possible confounders. Majority of them did not show any significant association with cancer development later in life except for the social class of the mother's husband and teenage smoking at age 16. Those whose fathers were in the unskilled or partly skilled social class were about 70% more likely to develop cancer later in life as compared to those whose fathers were in professional class. Also teenagers who were smoking at least 3 packets of cigarette per week by age 16 were more likely to develop cancer later in life (OR=2.78, 95% CI= 1.83 - 4.23) as compared to non-smokers.

Table 5-4: The risk of all cancers between ages 17 and 42 years old in the 1958 birth cohort (NCDS): All cancers incident rates and age-adjusted corrected odds ratios for childhood psychological measures.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	225	9,723	12.5	1.01	(0.97 , 1.05)	0.56	1.01	(0.97 , 1.04)	0.78
Hyperactive	225	9,715	12.6	1.08	(0.97 , 1.20)	0.15	1.06	(0.96 , 1.18)	0.24
Emotional problems	225	9,722	12.5	1.07	(0.99 , 1.16)	0.10	1.06	(0.98 , 1.15)	0.13
Conduct Problem	225	9,720	12.5	0.95	(0.86 , 1.04)	0.28	0.93	(0.85 , 1.02)	0.12
Child Behaviour at School (BSAG)									
Emotional problems	229	9,888	11.0	0.98	(0.94 , 1.01)	0.17	0.98	(0.94 , 1.01)	0.15
Conduct problems	229	9,888	11.0	1.02	(1.00 , 1.04)	0.05	1.02	(1.00 , 1.04)	0.07
Miscellaneous Nervous Syndrome	229	9,887	11.0	1.01	(0.73 , 1.40)	0.94	1.01	(0.73 , 1.39)	0.97
At Age 11									
Child Behaviour at Home (Rutter A)									
Total Score	217	9,444	15.0	1.03	(0.99 , 1.06)	0.17	1.05	(1.01 , 1.08)	0.01
Hyperactive	217	9,443	15.0	1.06	(0.95 , 1.19)	0.26	1.11	(1.01 , 1.23)	0.04
Emotional problems	217	9,443	15.0	1.02	(0.94 , 1.10)	0.68	1.06	(0.98 , 1.14)	0.15
Conduct Problem	217	9,441	15.1	1.05	(0.96 , 1.14)	0.33	1.07	(0.98 , 1.16)	0.13
Child Behaviour at School (BSAG)									
Emotional problems	223	9,555	14.0	1.00	(0.97 , 1.03)	0.83	1.00	(0.97 , 1.04)	0.88
Conduct problems	223	9,555	14.0	1.03	(1.01 , 1.06)	<0.01	1.04	(1.01 , 1.06)	<0.01
Miscellaneous Nervous Syndrome	223	9,555	14.0	1.11	(0.77 , 1.58)	0.58	1.11	(0.78 , 1.58)	0.55
At Age 16									
Child Behaviour at Home (Rutter A)									
Total Score	192	8,218	26.0	1.06	(1.02 , 1.10)	<0.01	1.07	(1.03 , 1.10)	<0.01
Hyperactive	192	8,210	26.1	1.19	(1.01 , 1.40)	0.04	1.18	(1.03 , 1.36)	0.02
Emotional problems	192	8,216	26.1	1.11	(1.01 , 1.21)	0.04	1.10	(1.00 , 1.21)	0.04
Conduct Problem	192	8,214	26.1	1.15	(1.04 , 1.28)	0.01	1.18	(1.08 , 1.29)	<0.01
Child Behaviour at School (Rutter B) total Score			22.1						
Well adjusted	159	7,327							
With behavioural disorder	44	1,331		1.53	(1.10 , 2.14)	0.01	1.59	(1.15 , 2.21)	0.01
Subscales for Rutter B									
Neurotic	202	8,629	22.3	1.16	(1.05 , 1.29)	0.01	1.18	(1.06 , 1.31)	<0.01
Antisocial	203	8,633	22.3	1.08	(1.01 , 1.15)	0.02	1.08	(1.02 , 1.15)	0.01

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

Table 5-5: The effect of childhood social, health behaviour and cognitive measures on the risk of all cancers between ages 17 and 42 in the NCDS: Incident rates and age-adjusted corrected OR.

Variable (Reference category)	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Mother's age at delivery (<21)	39	1,543	5.2						
22-25	65	2,706		0.95	(0.64 , 1.41)	0.78	0.94	(0.63 , 1.41)	0.77
26-30	81	3,337		0.95	(0.65 , 1.40)	0.81	0.96	(0.65 , 1.42)	0.84
31+	61	2,944		0.82	(0.55 , 1.22)	0.33	0.83	(0.55 , 1.26)	0.38
Maternal smoking during preg.(No)	204	9,121	5.2						
Smoker	42	1,415		1.33	(0.96 , 1.86)	0.09	1.30	(1.00 , 1.69)	0.05
Parity (No prev aft 28wks)	97	3,944	5.2						
1 After 28wks	70	3,285		0.87	(0.64 , 1.18)	0.38	0.87	(0.63 , 1.19)	0.37
2 after28wks	36	1,635		0.91	(0.62 , 1.33)	0.62	0.90	(0.61 , 1.32)	0.59
3+ after 28wks	43	1,670		1.05	(0.74 , 1.51)	0.77	1.08	(0.75 , 1.54)	0.69
HBP/proteinuria/eclampsia (None)	163	6,772	5.2						
Toxaemic/eclampsia/proteinuria	83	3,762		0.92	(0.71 , 1.20)	0.54	0.90	(0.68 , 1.18)	0.45
Foetal Distress(No abnormality)	220	9,602	5.2						
Abnormality	26	932		1.23	(0.82 , 1.85)	0.31	1.20	(0.78 , 1.83)	0.41
Social class of father (I or II)	31	1,877	5.2						
III non-manual	21	1,023		1.25	(0.72 , 2.18)	0.43	1.27	(0.74 , 2.18)	0.39
III Manual	122	5,053		1.44	(0.97 , 2.14)	0.07	1.43	(0.97 , 2.11)	0.07
IV or V	59	2,083		1.70	(1.10 , 2.62)	0.02	1.73	(1.11 , 2.72)	0.02
No male hhh	13	500		1.61	(0.84 , 3.07)	0.15	1.49	(0.78 , 2.84)	0.22
Birthweight in Kg (≥2.5 up to 3)	56	2,160	5.5						
<2.5	21	601		1.36	(0.82 , 2.25)	0.23	1.36	(0.82 , 2.24)	0.23
up to 3.5	102	3,829		1.02	(0.74 , 1.42)	0.90	1.02	(0.74 , 1.42)	0.90
up to 4	53	2,931		0.70	(0.48 , 1.02)	0.06	0.71	(0.49 , 1.04)	0.08
>4	13	974		0.53	(0.29 , 0.98)	0.04	0.53	(0.29 , 0.96)	0.04
WGA (Appropriate for GA)	167	7,395	16.9						
Small for gestational age	26	804		1.45	(0.96 , 2.19)	0.08	1.38	(0.94 , 2.04)	0.10
Large for GA	23	1,031		1.01	(0.65 , 1.56)	0.98	1.00	(0.65 , 1.54)	1.00
Breastfed (No)	65	2,983		13.12					
Under 1 month	52	2,377		1.00	(0.70 , 1.45)	0.98	1.02	(0.71 , 1.48)	0.90
Over 1 month	104	4,297		1.10	(0.81 , 1.51)	0.53	1.14	(0.84 , 1.53)	0.40
Mother's at sch after min age (No)	193	7,762	5.5						
Yes	52	2,741		0.77	(0.57 , 1.05)	0.09	0.77	(0.57 , 1.06)	0.11
Father's at sch after min age (No)	177	7,082	15.4						
Yes	43	2,316		0.75	(0.54 , 1.05)	0.09	0.79	(0.56 , 1.12)	0.19
Child's cognitive skills at age 7									
Arithmetic	225	9,865	11.3	0.96	(0.91 , 1.01)	0.15	0.96	(0.91 , 1.02)	0.17
Reading	228	9,881	0.0	1.00	(0.98 , 1.02)	0.92	1.00	(0.98 , 1.02)	0.83
Smoking at age 16 (Non-smoker)	108	5,487	24.5						
Less than 3 packets	65	2,472		1.34	(0.98 , 1.82)	0.06	1.30	(0.96 , 1.75)	0.09
3+ packets	24	431		2.85	(1.83 , 4.43)	<0.01	2.78	(1.83 , 4.23)	<0.01
Number of People in HH (1-3)	25	845	15.6						
4-5	133	5,660		0.78	(0.51 , 1.20)	0.26	0.84	(0.54 , 1.30)	0.43
6+	62	2,876		0.72	(0.45 , 1.15)	0.17	0.76	(0.48 , 1.20)	0.24

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiply-imputed datasets

Adulthood psychological factors

Table 5-6 shows the odds ratios and 95% CI for the age-adjusted univariable effects of adulthood psychological factors on the risk of cancer. All the three measures of adulthood psychological distress had a significant effect on cancer with those who were psychologically distressed having greater risk for cancer after age 16. However, these results are to be interpreted with caution since some of these measures might have been taken after the cancer diagnosis and as results could be a consequence of cancer diagnosis rather than predictors. However, this was partially addressed in the analysis by considering them as time-varying covariates.

Mid-life social factors and health risk behaviours

Most of the mid-life risk factors considered (Table 5-7) had a significant effect on cancer except for alcohol consumption at age 23 years and alcohol problems at age 42 years. The BMI measure at age 42 years also had little effect with only those who were underweight having higher risk for cancer. Cohort members who had achieved A-level or higher educational qualification and those who had regular physical exercise had a reduced risk of cancer. Those who were in the manual social class and those who were smokers at age 42 had a higher risk of cancer. However, as mentioned in the previous sub-section, the problem of the temporal precedence of these variables and the diagnosis of cancer cannot be fully resolved even after being treated as time-varying covariates.

Table 5-6: The effect of mid-life psychological factors on all cancers between ages 17 and 42 in the NCDS: Incident rates and age-adjusted corrected odds ratios.

				Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
	N_C[1]	N_{CF}[2]	M[3] (%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological risk factors									
Psychological distress at 23 yrs (Malaise)			15.5						
Normal	190	8,748		Ref					
Depressed	26	647		1.87	(1.24 , 2.81)	<0.01	1.95	(1.31 , 2.90)	<0.01
Psychological distress at 42 yrs (Malaise)			0.9						
Normal	185	9,588		Ref					
Depressed	69	1,430		2.48	(1.88 , 3.28)	<0.01	2.52	(1.91 , 3.32)	<0.01
GHQ12 at 42 years	254	11,020	0.8	1.05	(1.03 , 1.07)	<0.01	1.05	(1.03 , 1.07)	<0.01

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

Table 5-7: The effect of mid-life social factors and health risk behaviours on all cancers between ages 17 and 42 in the NCDS: Incident rates and age-adjusted corrected odds ratios.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Alcohol consumption at age 23			15.4						
None	52	1,746		Ref					
Light	67	2,956		0.76	(0.53 , 1.09)	0.14	0.62	(0.36 , 1.07)	0.09
Medium	89	4,077		0.73	(0.52 , 1.03)	0.07	0.69	(0.44 , 1.09)	0.11
Heavy	7	624		0.40	(0.18 , 0.89)	0.03	0.42	(0.17 , 1.07)	0.07
Educational level at age 23			19.3						
No qualification	34	1,121		Ref					
CSE 2-5/equiv nvq1	33	1,181		0.92	(0.57 , 1.49)	0.73	0.76	(0.48 , 1.21)	0.25
O level/equiv nvq2	76	3,290		0.76	(0.51 , 1.14)	0.18	0.68	(0.44 , 1.04)	0.07
A level/equiv nvq3	26	1,593		0.54	(0.33 , 0.90)	0.02	0.53	(0.31 , 0.88)	0.01
Higher qual nvq4	15	929		0.54	(0.30 , 0.99)	0.04	0.50	(0.29 , 0.86)	0.01
Degree/higher nvq5,6	16	857		0.63	(0.35 , 1.14)	0.12	0.55	(0.32 , 0.95)	0.03
Social class at age 33			19.5						
I or II: Proff/Manager	66	3,305		Ref					
III: Skilled Non-manual	65	2,165		1.55	(1.09 , 2.19)	0.01	1.43	(1.01 , 2.01)	0.04
III: Skilled manual	24	1,797		0.68	(0.42 , 1.10)	0.12	0.75	(0.48 , 1.18)	0.22
IV or V: Partly/ Unskilled	49	1,687		1.52	(1.05 , 2.21)	0.03	1.49	(1.05 , 2.11)	0.03
Smoking at age 42			0.0						
Never smoked	80	4,989		Ref					
Used to smoke	70	2,797		1.56	(1.13 , 2.14)	0.01	1.56	(1.13 , 2.14)	0.01
Smokes occasionally	6	485		0.84	(0.36 , 1.92)	0.67	0.84	(0.36 , 1.92)	0.67
Smokes everyday < 1 packet	54	1,414		2.37	(1.68 , 3.35)	<0.01	2.37	(1.68 , 3.35)	<0.01
Smoked everyday 1+ packets	47	1,428		2.05	(1.43 , 2.94)	<0.01	2.05	(1.43 , 2.94)	<0.01
Drinking problem at age 42 (CAGE)			1.4						
No	209	9,538		Ref					
Yes	42	1,420		1.36	(0.98 , 1.89)	0.07	1.37	(0.98 , 1.90)	0.06
Physical exercise at age 42			0.0						
No	86	2,857		Ref					
Yes	171	8,253		0.69	(0.53 , 0.89)	0.01	0.69	(0.53 , 0.89)	0.01
BMI at age 42			2.6						
Underweight	7	119		2.62	(1.22 , 5.62)	0.01	2.48	(1.15 , 5.35)	0.02
Normal	120	5,081		Ref					
Overweight	75	3,921		0.81	(0.61 , 1.08)	0.16	0.83	(0.62 , 1.10)	0.20
Obesity	48	1,709		1.19	(0.85 , 1.67)	0.30	1.19	(0.86 , 1.66)	0.30

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

Table 5-8: The adjusted effects (Odds ratio and 95% CI) of childhood psychological factors on all cancers risk between ages 17 and 42 in the NCDS.

	Age and confounders-adjusted OR(95% CI)[1]					
	Complete Cases			MI[2]		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	1.01	(0.97 , 1.05)	0.63	1.00	(0.96 , 1.04)	0.93
Hyperactive	1.07	(0.96 , 1.19)	0.23	1.05	(0.94 , 1.16)	0.40
Emotional problems	1.07	(0.98 , 1.16)	0.12	1.06	(0.98 , 1.15)	0.16
Conduct Problem	0.95	(0.86 , 1.04)	0.27	0.91	(0.83 , 1.00)	0.05
Child Behaviour at School (BSAG)						
Emotional problems	0.97	(0.93 , 1.00)	0.08	0.97	(0.94 , 1.00)	0.07
Conduct problems	1.02	(0.99 , 1.04)	0.14	1.02	(0.99 , 1.04)	0.15
Miscellaneous Nervous Syndrome	1.01	(0.73 , 1.40)	0.95	0.98	(0.70 , 1.35)	0.89
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	1.03	(0.98 , 1.07)	0.12	1.04	(1.01 , 1.07)	0.02
Hyperactive	1.06	(0.99 , 1.18)	0.33	1.10	(0.99 , 1.21)	0.07
Emotional problems	1.01	(0.93 , 1.09)	0.89	1.05	(0.98 , 1.13)	0.18
Conduct Problem	1.02	(0.93 , 1.12)	0.68	1.05	(0.96 , 1.15)	0.25
Child Behaviour at School (BSAG)						
Emotional problems	0.99	(0.96 , 1.02)	0.68	1.00	(0.96 , 1.03)	0.89
Conduct problems	1.03	(1.01 , 1.06)	<0.01	1.03	(1.01 , 1.05)	<0.01
Miscellaneous Nervous Syndrome	1.15	(0.80 , 1.64)	0.46	1.10	(0.77 , 1.57)	0.60
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	1.03	(0.99 , 1.07)	0.10	1.05	(1.02 , 1.08)	<0.01
Hyperactive	1.10	(0.91 , 1.33)	0.33	1.13	(0.98 , 1.30)	0.09
Emotional problems	1.11	(0.99 , 1.23)	0.06	1.10	(1.01 , 1.21)	0.03
Conduct Problem	1.05	(0.93 , 1.18)	0.43	1.12	(1.03 , 1.23)	0.01
Child Behaviour at School (Rutter B) total score						
Well adjusted						
With behavioural disorder	1.19	(0.83 , 1.70)	0.36	1.27	(0.90 , 1.78)	0.17
Subscales for Rutter B						
Neurotic	1.13	(1.01 , 1.26)	0.03	1.13	(1.02 , 1.26)	0.02
Antisocial	1.02	(0.95 , 1.11)	0.56	1.03	(0.96 , 1.10)	0.41

1 Adjusted for the effect of maternal smoking, social class of the father, birth weight and smoking for the age 16 psychological measures.

2 Analysis based on combined results of 10 multiple-imputed datasets

* For all the psychological measures, higher scores indicate worse conditions of hehavioural maladjustment.

Multivariable models

Adjusting for possible confounders

The results did not materially change after adjusting separately for each of the potential confounders considered in Table 5-5. After a series of model selection procedure to determine the possible confounding variables to be adjusted for simultaneously as described Section 4.7, the final model for potential confounders consisted of maternal smoking, social class of the mother's husband, pregnancy condition accompanied by toxaemic or eclampsia, and childhood cognitive ability as measured by arithmetic score. In addition, smoking at age 16 was included as a confounder for the age 16 psychological factors for both the models of cervical and overall cancer risk.

There were very little changes in the adjusted model results as compared to the unadjusted one in Table 5-4. All the seven year old measures remained non-significant showing no direct association between age seven behavioural maladjustment and cancer onset. The total Rutter score at age 11 remained significant though none of its subscales was significant. Teacher assessed conduct problems at both ages seven and 11 years remained significantly associated with cancer risk. The age 16 variables remained significant except the Rutter teacher scale, its antisocial subscale, and hyperactive subscale of Rutter A scale which turned non-significant after the inclusion of smoking at age 16 in the model. Overall, most risks attenuated slightly after adjustment for the potential confounders.

Possible mediation effects

Based on the conceptual framework in Figure 4-1, the possible pathways through which the childhood psychological factors might influence cancer onset were tested in a series of structural equation models. Figure 5-2 presents a simplified version of the hypothesized model in Figure 4-1 with the perinatal and childhood factors omitted in the diagram, although they were included in the actual SEM models as possible confounders. The choice of the variables included as possible mediators was constrained by the available data as well as the literature of the well known risk factors for cancer.

Four indirect pathways and a direct effect were explored simultaneously in a multivariable model to test for the effects of possible mediators between childhood psychological factors and cancer risk (Figure 5-2), all adjusted for the significant childhood confounder variables identified in the previous confounding models. In order to reduce the potential bias from measurement error in the observed variables, latent variables were used to summarise the items of the psychological scales and sub-scales. Path 1 explores the effect of each psychological factor on cancer risk, mediated by the effect of mid-teenage smoking behaviour at age 16 and smoking at age 42 years. Path 2 explores the effect of each psychological factor on cancer risk, through the adulthood psychological distress at age 23 and age 42 years. In path 3, the effect of each psychological factor is mediated by education achievement at age 23, social class of the cohort member at age 33, and smoking behaviour at age 42. Path 4 explores the effect of each psychological factor on cancer risk, mediated by the effect of education achievement at age 23, social class at 33, and alcohol problem at age 42 years.

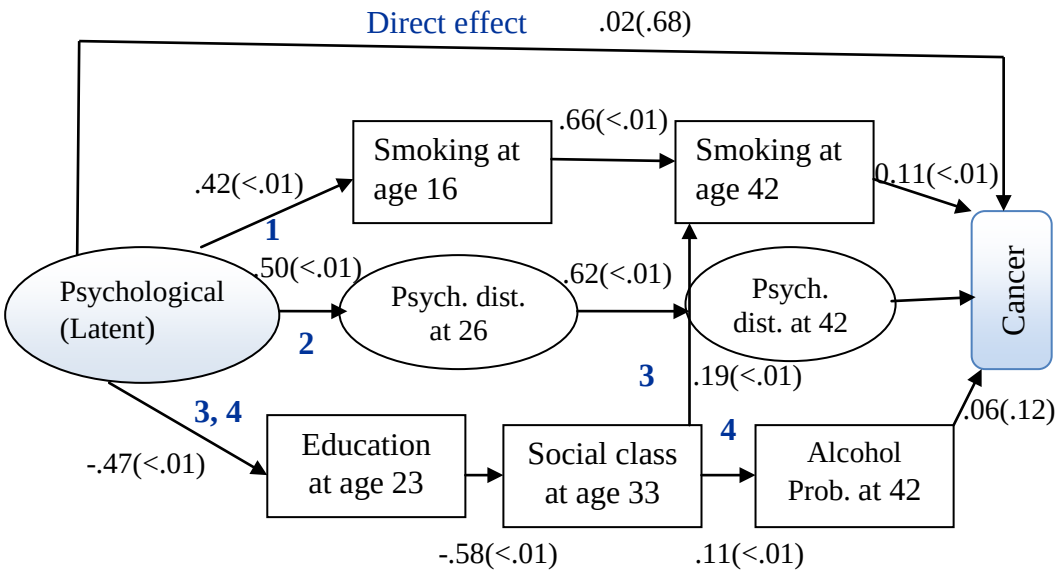


Figure 5-2: Direct and indirect effects of childhood psychological factors on cancer onset in the NCDS. The sample path coefficients (p-values) shown are for the conduct problems at age 16. The arrows are indicative rather than implying a chronological, directional relationship.

The path analysis enabled the simultaneous modelling of several related regression relationships, thus allowing us to assess both the direct and indirect effects of each psychological measure and the total effect of a variable upon the outcome. The total

effect is the combination of the direct effect and indirect effects. Rather than assuming that all the variables are situated at the same point in temporal space, the models were specified to take into account the hypothesized temporal relationship among the variables. For all the models, the overall model fit indicated that the models fitted the data well (RMSEA value were all below the recommended 0.06 cut-off and the RFI were all more than 0.9). Two sets of analyses were performed, one using full information maximum likelihood estimation for handling missing data and the other one based on 10 multiply-imputed datasets, both relying on MAR assumption. The results of these analyses did not differ in terms of significance. The results presented here are based on maximum likelihood estimation for handling missing data under MAR assumptions.

The direct and indirect effects of the latent childhood psychological factors on cancer are summarized in Table 5-9. For simplicity, the specific estimates for each variable in the pathway have been omitted. Since the psychological variables are measured on different scales, fully standardized coefficients have been presented to compare the relative strength of associations across each of the variables. As depicted in the table, the direct effects for all the psychological factors were not significant contrary to the results of the univariable models where a number of the variables, especially at age 16, significantly predicted cancer risk. This shows that the effects of childhood psychological factors are fully mediated by biological, behavioural, social, and cognitive pathways along the life course.

Although the childhood psychological factors did not have any significant direct effect on cancer risk, all the total indirect effects were significant except for the effect of emotional problems at age seven, which was only significant through the path mediated by smoking in adulthood. The standardized coefficient in the table represents the amount of change in the risk of cancer per standard deviation unit of the psychological measure. For example, an increase in one standard deviation in hyperactive problem score at age seven (higher hyperactive disorder) increases the standard deviation in the log-odds of being diagnosed with cancer by 0.09 through the indirect paths depicted in Figure 5-2, but has no direct effect. The specific indirect effect gives the effect of the psychological measure through a specific path. For example, the indirect effect of hyperactive problems at age seven in path 1 is the effect of this measure mediated by smoking at age 16 and smoking at age 42 years.

Table 5-9: Direct and indirect effects (standardized coefficients and significance p-values) of the latent childhood psychological variables on the risk of all cancers in the NCDS.

	Direct Effect		Specific Indirect Effects								Tot. Indirect		Total Effect		
			Path 1[1]		Path 2[2]		Path 3[3]		Path 4[4]						
	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	SE	Sig.
Age 7(Rutter A)															
Hyperactive	-0.01	0.77	0.03	<0.01	0.05	<0.01	0.01	<0.01	0.001	0.12	0.09	<0.01	0.07	(0.04)	0.06
Emotional problems	0.07	0.06	-0.01	<0.01	0.01	0.05	-0.001	0.02	0.000	0.19	-0.01	0.24	0.07	(0.04)	0.08
Conduct problems	-0.08	0.14	0.03	<0.01	0.04	<0.01	0.01	<0.01	0.001	0.43	0.08	<0.01	-0.01	(0.05)	0.86
Age 7 (BSAG)															
Emotional problems	-0.06	0.19	0.01	0.02	0.03	<0.01	0.01	<0.01	0.001	0.43	0.04	<0.01	-0.02	(0.04)	0.71
Conduct problems	-0.01	0.73	0.02	<0.01	0.03	<0.01	0.01	<0.01	0.001	0.12	0.05	<0.01	0.04	(0.03)	0.19
Misc Nervous Synd	-0.03	0.67	0.01	0.14	0.01	0.03	0.01	<0.01	0.001	0.12	0.03	<0.01	-0.003	(0.07)	0.97
Age 11 (Rutter A)															
Hyperactive	-0.02	0.77	0.03	<0.01	0.06	<0.01	0.01	<0.01	0.002	0.13	0.10	<0.01	0.08	(0.04)	0.06
Emotional problems	-0.01	0.84	-0.002	0.21	0.03	<0.01	0.002	<0.01	0.000	0.16	0.03	<0.01	0.02	(0.54)	0.04
Conduct problems	-0.04	0.38	0.04	<0.01	0.05	<0.01	0.01	<0.01	0.002	0.11	0.10	<0.01	0.06	(0.04)	0.14
Age 11 (BSAG)															
Emotional problems	-0.04	0.23	0.01	<0.01	0.04	<0.01	0.01	<0.01	0.001	0.13	0.06	<0.01	0.02	(0.03)	0.52
Conduct problems	0.01	0.74	0.03	<0.01	0.03	<0.01	0.01	<0.01	0.001	0.12	0.07	<0.01	0.08	(0.03)	0.01
Misc Nervous Synd	-0.01	0.95	0.02	<0.01	0.01	0.12	0.01	<0.01	0.001	0.20	0.04	<0.01	0.04	(0.08)	0.64
Age 16 (Rutter A)															
Hyperactive	0.02	0.71	0.03	<0.01	0.06	<0.01	0.01	<0.01	0.002	0.15	0.10	<0.01	0.12	(0.04)	0.01
Emotional problems	0.05	0.24	0.01	<0.01	0.06	<0.01	0.01	<0.01	0.001	0.14	0.07	<0.01	0.12	(0.04)	<0.01
Conduct problems	0.02	0.68	0.03	<0.01	0.06	<0.01	0.01	<0.01	0.002	0.14	0.10	<0.01	0.12	(0.04)	<0.01
Age 16 (Rutter B)															
Neurotic	0.03	0.46	0.02	<0.01	0.05	<0.01	0.01	<0.01	0.002	0.14	0.09	<0.01	0.12	(0.04)	<0.01
Antisocial	-0.01	0.78	0.05	<0.01	0.05	<0.01	0.01	<0.01	0.003	0.13	0.10	<0.01	0.088	(0.04)	0.02

1 Through mid-teenage smoking behaviour and adult smoking behaviour at age 42

2 Through adulthood psychological distress at age 23 and age 42

3 Through education achievement at age 23, social class at age 33 and adulthood smoking behaviour at age 42.

4 Through education achievement at age 23, social class at age 33 and alcohol problem at age 42

Except for the emotional problems at age seven, the results for path 1 suggest that children who showed higher level of behavioural maladjustment were more likely to indulge in risky smoking behaviour in mid teenage which would continue to adulthood and eventually increase the risk of cancer. The path 2 results suggest that childhood psychological problems would continue into adulthood, and their effect over the life course would increase the risk of cancer. In path 3 and 4, the specific estimates for the effects of childhood psychological factors on education attainment and that of educational attainment on social class at age 33 were negative showing that adolescents with higher level of behavioural maladjustment were more likely to leave school with no qualifications than other adolescents and were also more likely to be in manual social classes in adulthood, thus increasing their likelihood of indulging in adulthood health risky behaviour such as smoking and alcohol consumption, and ultimately to higher risks of developing cancer. The age seven and age 11 measures did not show a total effect on

cancer except for the emotional problems at age 11 (Rutter A) and conduct problems at age 11 (BSAG). All the age 16 measures showed a significant total effect. The pathway through drinking problems at age 42 (path 4) was not significant for all the measures showing a lack of strong mediating effect of alcohol consumption. The largest effect was for path 2 implying that children who show higher level of internalising and externalising behaviour were also more likely to report a history of psychological distress along the life course and were eventually at a higher risk of cancer.

5.2.2. Cervical cancer

As well as the analysis of all incident cancer, specific analysis was performed on cervical cancer. In addition to the variables tested in all incident cancer as possible confounders or mediators, other variables deemed to be risk factors for cervical cancer, as they are likely to increase the risk of HPV infection, were considered. These included the number of cohabiting or marriage partners, the age at first baby, and the number of children a woman had.

Bivariate results

Childhood psychological factors

The age-adjusted odds ratios and 95% CIs for the effect of childhood psychological factors on cervical cancer for the NCDS are shown in Table 5-10. Similar to results for all cancer sites, no significant associations were found between cervical cancer and most of the age seven and age eleven psychological measures except for the conduct problems in school as assessed by teacher (BSAG scale) at eleven years (OR=1.06, 95% CI= 1.03-1.09) and the Rutter total score at age 11 years (OR=1.08, 95% CI=1.02-1.14). However, significant associations were found for almost all the sixteen-year psychological measures for both the teacher and the mother scales, with children showing more behavioural deviance having higher risk of developing cervical cancer later in life.

Table 5-10: The risk of cervical cancer between ages 17 and 42 years old in the NCDS: Cervical cancer incident rates and age-adjusted corrected ORs for childhood psychological factors.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR (95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological factors at age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	79	4,990	12.2	1.06	(1.00 , 1.12)	0.04	1.03	(0.97 , 1.10)	0.32
Hyperactive	79	4,988	12.2	1.11	(0.92 , 1.35)	0.28	1.07	(0.88 , 1.31)	0.67
Emotional problems	79	4,989	12.2	1.11	(0.97 , 1.27)	0.13	1.06	(0.93 , 1.22)	0.39
Conduct Problem	79	4,989	12.2	1.13	(0.97 , 1.30)	0.11	1.10	(0.96 , 1.28)	0.18
Child Behaviour at School (BSAG)									
Emotional problems	79	5,076	10.7	1.02	(0.97 , 1.08)	0.40	1.02	(0.97 , 1.08)	0.34
Conduct problems	79	5,076	10.7	1.05	(1.03 , 1.09)	<0.01	1.05	(1.02 , 1.09)	<0.01
Miscellaneous Nervous Synd	79	5,075	10.7	1.06	(0.60 , 1.89)	0.84	1.07	(0.57 , 1.85)	0.94
Psychological factors at age 11									
Child Behaviour at Home (Rutter A)									
Total Score	76	4,819	15.2	1.08	(1.02 , 1.14)	0.01	1.10	(1.04 , 1.16)	<0.01
Hyperactive	76	4,818	15.2	1.16	(0.96 , 1.40)	0.12	1.25	(0.01 , 1.49)	0.01
Emotional problems	76	4,819	15.2	1.05	(0.92 , 1.19)	0.46	1.07	(0.94 , 1.22)	0.30
Conduct Problem	76	4,819	15.2	1.26	(1.09 , 1.46)	<0.01	1.29	(1.11 , 1.49)	<0.01
Child Behaviour at School (BSAG)									
Emotional problems	76	4,876	14.2	1.03	(0.99 , 1.08)	0.11	1.04	(0.99 , 1.08)	0.11
Conduct problems	76	4,876	14.2	1.08	(1.05 , 1.11)	<0.01	1.09	(1.06 , 1.11)	<0.01
Miscellaneous Nervous Synd	76	4,876	14.2	1.63	(0.92 , 2.88)	0.10	1.57	(0.88 , 2.80)	0.13
Psychological factors at age 16									
Child Behaviour at Home (Rutter A)									
Total Score	65	4,210	25.9	1.12	(1.07 , 1.17)	<0.01	1.11	(1.07 , 1.16)	<0.01
Hyperactive	65	4,205	25.9	1.43	(1.14 , 1.78)	<0.01	1.43	(1.14 , 1.78)	<0.01
Emotional problems	65	4,208	25.9	1.21	(1.05 , 1.38)	0.01	1.17	(1.02 , 1.34)	0.03
Conduct Problem	65	4,207	25.9	1.29	(1.10 , 1.51)	<0.01	1.31	(1.14 , 1.52)	<0.01
Behaviour at School (Rutter B) total score			21.4						
Well adjusted	46	3,876							
With behavioural disorder	25	592		3.55	(2.18 , 5.77)	<0.01	3.25	(2.06 , 5.12)	<0.01
Subscales									
Neurotic	70	4,450	21.7	1.24	(1.05 , 1.47)	0.01	1.24	(1.05 , 1.46)	0.01
Antisocial	71	4,450	21.7	1.31	(1.22 , 1.41)	<0.01	1.18	(1.10 , 1.27)	<0.01

1 Number of women who reported having cervical cancer between the age of 17 to 42

2 Women who did not report any case of cervical cancer; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

Table 5-11: The effect of perinatal and childhood social and cognitive measures on the risk of cervical cancer between ages 17 and 42 in the NCDS: Incident rates and age-adjusted OR.

				Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
	N_C[1]	N_{CF}[2]	M[3]						
Variable (Reference category)			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Mother's age at delivery (<21)	16	788	5.2						
22-25	21	1,391		0.74	(0.39 , 1.42)	0.37	0.74	(0.39 , 1.43)	0.37
26-30	24	1,697		0.69	(0.37 , 1.30)	0.25	0.70	(0.37 , 1.32)	0.27
31+	24	1,511		0.78	(0.41 , 1.46)	0.44	0.79	(0.42 , 1.50)	0.47
Maternal smoking during preg (No)	68	4,648	5.1						
Smoker	17	743		1.59	(0.94 , 2.71)	0.09	2.05	(1.35 , 3.14)	<0.01
Parity (No prev aft 28wks)	32	2,060	5.1						
1 After 28wks	20	1,617		0.80	(0.46 , 1.41)	0.45	0.77	(0.43 , 1.39)	0.39
2 after28wks	15	860		1.15	(0.62 , 2.12)	0.66	1.16	(0.63 , 2.16)	0.63
3+ after 28wks	18	854		1.37	(0.77 , 2.45)	0.28	1.31	(0.73 , 2.35)	0.36
HBP/proteinuria or eclampsia (No)	49	3,521	5.1						
Toxaemic/eclampsia/proteinuria	36	1,870		1.39	(0.90 , 2.13)	0.14	1.25	(0.81 , 1.92)	0.32
Foetal Distress (No abnormality)	77	4,963	5.1						
Abnormality	8	427		1.27	(0.61 , 2.63)	0.52	1.08	(0.53 , 2.24)	0.83
Social class of father (I/II/III non-man.)	11	1,464	5.1						
III Manual	42	2,598		2.07	(1.07 , 4.03)	0.03	2.04	(1.05 , 3.94)	0.03
IV or V	27	1,070		3.25	(1.61 , 6.56)	0.00	3.32	(1.63 , 6.78)	<0.01
No male hhh.	5	259		2.71	(0.94 , 7.80)	0.07	2.42	(0.85 , 6.91)	0.10
Birthweight (up to 3 kg)	19	1,247	5.5						
<2.5 kg	7	375		1.28	(0.54 , 3.05)	0.58	1.38	(0.58 , 3.24)	0.47
up to 3.5 kg	34	2,087		1.06	(0.60 , 1.85)	0.85	1.01	(0.58 , 1.77)	0.97
up to 4 kg	18	1,286		0.92	(0.48 , 1.75)	0.80	0.74	(0.38 , 1.44)	0.38
>4 kg	7	374		1.28	(0.54 , 3.06)	0.57	0.83	(0.35 , 1.97)	0.67
Weight for gestational age (AGA)	52	3,811	16.8						
Small for gestational age	9	412		1.67	(0.82 , 3.39)	0.16	1.56	(0.82 , 2.97)	0.18
Large for GA	9	506		1.36	(0.67 , 2.77)	0.39	1.23	(0.60 , 2.52)	0.58
Breastfed (No)	24	1,514	12.7						
Under 1 month	16	1,237		0.83	(0.44 , 1.55)	0.55	0.97	(0.53 , 1.77)	0.92
Over 1 month	37	2,209		1.05	(0.63 , 1.75)	0.86	1.14	(0.69 , 1.88)	0.62
Mother's educ: at sch after 16 (No)	71	3,976	5.4						
Yes	14	1,399		0.58	(0.33 , 1.03)	0.06	0.59	(0.32 , 1.09)	0.09
Father's educ: at sch after 16 (No)	71	3,586	15.4						
Yes	8	1,216		0.35	(0.17 , 0.73)	0.01	0.44	(0.22 , 0.88)	0.02
Childs's Arithmetic skills at age 7	77	5,070	10.8	0.91	(0.83 , 0.99)	0.03	0.90	(0.82 , 0.99)	0.03
Reading skills at age 7	89	5,682	0.0	0.96	(0.94 , 0.99)	0.01	0.99	(0.96 , 1.01)	0.32
History of eczema at age 7 or 11 (No)	70	4,614	15.4						
Yes	9	357		1.73	(0.87 , 3.47)	0.12	1.34	(0.69 , 2.58)	0.39
Smoking at age 16 (Non-smoker)	22	2,886	23.8						
Less than 3 packets	32	1,298		3.19	(1.85 , 5.49)	<0.01	2.56	(1.41 , 4.63)	<0.01
3+ packets	16	146		14.01	(7.35 , 26.69)	<0.01	7.65	(3.94 , 14.85)	<0.01

1 Number of women who reported having cervical cancer between the age of 17 to 42

2 Women who did not report any case of cervical cancer; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

Childhood health behaviour, social, and cognitive measures

Among the childhood health behaviours, teenage smoking was the most remarkable significant factor with the odds of developing the disease for those who smoked more than three packets a day 7.7 times larger than the odds of non-smokers (OR=7.65, 95% CI=3.94-14.84) (Table 5-11). Those whose mothers smoked during pregnancy and those whose fathers were in the manual social class also had significantly higher risk for cervical cancer. The child's cognitive ability was also significantly associated with cervical cancer risk with children having higher scores in reading, and arithmetic scores having a reduced risk.

Mid-life risk factors related to the exposure to HPV infection

Table 5-12 presents the age-adjusted estimates for the association between cervical cancer and the factors likely to increase HPV infection. Women who reported having more than three partners were at a higher risk of developing cervical cancer (OR = 4.81, 95% CI=2.69- 8.60) as compared to those who had 0-1 partner. Those who had the first baby early, before age 20, had an increased risk of cervical cancer, compared to those who had the first baby at age 25 or older. Also having many children (3+) as compared to no children was found to increase the risk of cervical cancer.

Table 5-12: The risk of cervical cancer between ages 17 and 42 years in the NCDS: Cervical cancer incident rates and age-adjusted ORs for factors likely to expose women to HPV.

				Age-adjusted OR (95% CI)					
	N_C[1]	N_{CF}[2]	M[3]	Complete Cases			MI[4]		
Variable (Reference category)			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Number of partners (0-1)	38	3,605	12.8						
2	18	1,033		1.68	(0.96 , 2.94)	0.07	1.79	(1.06 , 3.04)	0.03
3+	16	320		4.75	(2.65 , 8.53)	<0.01	4.81	(2.69 , 8.60)	<0.01
Number of own children (0-2)	43	3,918	13.9						
3+	29	977		2.70	(1.69 , 4.33)	<0.01	2.55	(1.62 , 4.02)	<0.01
Age at first child (25+)	17	1,840	13.9						
No child	9	1,135		0.88	(0.39 , 1.97)	0.76	0.78	(0.36 , 1.71)	0.53
<20	23	499		4.89	(2.61 , 9.16)	<0.01	3.15	(1.76 , 5.66)	<0.01
20-24	23	1,420		1.73	(0.93 , 3.25)	0.09	1.56	(0.85 , 2.83)	0.15

1 Number of women who reported having cervical cancer between the age of 17 to 42

2 Women who did not report any case of cervical cancer; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

Adulthood psychological factors and health risk behaviours

Table 5-13 shows the age-adjusted odds ratios and 95% CI for the effects of adulthood psychological factors on the risk of cervical cancer. Similar to the results for all cancer sites, all the mid-life psychological factors assessed had a significant positive effect on cervical cancer.

Table 5-13: The effect of midlife psychological factors on the risk of cervical cancer between ages 17 and 42 in the NCDS: Cervical cancer incident rates and age-adjusted odds ratios.

				Age-adjusted OR(95% CI)					
	N_C[1]	N_{CF}[2]	M[3]	Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Pychological distress at 23 years (Malaise)									
Normal	58	4,402	14						
Depressed	9	491		2.19	(1.08 , 4.41)	<0.01	2.63	(1.44 , 4.79)	<0.01
Pychological distress at 42 years (Malaise)									
Normal	51	4,766	0.5						
Depressed	38	885	0.5	3.98	(2.61 , 6.06)	<0.01	4.91	(3.23 , 7.48)	<0.01
GHQ12 at 42 years	89	5,651	0.5	1.06	(1.02 , 1.10)	<0.01	1.07	(1.04 , 1.11)	<0.01

1 Number of women who reported having had cervical cancer

2 Women who did not report any case of cervical cancer

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Mid-life health risk behaviours

Table 5-14 shows the odds ratios and 95% CI for the age-adjusted univariable effects of mid life risk behaviours on the risk of cervical cancer. All measures of adulthood risky health behaviours had a significant effect on cervical cancer except alcohol consumption at age 23, and BMI at age 42 years. Women who had achieved A-level or higher educational qualification and those who had regular physical exercise had a reduced risk of cervical cancer. On the other hand, women who were in the manual social class, those who were smokers by age 42, and those who had drinking problems at age 42 had a higher risk of cervical cancer.

Table 5-14: The effect of mid-life health risk behaviours on the risk of cervical cancer between ages 17 and 42 in the NCDS: Cervical cancer incident rates and age-adjusted ORs.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Alcohol consumption at age 23			14.0						
None	20	1,343		Ref					
Light	22	1,654		0.89	(0.49 , 1.63)	0.71	0.43	(0.19 , 0.97)	0.04
Medium	21	1,818		0.78	(0.42 , 1.43)	0.42	0.48	(0.23 , 1.00)	0.05
Heavy	4	82		3.56	(1.22 , 10.43)	0.02	0.47	(0.15 , 1.44)	0.18
Educational level at age 23			17.2						
No qualification	15	633		Ref					
CSE 2-5/equiv nvq1	10	690		0.62	(0.28 , 1.39)	0.25	0.57	(0.25 , 1.33)	0.19
O level/equiv nvq2	30	1,845		0.68	(0.36 , 1.26)	0.21	0.57	(0.28 , 1.14)	0.11
A level and Higher	10	3168		0.28	(0.12 , 0.62)	<0.01	0.22	(0.09 , 0.53)	<0.01
Social class at age 33			18.8						
I or II: Proff/Manager	18	1,521		Ref					
III: skilled Non-manual	20	1,709		0.99	(0.52 , 1.87)	0.97	1.59	(0.87 , 2.90)	0.13
III: Skilled manual	4	349		1.07	(0.36 , 3.15)	0.91	0.73	(0.26 , 2.03)	0.54
IV or V-Partly/ Unskilled	22	1,043		1.77	(0.95 , 3.30)	0.07	2.58	(1.40 , 4.77)	<0.01
Smoking at age 42			0.0						
Never smoked	13	2,610		Ref					
Used to smoke	18	1,394		2.56	(1.25 , 5.23)	0.01	2.43	(1.19 , 4.96)	0.02
Smokes occasionally	2	230		2.15	(0.48 , 9.51)	0.32	1.96	(0.44 , 8.70)	0.38
Smokes everyday < 1 packet	29	813		7.0	(3.62 , 13.39)	<0.01	7.64	(3.97 , 14.69)	<0.01
Smoked everyday 1+ packets	27	635		8.24	(4.25 , 15.98)	<0.01	7.06	(3.64 , 13.69)	<0.01
Drinking problem at age 42 (CAGE)			1.8						
No	67	5,079		Ref					
Yes	21	501		3.19	(1.95 , 5.21)	<0.01	2.10	(1.29 , 3.43)	<0.01
Physical Exercise at age 42			0.0						
No	33	1,536		Ref					
Yes	56	4,145		0.63	(0.41 , 0.97)	0.04	0.59	(0.38 , 0.90)	0.02
BMI at age 42			3.1						
Underweight	2	96		1.78	(0.43 , 7.34)	0.42	2.29	(0.56 , 9.37)	0.25
Normal	46	3,094		Ref					
Overweight	21	1,458		0.98	(0.59 , 1.64)	0.94	0.62	(0.37 , 1.02)	0.06
Obesity	18	856		1.44	(0.83 , 2.48)	0.19	1.15	(0.67 , 1.99)	0.61

1 # of Women who reported having had cervical cancer; 2 Women who did not report any case of cervical cancer

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiply-imputed datasets

Ref= Reference category

Multivariable models

Adjusting for possible confounders

After a series of model selection procedures, the final multivariable model adjusting for all the significant confounders consisted of maternal smoking, social class of the

mother's husband, pregnancy condition accompanied by toxaemic or eclampsia, and childhood cognitive ability as measured by arithmetic score. In addition, smoking at age 16 was included as a confounder for the age 16 psychological measures.

The Rutter total score and its sub-scales at age seven remained non-significant in the adjusted model showing no direct association between the age seven behavioural maladjustment reported by the mother and cervical cancer onset (Table 5-15). Conduct problems assessed by the teacher at both ages seven and 11 were positively associated with cervical cancer risk. Other significant predictors were total Rutter score, and the hyperactive and conduct problems of the Rutter scale at age 11. The age 16 variables remained significant except the neurotic subscale of the Rutter teacher scale and hyperactive and conduct problem subscale of Rutter parent's scale which turned non-significant after the inclusion of smoking at age 16 in the model. Overall, there were no major effects of the potential confounding variables but most risks attenuated slightly after the adjustment.

Possible mediation effects

The possible pathways through which the childhood psychological factors before age 16 might influence cervical cancer onset between age 17 and 42 were tested in a series of structural equation models. Four indirect pathways and a direct effect were explored simultaneously in a multivariable model to test for the effects of possible mediators between childhood psychological factors and cervical cancer risk, all adjusted for the significant confounder variables identified in the previous confounding models. Latent variables were used to summarise the items of the psychological scales and sub-scales. Figure 5-3 presents the hypothesised pathways linking childhood psychological measures and cervical cancer. In path 1, it is hypothesised that the childhood behavioural problem would increase their risk of smoking when they are teenagers and continue smoking to adulthood, which will eventually increase their risk for cervical cancer. Path 2 explores the effect of each childhood psychological factor on cervical cancer risk, through the adulthood psychological distress at age 23 and age 42 years, which depicts the continuities over time in the individual emotional and behavioural difficulties. In path 3, it is hypothesised that the effect of each psychological measure on cervical cancer is mediated by education attainment at age 23, social class of the cohort member at age 33 and smoking behaviour at age 42. In path 4, it is hypothesised that children with

behavioural difficulties are more likely to have many partners, thus exposing them to HPV and subsequently to cervical cancer.

Table 5-15: The adjusted effects (ORs and 95% CI) of childhood psychological factors on cervical cancer risk between ages 17 and 42 in the NCDS.

	Age and confounders-adjusted OR(95% CI)[1]					
	Complete Cases			MI[2]		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	1.04	(0.97 , 1.11)	0.26	1.03	(0.97 , 1.10)	0.30
Hyperactive	1.07	(0.87 , 1.32)	0.52	1.04	(0.85 , 1.28)	0.68
Emotional problems	1.06	(0.93 , 1.22)	0.39	1.05	(0.92 , 1.21)	0.47
Conduct problems	1.09	(0.93 , 1.26)	0.29	1.06	(0.92 , 1.23)	0.42
Child Behaviour at School (BSAG)						
Emotional problems	1.00	(0.94 , 1.06)	0.91	1.01	(0.96 , 1.07)	0.65
Conduct problems	1.05	(1.02 , 1.08)	<0.01	1.05	(1.02 , 1.08)	<0.01
Miscellaneous Nervous Syndrome	1.01	(0.57 , 1.79)	0.98	0.96	(0.53 , 1.76)	0.91
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	1.08	(1.02 , 1.15)	0.01	1.09	(1.03 , 1.15)	<0.01
Hyperactive	1.18	(0.98 , 1.43)	0.09	1.22	(1.03 , 1.46)	0.02
Emotional problems	1.04	(0.91 , 1.20)	0.54	1.07	(0.93 , 1.21)	0.35
Conduct problems	1.25	(1.07 , 1.45)	<0.01	1.24	(1.08 , 1.44)	<0.01
Child Behaviour at School (BSAG)						
Emotional problems	1.01	(0.97 , 1.06)	0.53	1.03	(0.98 , 1.07)	0.27
Conduct problems	1.08	(1.05 , 1.12)	<0.01	1.08	(1.05 , 1.11)	<0.01
Miscellaneous Nervous Syndrome	1.83	(0.99 , 3.39)	0.05	1.48	(0.81 , 2.69)	0.20
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	1.08	(1.02 , 1.15)	0.01	1.08	(1.03 , 1.13)	<0.01
Hyperactive	1.25	(0.89 , 1.75)	0.21	1.27	(0.99 , 1.63)	0.06
Emotional problems	1.25	(1.06 , 1.47)	0.01	1.17	(1.02 , 1.35)	0.03
Conduct problems	1.07	(0.89 , 1.29)	0.45	1.16	(0.99 , 1.35)	0.07
Child Behaviour at School (Rutter B) total score						
Well adjusted						
With behavioural disorder	1.81	(1.03 , 3.18)	0.04	1.71	(1.06 , 2.76)	0.03
Subscales for Rutter B						
Neurotic	1.07	(0.87 , 1.30)	0.53	1.11	(0.94 , 1.31)	0.23
Antisocial	1.18	(1.04 , 1.34)	0.01	1.14	(1.03 , 1.25)	0.01

1 Adjusted for the effect of maternal smoking, social class of the father, high blood pressure/eclamptia, mathematic score and smoking for the age 16 psychological measures.

2 Analysis based on combined results of 10 multiple-imputed datasets

* For all the psychological measures, higher scores indicate worse conditions of hehavioural maladjustment.

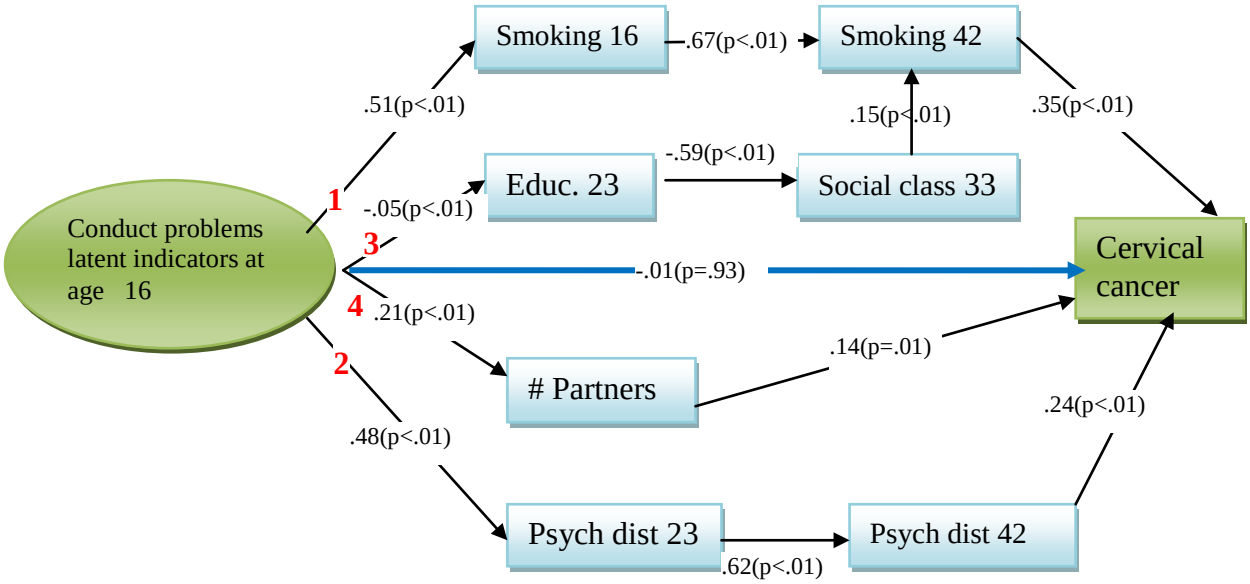


Figure 5-3 : Hypothesised relationship between psychological factors before age 16 and cervical cancer risk after age 16. Conduct problems is used as an example, but the model was tested for all the other psychological measures. The arrows are indicative rather than implying a chronological, directional relationship.

Figure 5-3 shows the standardized regression coefficients for each path for the hypothesised relationship between conduct problems at age 16 and cervical cancer risk between age 17 and 42 years. The model fitted the data well with RMSEA of 0.04 and RFI of 0.98. There was also a good model fit for all the other psychological measures; the RMSEA values were all below the recommended 0.06 cut-off and the RFI were all more than 0.9. As shown in the figure, the direct effect of conduct problem at age 16 on cervical cancer was not significant ($p = 0.93$). However, the effects through other pathways were all significantly associated with cervical cancer. The regression estimate for the specific indirect pathway is obtained by the product of the estimates for relationship between each variable in the pathway. For example, specific estimate for path 2 which is 0.07 in Table 5-16 is obtained by the product of 0.48, 0.62 and 0.24. The total indirect effect is the sum of all the specific indirect effects, while the total effect is the sum of total indirect and the direct effect.

The path 1 effects show that children with conduct problems are at a higher risk of early smoking, which also predicts smoking in adulthood and eventually the risk of cervical cancer. Path 2 shows that children with conduct problems by age 16 are more at risk of

psychological distress by age 26 and age 42 and a higher risk for cervical cancer. Path 3 depicts that those children with conduct problems are less likely to attain higher education, and are later more likely to be in manual social class, and indulge in risky behaviour such as smoking which increases their risk for cervical cancer. Path 4 shows that children with conduct problems are more likely to have more cohabiting or marriage partners and thus having higher risk for cervical cancer.

Table 5-16: Direct and indirect effects (standardized coefficients and significance p-values) of the latent childhood psychological variables on the risk of cervical cancer in the NCDS.

	Direct Effect		Specific Indirect Effect								Tot. Indire		Total Effect		
			Path 1[1]		Path 2[2]		Path 3[3]		Path 4[4]						
	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	SE	Sig.
Age 7(Rutter A)															
Hyperactive	-0.13	0.12	0.10	<0.01	0.083	<0.01	0.02	<0.01	0.03	<0.01	0.23	<0.01	0.11	(0.06)	0.08
Emotional problems	0.05	0.40	-0.01	0.19	0.023	<0.01	0.002	0.19	0.003	0.38	0.02	0.07	0.07	(0.06)	0.24
Conduct problems	-0.09	0.20	0.09	<0.01	0.071	<0.01	0.02	<0.01	0.03	<0.01	0.21	<0.01	0.12	(0.03)	0.02
Age 7 (BSAG)															
Emotional problems	-0.06	0.22	0.03	<0.01	0.054	<0.01	0.02	<0.01	0.01	0.06	0.11	<0.01	0.05	(0.05)	0.24
Conduct problems	-0.02	0.70	0.06	<0.01	0.044	<0.01	0.02	<0.01	0.02	<0.01	0.13	<0.01	0.12	(0.04)	0.01
Age 11 (Rutter A)															
Hyperactive	-0.05	0.58	0.11	<0.01	0.082	<0.01	0.02	<0.01	0.03	<0.01	0.24	<0.01	0.19	(0.07)	0.01
Emotional problems	-0.13	0.08	0.06	<0.01	0.10	<0.01	0.02	<0.01	0.03	<0.01	0.20	<0.01	0.07	(0.06)	0.28
Conduct problems	0.004	0.96	0.10	<0.01	0.07	<0.01	0.02	<0.01	0.03	<0.01	0.22	<0.01	0.22	(0.06)	<0.01
Age 11 (BSAG)															
Emotional problems	-0.06	0.24	0.04	<0.01	0.059	<0.01	0.03	<0.01	0.01	<0.01	0.14	<0.01	0.08	(0.05)	0.11
Conduct problems	0.01	0.75	0.08	<0.01	0.045	<0.01	0.02	<0.01	0.02	<0.01	0.16	<0.01	0.18	(0.04)	<0.01
Age 16 (Rutter A)															
Hyperactive	0.04	0.67	0.11	<0.01	0.074	<0.01	0.01	<0.01	0.03	<0.01	0.23	<0.01	0.27	(0.07)	<0.01
Emotional problems	0.03	0.69	0.05	<0.01	0.082	<0.01	0.02	<0.01	0.02	<0.01	0.17	<0.01	0.20	(0.06)	<0.01
Conduct problems	-0.01	0.93	0.12	<0.01	0.073	<0.01	0.02	<0.01	0.03	<0.01	0.23	<0.01	0.23	(0.07)	<0.01
Age 16 (Rutter B)															
Neurotic	-0.01	0.86	0.08	<0.01	0.071	<0.01	0.02	<0.01	0.02	<0.01	0.19	<0.01	0.18	(0.06)	<0.01
Antisocial	0.06	0.29	0.11	<0.01	0.055	<0.01	0.01	<0.01	0.02	<0.01	0.20	<0.01	0.31	(0.05)	<0.01

1 Through mid-teenage smoking behaviour and adult smoking behaviour at age 42

2 Through adulthood psychological distress at age 23 and age 42

3 Through education achievement at age 23, social class at age 33 and adulthood smoking behaviour at age 42.

4 Through number of partners

The direct and indirect effects for all the other latent childhood psychological factors on cervical cancer are summarized in Table 5-16. The specific estimates for each variable in the pathway have been omitted to simplify the table. As depicted in the table, there were no significant direct effects between any of the childhood psychological factors and cervical cancer. However, the total indirect effects were significant for all the behavioural measures except for the emotional problems at age 7. This shows that the childhood behavioural difficulties alone do not affect the risk of cervical cancer, but their

influence on other health risk behaviours, and their continuities over time increases the risk.

Except for the emotional problems at age seven, the results for path 1 suggest that children who showed higher level of behavioural maladjustment were more likely to indulge in risky smoking behaviour in mid teenage which would continue to adulthood and eventually increase the risk of cervical cancer. The path 2 results suggest that childhood psychological problems would continue into adulthood, and their effect over the life course would increase the risk of cervical cancer. In path 3, the specific estimates were all negative showing that adolescents with higher level of behavioural maladjustment were more likely to leave school with no qualifications than other adolescents and were also more likely to be in manual social classes in adulthood, thus increasing their likelihood of indulging in adulthood health risky behaviour such as smoking.

Despite not having any direct effect, the indirect effects of all the outwardly expressed behaviours- conduct problems assessed by the mother at ages 7,11 and 16, and by the teacher at age 7 and 11 years- were of large magnitude such that their total effect were all significant. In contrast, only the age 16 emotional problems had a significant total effect. Since the entire path coefficients were standardised, we are able to compare the relative strength of association across each of the variables. The conduct problems at home and in school had their largest effect through smoking, while emotional problems had their largest effect through adulthood psychological measures for most of the variables. The effects at age 16 were stronger than those at ages 7and 11 years.

5.2.3. Cancer sites other than cervical cancer

Since cervical cancer comprised almost a third of all the reported cancer cases, and given that the results for cervical cancer and overall cancer followed the same pattern in most cases, further analysis was carried out to compare the results of all cancer sites and all cancer sites excluding cervical cancer cases. Table 5-17 shows the age-adjusted estimates (OR and 95% CI) from the two analyses. After exclusion of cervical cancer cases, no associations were observed between any of the childhood summary measures of behavioural difficulties and incident cancer. A further analysis adjusting for other cancer risk factors did not show any association either (results not shown). Therefore, the

observed association between the childhood behavioural difficulties and overall cancer risk are likely a result of their association with cervical cancer alone.

Table 5-17 : The effect of childhood psychological factors on all other cancer sites other than the cervical cancer: odds ratios and 95% CI for the complete case analysis.

	Age-adjusted OR (95% CI)					
	All cancers (CC)			Cervical Cancer Excluded		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	1.01	(0.97 , 1.05)	0.56	0.95	(0.89 , 1.01)	0.09
Hyperactive	1.08	(0.97 , 1.20)	0.15	1.07	(0.91 , 1.27)	0.42
Emotional problems	1.07	(0.99 , 1.16)	0.10	0.96	(0.84 , 1.09)	0.51
Conduct Problem	0.95	(0.86 , 1.04)	0.28	0.89	(0.76 , 1.03)	0.11
Child Behaviour at School (BSAG)						
Emotional problems	0.98	(0.94 , 1.01)	0.17	0.99	(0.94 , 1.04)	0.63
Conduct problems	1.02	(1.00 , 1.04)	0.05	1.02	(0.99 , 1.07)	0.22
Miscellaneous Nervous Syndrome	1.01	(0.73 , 1.40)	0.94	0.71	(0.34 , 1.50)	0.37
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	1.03	(0.99 , 1.06)	0.17	0.99	(0.93 , 1.05)	0.73
Hyperactive	1.06	(0.95 , 1.19)	0.26	1.06	(0.90 , 1.25)	0.50
Emotional problems	1.02	(0.94 , 1.10)	0.68	0.95	(0.83 , 1.08)	0.44
Conduct Problem	1.05	(0.96 , 1.14)	0.33	1.01	(0.87 , 1.18)	0.86
Child Behaviour at School (BSAG)						
Emotional problems	1.00	(0.97 , 1.03)	0.83	1.01	(0.97 , 1.06)	0.56
Conduct problems	1.03	(1.01 , 1.06)	<0.01	1.04	(1.00 , 1.08)	0.05
Miscellaneous Nervous Syndrome	1.11	(0.77 , 1.58)	0.58	1.05	(0.56 , 1.99)	0.87
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	1.06	(1.02 , 1.10)	<0.01	0.98	(0.92 , 1.04)	0.52
Hyperactive	1.19	(1.01 , 1.40)	0.04	0.90	(0.64 , 1.25)	0.53
Emotional problems	1.11	(1.01 , 1.21)	0.04	0.97	(0.84 , 1.13)	0.71
Conduct Problem	1.15	(1.04 , 1.28)	0.01	1.01	(0.84 , 1.21)	0.91
Child Behaviour at School (Rutter B)						
Total Score						
Well adjusted	Ref					
With behavioural disorder	1.53	(1.10 , 2.14)	0.01	0.75	(0.37 , 1.51)	0.42
Subscales						
Neurotic	1.16	(1.05 , 1.29)	0.01	1.05	(0.89 , 1.24)	0.56
Antisocial	1.08	(1.01 , 1.15)	0.02	0.98	(0.83 , 1.17)	0.85

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

5.3. The BCS70 Results

5.3.1. All cancer sites

Unadjusted models

Childhood psychological factors

Table 5-18 shows the number of incident cases of cancer between age 17 and 30 years for each group of the childhood psychological measure, and the age-adjusted odds ratio (95% CI) for the association between the summary measures of behavioural or emotional problems and cancer. Both the results for complete case analysis and that for MI are presented. No associations were observed between most of the summary measures of childhood behavioural or emotional problems and cancer. Only hyperactive behaviours and self esteem at age 10 and the conduct problems at age 16 were significantly associated with the cancer risk. Children with low self esteem, those with conduct problems by age 16, and those who were hyperactive by age 10 had higher risk for cancer.

Perinatal and childhood social and environmental measures

A number of perinatal and childhood social and environmental measures were tested for their association with cancer but none of them except the social class of the mother's husband was significantly associated with cancer (Table 5-19).

Adulthood psychological factors

Those who reported psychological distress at age 26 and 30 assessed by Malaise inventory as well as those who had higher scores on the GHQ12 at age 30 were at a higher risk of cancer as compared to those who did not report psychological distress (Table 5-20).

Adulthood risky health behaviours

Only alcohol consumption at age 26 and smoking by age 30 had significant effects on cancer risk (Table 5-21).

Table 5-18: The risk of all cancers between ages 17 and 30 years old in the 1970 birth cohort: All cancer incident rates and age-adjusted corrected odds ratios for childhood psychological factors.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological factors at age 5*									
Child Behaviour at Home (Rutter A)									
Total Score	104	9,006	18.7	1.02	(0.98 , 1.06)	0.39	1.02	(0.97 , 1.06)	0.46
Hyperactive	104	8,995	18.8	1.07	(0.94 , 1.21)	0.29	1.08	(0.96 , 1.22)	0.22
Emotional problems	104	8,993	18.8	1.04	(0.94 , 1.15)	0.46	1.02	(0.93 , 1.13)	0.66
Conduct Problem	104	8,995	18.8	1.00	(0.92 , 1.08)	0.94	1.00	(0.92 , 1.08)	0.91
Psychological factors at age 10									
Child Behaviour at Home (Rutter A)									
Total Score	107	9,534	13.9	1.01	(1.00 , 1.03)	0.09	1.01	(1.00 , 1.03)	0.16
Hyperactive	107	9,520	14.0	1.01	(1.00 , 1.02)	0.02	1.01	(1.00 , 1.02)	0.03
Emotional problems	107	9,524	14.0	1.01	(0.99 , 1.02)	0.34	1.00	(0.99 , 1.01)	0.55
Conduct Problem	107	9,519	14.1	1.00	(0.99 , 1.02)	0.58	1.00	(0.99 , 1.02)	0.59
At Home (Conners'Mother self completion)									
Impulsive	107	9,515	14.1	1.00	(0.99 , 1.01)	0.78	1.00	(0.99 , 1.01)	0.87
Hyperactive/Inattention	107	9,517	14.1	1.00	(0.99 , 1.01)	0.37	1.00	(0.99 , 1.01)	0.39
Clumsy	107	9,496	14.3	1.00	(0.99 , 1.02)	0.82	1.00	(0.99 , 1.02)	0.84
Poor Motor Coordination	107	9,496	14.3	1.00	(0.98 , 1.02)	0.73	1.00	(0.98 , 1.02)	0.67
At School (Child Development Behaviour)									
Antisocial Behaviour	99	8,864	20.0	1.01	(0.99 , 1.04)	0.27	1.02	(1.00 , 1.04)	0.12
Disorganised activity	99	8,864	20.0	1.02	(1.00 , 1.04)	0.12	1.02	(1.00 , 1.04)	0.02
Neurotism/Anciety	99	8,864	20.0	1.02	(1.00 , 1.04)	0.13	1.02	(1.00 , 1.04)	0.08
Clumsiness	99	8,864	20.0	1.02	(0.99 , 1.05)	0.27	1.01	(0.99 , 1.04)	0.31
Poor hand-Eye Coordination	99	8,863	20.0	0.98	(0.96 , 1.00)	0.12	0.98	(0.96 , 1.00)	0.07
Hyper/Kinesis	99	8,863	20.0	1.00	(0.97 , 1.02)	0.83	1.00	(0.97 , 1.03)	0.95
Introversion/Extroversion	99	8,862	20.0	1.01	(0.99 , 1.03)	0.17	1.01	(1.00 , 1.03)	0.13
Behavioural Trauma	99	8,862	20.0	1.03	(0.97 , 1.10)	0.35	1.03	(0.96 , 1.11)	0.40
Dressing	96	8,566	22.7	0.98	(0.97 , 1.00)	0.03	0.99	(0.97 , 1.01)	0.16
At School (Self Completion)									
Locus of Control[5]	97	8,814	20.4	0.99	(0.96 , 1.03)	0.67	0.98	(0.94 , 1.02)	0.39
Self Esteem[6]	99	8,847	20.1	0.95	(0.92 , 0.99)	0.01	0.95	(0.92 , 0.98)	<0.01
Psychological factors at age 16									
Child Behaviour at Home (Rutter A)									
Total Score	74	6,864	38.1	1.05	(0.99 , 1.10)	0.10	1.04	(1.00 , 1.09)	0.05
Hyperactive	73	6,754	39.0	1.11	(0.91 , 1.36)	0.29	1.13	(0.97 , 1.32)	0.12
Emotional problems	73	6,793	38.7	1.03	(0.89 , 1.18)	0.73	1.04	(0.92 , 1.18)	0.55
Conduct Problem	74	6,795	38.7	1.11	(1.02 , 1.21)	0.02	1.10	(1.02 , 1.18)	0.01

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

5 Higher scores indicate greater internalization; 6 Higher score indicate higher self-esteem

* For other psychological measures, higher score indicate worse conditions of hehavioural maladjustment.

Table 5-19: The effect of perinatal, and childhood social and environmental measures on the risk of all cancers between ages 17 and 30 in the BCS70: Incident rates and age-adjusted corrected odds ratios.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Mother's age at delivery			8.19						
<21	30	2,013		Ref					
22-25	35	3,325		0.707	(0.43 , 1.15)	0.16	0.71	(0.44 , 1.15)	0.16
26-30	30	2,907		0.695	(0.42 , 1.15)	0.16	0.69	(0.41 , 1.14)	0.14
31+	25	1,917		0.879	(0.52 , 1.50)	0.64	0.89	(0.52 , 1.53)	0.68
Maternal smoking during pregnancy			7.71						
Non-Smoker	67	6,201		Ref					
Smoker	53	4,015		1.224	(0.85 , 1.75)	0.27	1.18	(0.82 , 1.69)	0.37
Parity			7.8						
No prev aft 28wks	39	3,856		Ref					
1 After 28wks	46	3,451		1.313	(0.86 , 2.01)	0.21	1.36	(0.89 , 2.09)	0.16
2 after28wks	17	1,645		1.04	(0.59 , 1.84)	0.89	1.09	(0.62 , 1.91)	0.78
3+ after 28wks	18	1,254		1.439	(0.82 , 2.52)	0.20	1.47	(0.83 , 2.62)	0.19
Social class of mother's husband			6.4						
I or II	23	3,066		Ref					
III non-manual	14	1,024		1.841	(0.95 , 3.58)	0.07	1.70	(0.88 , 3.25)	0.11
III Manual	56	4,677		1.573	(0.97 , 2.56)	0.07	1.53	(0.93 , 2.50)	0.09
IV or V	23	1,599		1.911	(1.07 , 3.41)	0.03	1.79	(1.03 , 3.12)	0.04
Birthweight			7.77						
<2.5	8	589		Ref					
upto 3	34	1,951		1.22	(0.56 , 2.64)	0.61	1.20	(0.56 , 2.59)	0.64
upto 3.5	39	4,029		0.679	(0.32 , 1.45)	0.32	0.70	(0.33 , 1.49)	0.36
upto 4	32	2,786		0.807	(0.37 , 1.75)	0.59	0.81	(0.37 , 1.77)	0.60
>4	7	854		0.61	(0.22 , 1.68)	0.34	0.60	(0.22 , 1.65)	0.32
Breastfed			18.9						
No	72	5,540		Ref					
Under 1 month	15	1,472		0.806	(0.46 , 1.41)	0.45	0.85	(0.47 , 1.52)	0.58
Over 1 month	17	1,966		0.682	(0.40 , 1.16)	0.16	0.69	(0.41 , 1.17)	0.17
Mother's Education			21.6						
No Qualification	58	4,634		Ref					
Vocational, O-level	27	2,957		0.737	(0.47 , 1.16)	0.19	0.80	(0.50 , 1.26)	0.34
A Level +	14	1,094		1.051	(0.59 , 1.89)	0.87	1.06	(0.59 , 1.89)	0.85
Father's Education			22.7						
No Qualification	46	3,746		Ref					
Vocational, O-level	30	2,301		1.067	(0.67 , 1.69)	0.78	1.02	(0.66 1.59)	0.92
A Level +	15	2,118		0.592	(0.33 , 1.06)	0.08	0.61	(0.33 , 1.12)	0.11
No Male hhh	8	394		1.739	(0.82 , 3.69)	0.15	1.55	(0.74 , 3.25)	0.24

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data;

4 Based on combined results of 10 MI datasets

Table 5-20: The age-adjusted effects (odds ratio and 95% CI) of mid-life psychological factors on overall cancer risk between ages 17 and 30 in the BCS70.

	N_C[1]	N_{CF}[2]	M[3] (%)	Age-adjusted OR(95% CI) Complete Cases OR (95% CI)	Sig	MI[4] OR (95% CI)	Sig
Psychological distress at 26 (Malaise Inventory)			32.3				
Normal	59	6,540					
Depressed	21	965		2.44 (1.48 , 4.01)	<0.01	2.18 (1.26 , 3.75)	0.01
Psychological distress at 30 (Malaise Inventory)			0.88				
Normal	94	9,600					
Depressed	31	1,375		2.32 (1.54 , 3.48)	<0.01	2.31 (1.54 , 3.47)	<0.01
GHQ12 at 30 years	125	10,978	0.86	1.07 (1.04 , 1.10)	<0.01	1.07 (1.04 , 1.11)	<0.01

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

Multivariable models

For the analysis of risk factors of all cancers, the model was only adjusted for the effect of social class of the father at birth. Compared to the unadjusted model, all the effects slightly attenuated but followed same pattern of significance (Results not shown).

Possible mediation effect

A similar mediation model used in the NCDS was also tested in the BCS70 (Figure 5-2), with the four pathways being tested. Table 5-22 presents the direct and indirect effects (standardized coefficients and significance p-values) of the latent psychological variables on the risk of all cancers in the BCS70 for the variables that were significant in the univariable model. The same model was tested for all the other psychological measures but neither had a direct nor total effect on cancer risk (Results omitted from the table). Overall, there was no direct effect of any of the childhood psychological problems on cancer risk. However, the total indirect effect was significant for all the measures shown, but the magnitude of their indirect effects were not large enough such that all but conduct problems at age 16, did not show any total effect. As in the NCDS, the effects were stronger for age 16-year measures. Path 2, which shows continuities of the childhood behavioural and emotional problems to mid-life psychological distress, had the largest standardised estimates which were all significant.

Table 5-21: The effect of mid-life health risk behaviours on the risk of all cancers between ages 17 and 30 in the BCS70: All cancer incident rates and age-adjusted ORs.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Alcohol consumption at age 23			33.9						
None	33	1,811							
Light	12	1,249		0.54	(0.28 , 1.05)	0.07	0.65	(0.36 , 1.19)	0.17
Medium	23	3,009		0.42	(0.25 , 0.72)	<0.01	0.51	(0.31 , 0.84)	0.01
Heavy	9	1,256		0.41	(0.20 , 0.86)	0.02	0.42	(0.20 , 0.91)	0.03
Educational level at age 26			36.1						
No qualification	5	347							
CSE 2-5/equiv nvq1	6	1,236		0.33	(0.10 , 1.09)	0.07	0.62	(0.22 , 1.73)	0.36
O level/equiv nvq2	40	2,956		0.86	(0.34 , 2.18)	0.75	0.89	(0.37 , 2.13)	0.80
A level and Higher	19	1466		0.48	(0.18 , 1.30)	0.15	0.54	(0.25 , 1.18)	0.12
Social class at age 30			1.9						
I or II: Proff/Manager	37	3,935							
III: Skilled Non-manua	44	2,879		1.62	(1.04 , 2.50)	0.03	1.59	(1.03 , 2.46)	0.04
III: Skilled manual	21	2,204		1.02	(0.60 , 1.75)	0.93	1.01	(0.59 , 1.72)	0.98
IV or V: Partly/ Unskilled	22	1,840		1.28	(0.76 , 2.17)	0.36	1.24	(0.73 , 2.10)	0.42
Smoking at age 30			0.0						
Never smoked	48	4,893							
Used to smoke	17	2,108		0.84	(0.48 , 1.46)	0.53	0.84	(0.48 , 1.46)	0.53
Smokes occasionally	7	855		0.89	(0.40 , 1.96)	0.77	0.89	(0.40 , 1.96)	0.77
Smokes everyday < 1 packe	26	2,100		1.27	(0.79 , 2.05)	0.32	1.27	(0.79 , 2.05)	0.32
Smoked everyday 1+ packet	27	1,118		2.47	(1.54 , 3.96)	<0.01	2.47	(1.54 , 3.96)	<0.01
Physical Exercise at age 30			0.06						
No	30	2,334							
Yes	95	8,733		0.84	(0.56 , 1.26)	0.40	0.84	(0.56 , 1.26)	0.40
BMI at age 30			2.7						
Underweight	8	249		2.82	(1.36 , 5.85)	0.01	2.67	(1.28 , 5.55)	0.01
Normal	72	6,005							
Overweight	28	3,309		0.71	(0.46 , 1.11)	0.13	0.70	(0.45 , 1.08)	0.11
Obesity	16	1,210		1.13	(0.66 , 1.94)	0.66	1.11	(0.64 , 1.90)	0.71

1 Cancer cases; 2 Non-cancer cases; 3 Percentage of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

5.3.2. Cervical cancer

Unadjusted models

Childhood psychological factors

Table 5-23 shows the number of incident cases of cervical cancer between age 17 and 30 years for each group of the childhood psychological measure, and the age-adjusted odds

ratios (95% CIs) for the association between the summary measures of behavioural or emotional problems and cervical cancer. Both the results for complete case analysis and that for MI are presented. A number of childhood psychological factors were found to be significantly associated with cervical cancer risk in mid life. All the age five measures except the emotional problems were positively and significantly associated with cervical cancer risk. Among the ten-year old psychological factors at home, only the hyperactive problems positively and significantly predicted the cervical cancer risk. Among the child's behaviour at school, the antisocial behaviour, disorganised activity, and neuroticism behaviours were positively associated with cervical cancer risk. Also children with higher self esteem by age 10 had a reduced risk of cervical cancer later in life. All the 16 year old behavioural problems at home were positively and significantly associated with the risk of cervical cancer after age 17 years.

Table 5-22: Direct and indirect effects (standardized coefficients and significance p-values) of the latent childhood psychological variables on the risk of all cancers in the BCS70.

	Direct Effect		Specific Indirect Effect								Total Indirect		Total Effect		
			Path 1[1]		Path 2[2]		Path 3[3]		Path 4[4]						
	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	SE	Sig.
Age 5 (Rutter A)															
Hyperactive	0.01	0.84	0.01	0.01	0.03	<0.01	0.003	<0.01	0.01	<0.01	0.05	<0.01	0.06	(0.05)	0.24
Emotional problems	0.01	0.91	0.00	0.06	0.02	<0.01	0.001	0.02	0.00	0.01	0.02	<0.01	0.03	(0.05)	0.59
Conduct Problem	-0.07	0.17	0.02	<0.01	0.03	<0.01	0.004	<0.01	0.01	<0.01	0.06	<0.01	0.00	(0.04)	0.95
Age 10 School (Self Completion)															
Locus of Control	0.07	0.35	-0.03	0.01	-0.06	<0.01	-0.004	0.01	-0.02	<0.01	-0.11	<0.01	-0.04	(0.06)	0.45
Self Esteem	-0.04	0.69	-0.02	0.13	-0.06	0.01	-0.002	0.14	-0.01	<0.01	-0.10	<0.01	-0.14	(0.07)	0.05
Age 16 (Rutter A)															
Hyperactive	-0.02	0.73	0.02	0.01	0.05	<0.01	0.003	0.73	0.01	<0.01	0.08	<0.01	0.06	(0.06)	0.30
Emotional problems	-0.04	0.60	0.00	0.06	0.06	<0.01	0.003	<0.01	0.01	<0.01	0.07	<0.01	0.04	(0.06)	0.55
Conduct Problem	0.03	0.60	0.02	0.05	0.04	<0.01	0.002	0.05	0.01	<0.01	0.08	<0.01	0.11	(0.06)	0.04

1 Through adult smoking behaviour at age 30

2 Through adulthood psychological distress at age 26 and age 30

3 Through education achievement at age 26, social class at age 30 and adulthood smoking bahaviour at age 30.

4 Through education achievement at age 26, and alcohol consumption at age 26

Perinatal and childhood social and environmental measures

Similar to the results of all cancers, a number of perinatal and childhood social and environmental measures were tested for their association with cervical cancer but none of them except the social class of the mother's husband was significantly associated with cervical cancer risk (Table 5-24).

Table 5-23: The risk of cervical cancer between ages 17 and 30 years old in the BCS70: Cervical cancer incident rates and age-adjusted corrected odds ratios for childhood psychological factors.

	N_C[1]	N_{CF}[2]	M[3] (%)	Age-adjusted OR(95% CI) Complete Cases OR	(95% CI)	Sig	MI[4] OR	(95% CI)	Sig
Psychological factors at age 5*									
Child Behaviour at Home (Rutter A)									
Total Score	48	4,620	19.0	1.08	(1.03 , 1.15)	<0.01	1.08	(1.02 , 1.14)	0.01
Hyperactive	48	4,612	19.1	1.23	(1.04 , 1.46)	0.02	1.24	(1.05 , 1.46)	0.01
Emotional problems	48	4,613	19.1	1.09	(0.94 , 1.25)	0.25	1.07	(0.93 , 1.22)	0.36
Conduct Problem	48	4,613	19.1	1.17	(1.05 , 1.31)	0.01	1.16	(1.04 , 1.29)	0.01
Psychological factors at age 10									
Child Behaviour at Home (Rutter A)									
Total Score	48	4,926	13.6	1.01	(0.99 , 1.04)	0.24	1.02	(0.99 , 1.04)	0.21
Hyperactive	48	4,919	13.7	1.02	(1.00 , 1.03)	0.02	1.02	(1.00 , 1.03)	0.01
Emotional problems	48	4,922	13.7	1.00	(0.98 , 1.02)	0.93	1.00	(0.98 , 1.02)	0.92
Conduct Problem	48	4,917	13.8	1.01	(0.98 , 1.03)	0.55	1.01	(0.99 , 1.04)	0.42
At Home (Conners' Mother self completion)									
Impulsive	48	4,917	13.8	1.01	(0.99 , 1.03)	0.30	1.01	(0.99 , 1.03)	0.27
Hyperactive/Inattention	48	4,918	14	1.02	(1.00 , 1.03)	0.01	1.02	(1.01 , 1.03)	0.01
Clumsy	48	4,908	14	0.99	(0.97 , 1.02)	0.70	1.00	(0.97 , 1.02)	0.74
Poor Motor Coordination	48	4,910	14	0.99	(0.95 , 1.03)	0.71	0.99	(0.95 , 1.03)	0.55
At School (Child Development Behaviour)									
Antisocial Behaviour	44	4,563	20.0	1.06	(1.02 , 1.09)	<0.01	1.06	(1.02 , 1.09)	<0.01
Disorganised activity	44	4,563	20.0	1.06	(1.02 , 1.09)	<0.01	1.06	(1.03 , 1.09)	<0.01
Neuroticism/Anxiety	44	4,563	20.0	1.04	(1.02 , 1.07)	<0.01	1.04	(1.01 , 1.07)	0.01
Clumsiness	44	4,563	20.0	1.04	(1.00 , 1.08)	0.03	1.03	(1.00 , 1.07)	0.07
Poor hand-Eye Coordination	44	4,562	20.0	0.96	(0.93 , 0.99)	0.01	0.96	(0.94 , 0.99)	0.01
Hyper/Kinesis	44	4,563	20.0	1.03	(0.99 , 1.08)	0.11	1.03	(0.99 , 1.08)	0.12
Introversion/Extroversion	44	4,562	20.0	1.01	(0.98 , 1.03)	0.54	1.01	(0.98 , 1.04)	0.45
Behavioural Trauma	44	4,561	20.0	1.05	(0.96 , 1.15)	0.31	1.05	(0.95 , 1.15)	0.34
Dressing	44	4,410	22.6	0.97	(0.96 , 0.99)	0.01	0.98	(0.96 , 1.00)	0.04
At School (Self Completion)									
Locus of Control[5]	43	4,542	20.4	0.94	(0.90 , 0.99)	0.03	0.94	(0.89 , 1.01)	0.08
Self Esteem[6]	44	4,554	20.1	0.93	(0.89 , 0.98)	0.01	0.94	(0.89 , 0.98)	0.01
Psychological factors at age 16									
Child Behaviour at Home (Rutter A)									
Total Score	32	3,683	35.5	1.13	(1.08 , 1.18)	<0.01	1.10	(1.06 , 1.15)	<0.01
Hyperactive	31	3,621	36.6	1.55	(1.26 , 1.91)	<0.01	1.43	(1.21 , 1.69)	<0.01
Emotional problems	31	3,650	36.1	1.23	(1.04 , 1.46)	0.02	1.16	(1.01 , 1.35)	0.04
Conduct Problem	32	3,652	36.0	1.28	(1.17 , 1.39)	<0.01	1.21	(1.13 , 1.29)	<0.01

1 Number of women who reported having had cervical cancer; 2 Women who did not report any case of cervical ca

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

5 Higher scores indicate greater internalization; 6 Higher score indicate higher self-esteem.

* For the rest of psychological measures, higher score indicate worse conditions of behavioural maladjustment.

Table 5-24: The effect of childhood social, health behaviour, and cognitive measures on the risk of cervical cancer between ages 17 and 30 in the BCS70: Incident rates and age-adjusted corrected odds ratios.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Mother's age at delivery			7.7						
<21	17	1,040							
22-25	13	1,719		0.47	(0.23 , 0.97)	0.04	0.47	(0.23 , 0.98)	0.04
26-30	19	1,518		0.76	(0.40 , 1.47)	0.42	0.74	(0.39 , 1.43)	0.37
31+	6	981		0.40	(0.16 , 1.01)	0.05	0.40	(0.16 , 1.02)	0.06
Maternal smoking during pregnancy			7.4						
Non-Smoker	26	3,198							
Smoker	29	2,080		1.71	(1.01 , 2.90)	0.05	1.65	(0.97 , 2.78)	0.06
Parity			7.5						
No prev aft 28wks	21	2,035							
1 After 28wks	20	1,735		1.12	(0.61 , 2.07)	0.72	1.15	(0.62 , 2.14)	0.65
2 after28wks	5	865		0.61	(0.23 , 1.61)	0.32	0.66	(0.25 , 1.76)	0.41
3+ after 28wks	9	639		1.41	(0.65 , 3.08)	0.39	1.40	(0.64 , 3.06)	0.40
Social class of mother's husband			6.5						
I or II	8	1,579							
III non-manual	6	512		2.36	(0.82 , 6.81)	0.11	2.15	(0.72 , 6.41)	0.17
III Manual	30	2,406		2.34	(1.07 , 5.11)	0.03	2.28	(1.03 , 5.04)	0.04
IV or V	10	836		2.33	(0.92 , 5.90)	0.08	2.14	(0.84 , 5.48)	0.11
Birthweight			7.5						
<2.5	5	319							
upto 3	18	1,137		0.94	(0.35 , 2.54)	0.90	0.94	(0.35 , 2.53)	0.90
upto 3.5	20	2,190		0.54	(0.20 , 1.44)	0.22	0.58	(0.22 , 1.55)	0.28
upto 4	10	1,315		0.46	(0.16 , 1.36)	0.16	0.48	(0.16 , 1.40)	0.18
>4	2	313		0.48	(0.09 , 2.45)	0.37	0.46	(0.09 , 2.38)	0.36
Breastfed			19.2						
No	32	2,835							
Under 1 month	7	739		0.89	(0.39 , 2.01)	0.77	0.94	(0.41 , 2.15)	0.89
Over 1 month	9	1,036		0.80	(0.38 , 1.68)	0.56	0.83	(0.38 , 1.81)	0.63
Mother's Education			22.0						
No Qualification	28	2,380							
Vocational, O-level	14	1,529		0.79	(0.42 , 1.50	0.47	0.77	(0.41 1.45	0.42
A Level +	6	540		1.01	(0.42 , 2.43)	0.99	0.93	(0.39 , 2.20)	0.87
Father's Education			22.9						
No Qualification	23	1,896							
Vocational, O-level	15	1,194		1.05	(0.55 , 2.00)	0.89	1.04	(0.53 2.06)	0.90
A Level +	4	1,081		0.34	(0.12 , 0.98)	0.05	0.39	(0.13 , 1.20)	0.10
No Male hhh	5	222		1.99	(0.76 , 5.25)	0.16	1.84	(0.70 , 4.85)	0.22

1 Cervix cancer cases; 2 Women who did not report any case of cervical cancer; 3 % of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

Adulthood psychological factors

Those who reported psychological distress at age 26 and 30 assessed by Malaise inventory as well as those who had higher scores on the GHQ12 at age 30 were at a higher risk of cervical cancer as compared to those who did not report psychological distress (Table 5-25).

Table 5-25: The risk of cervical cancer between ages 17 and 30 years old in the BCS70: Cervical cancer incident rates and age-adjusted corrected odds ratios for mid life psychological factors.

				Age-adjusted OR(95% CI)					
	N_C[1]	N_{CF}[2]	M[3]	Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological distress at 26 yrs (Malaise Inventc			26.9						
Normal	24	3,499							
Depressed	10	676		2.23	(1.06 , 4.65)	0.03	2.18	(1.13 , 4.21)	0.02
Psychological distress at 30 yrs (Malaise Inventc			0.8						
Normal	37	4,847							
Depressed	19	811		3.09	(1.78 , 5.38)	<0.01	3.08	(1.77 , 5.35)	<0.01
GHQ12 at 30 years	56	5,660	0.7	1.06	(1.01 , 1.12)	0.01	1.06	(1.01 , 1.12)	0.01

1 Number of women who reported having had cervical cancer

2 Women who did not report any case of cervical cancer

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Adulthood risk behaviours

The odds ratios and 95% CIs for the age-adjusted univariable effects of adulthood risk behaviours on the risk of cervical cancer for the BCS70 are summarised in Table 5-26. Partnership (cohabitation or marriage) was defined as a continuous period spent living with the same partner. The risk for cervical cancer was almost 4-fold (OR=3.65, 95% CI= 2.12-6.29) for women who had reported having more than two partners between age 16 and age 30 as compared to women who had no or one partner. Also those who were smokers at age 30 had an increased risk of cervical cancer compared to the non-smokers. Those who had attained A-level or higher education qualification had a reduced risk; however, women's own social class did not show any statistical significance. Physical activity at age 30 and alcohol consumption at age 23 were also not significant predictors of cervical cancer risk at age 30.

Table 5-26: The risk of cervical cancer between ages 17 and 30 years old in the BCS70: Cervical cancer incident rates and age-adjusted corrected odds ratios for mid life risky health behaviours.

	N_C[1]	N_{CF}[2]	M[3]	Age-adjusted OR(95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
# of partners (cohabiting or married)			3.0						
0-1	31	4,583							
2+	24	948		3.74	(2.19 , 6.41)	<0.01	3.65	(2.12 , 6.29)	<0.01
Alcohol consumption at age 23			29.1						
None	16	1,315							
Light	3	923		0.31	(0.09 , 1.05)	0.06	0.55	(0.20 , 1.54)	0.26
Medium	9	1,621		0.47	(0.21 , 1.06)	0.07	0.56	(0.27 , 1.13)	0.11
Heavy	4	194		1.84	(0.61 , 5.49)	0.28	1.31	(0.49 , 3.49)	0.59
Educational level at age 26			30.9						
No qualification	3	164							
CSE 2-5/equiv nvq1	1	655		0.12	(0.01 , 1.13)	0.06	0.56	(0.13 , 2.39)	0.44
O level/equiv nvq2	19	1,720		0.53	(0.16 , 1.78)	0.30	0.70	(0.21 , 2.32)	0.56
A level and Higher	5	1412		0.18	(0.04 , 0.77)	0.02	0.27	(0.08 , 0.95)	0.04
Social class at age 30			2.4						
I or II: Proff/Manager	11	1,863							
III: Skilled Non-manual	26	2,216		1.93	(0.95 , 3.91)	0.07	1.85	(0.92 , 3.74)	0.09
III: Skilled manual	7	489		2.46	(0.95 , 6.36)	0.06	2.29	(0.88 , 5.92)	0.09
IV or V: Partly/ Unskilled	11	999		1.86	(0.81 , 4.30)	0.14	1.74	(0.76 , 4.00)	0.19
Smoking at age 30			0.0						
Never smoked	8	2,653							
Used to smoke	12	1,124		3.45	(1.41 , 8.43)	0.01	3.45	(1.41 , 8.43)	0.01
Smokes occasionally	4	417		3.35	(1.01 , 11.12)	0.05	3.35	(1.01 , 11.12)	0.05
Smokes everyday < 1 pkt	15	1,099		4.37	(1.85 , 10.30)	<0.01	4.37	(1.85 , 10.30)	<0.01
Smoked everyday 1+ pkts	17	409		13.14	(5.67 , 30.45)	<0.01	13.14	(5.67 , 30.45)	<0.01
Physical Exercise at age 30			0.0						
No	12	1,253							
Yes	44	4,447		1.00	(0.53 , 1.90)	0.99	1.00	(0.53 , 1.90)	0.99
BMI at age 30			3.4						
Underweight	5	198		2.99	(1.16 , 7.68)	0.02	2.89	(1.13 , 7.43)	0.03
Normal	32	3,487							
Overweight	10	1,214		0.93	(0.46 , 1.89)	0.84	0.91	(0.45 , 1.85)	0.80
Obesity	9	608		1.67	(0.80 , 3.51)	0.17	1.67	(0.79 , 3.49)	0.18

1 Number of women who reported having had cervical cancer

2 Women who did not report any case of cervical cancer

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Table 5-27: The adjusted effects (Odds ratios and 95% CI) of childhood psychological factors on cervical cancer risk between ages 17 and 30 in the BCS70.

	Age and confounders-adjusted OR(95% CI)[1]					
	Complete Cases			MI[2]		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological factors at age 5*						
Child Behaviour at Home (Rutter A)						
Total Score	1.06	(1.00 , 1.12)	0.04	1.06	(1.00 , 1.13)	0.04
Hyperactive	1.21	(1.01 , 1.45)	0.04	1.20	(1.01 , 1.42)	0.04
Emotional problems	1.05	(0.91 , 1.22)	0.48	1.04	(0.90 , 1.20)	0.61
Conduct Problem	1.11	(0.99 , 1.24)	0.07	1.13	(1.00 , 1.27)	0.04
Psychological factors at age 10						
Child Behaviour at Home (Rutter A)						
Total Score	1.01	(0.98 , 1.04)	0.44	1.02	(0.99 , 1.04)	0.21
Hyperactive	1.01	(1.00 , 1.03)	0.03	1.01	(1.00 , 1.03)	0.02
Emotional problems	1.00	(0.98 , 1.02)	0.91	1.00	(0.98 , 1.01)	0.87
Conduct Problem	1.00	(0.98 , 1.03)	0.88	1.01	(0.98 , 1.03)	0.64
At Home (Conners'Mother self completion)						
Impulsive	1.01	(0.99 , 1.03)	0.47	1.01	(0.99 , 1.03)	0.45
Hyperactive/Inattention	1.02	(1.00 , 1.03)	0.05	1.02	(1.00 , 1.03)	0.03
Clumsy	0.99	(0.96 , 1.02)	0.65	0.99	(0.97 , 1.02)	0.65
Poor Motor Coordination	0.99	(0.94 , 1.04)	0.64	0.99	(0.95 , 1.03)	0.56
At School (Child Development Behaviour)						
Antisocial Behaviour	1.05	(1.02 , 1.09)	<0.01	1.05	(1.02 , 1.08)	<0.01
Disorganised activity	1.05	(1.01 , 1.09)	0.01	1.05	(1.02 , 1.09)	<0.01
Neurotism/Anciety	1.04	(1.02 , 1.07)	<0.01	1.04	(1.01 , 1.07)	0.01
Clumsiness	1.05	(1.01 , 1.09)	0.02	1.03	(0.99 , 1.07)	0.10
Poor hand-Eye Coordination	0.96	(0.93 , 0.99)	0.01	0.97	(0.94 , 1.00)	0.03
Hyper/Kinesis	1.03	(0.99 , 1.07)	0.18	1.03	(0.98 , 1.07)	0.21
Introversion/Extroversion	1.01	(0.98 , 1.03)	0.56	1.01	(0.99 , 1.04)	0.38
Behavioural Trauma	1.04	(0.95 , 1.14)	0.40	1.03	(0.94 , 1.14)	0.51
Dressing	0.98	(0.96 , 1.00)	0.02	0.98	(0.96 , 1.00)	0.04
At School (Self Completion)						
Locus of Control[3]	0.96	(0.91 , 1.02)	0.16	0.96	(0.89 , 1.03)	0.24
Self Esteem[4]	0.94	(0.89 , 0.99)	0.01	0.95	(0.90 , 1.00)	0.03
Psychological factors at age 16						
Child Behaviour at Home (Rutter A)						
Total Score	1.13	(1.07 , 1.20)	<0.01	1.09	(1.05 , 1.14)	<0.01
Hyperactive	1.56	(1.23 , 1.97)	<0.01	1.39	(1.17 , 1.66)	<0.01
Emotional problems	1.23	(1.04 , 1.47)	0.02	1.14	(0.98 , 1.32)	0.10
Conduct Problem	1.30	(1.17 , 1.44)	<0.01	1.19	(1.11 , 1.29)	<0.01

1 Adjusted for the effect of maternal age at delivery, maternal smoking and social class of the father.

2 Analysis based on combined results of 10 multiple-imputed datasets

3 Higher scores indicate greater internalization; 4 Higher score indicate higher self-esteem.

* For the rest of the psychological measures, higher score indicate worse conditions of hehavioural maladjustment.

Multivariable models

Among the several possible confounders tested, only maternal age at delivery, maternal smoking, and social class of the father turned out to be significant and were adjusted for in a multivariable model. The same pattern of association between childhood psychological factors and cervical cancer was observed after adjusting for these possible confounders as for the unadjusted models (Table 5-27).

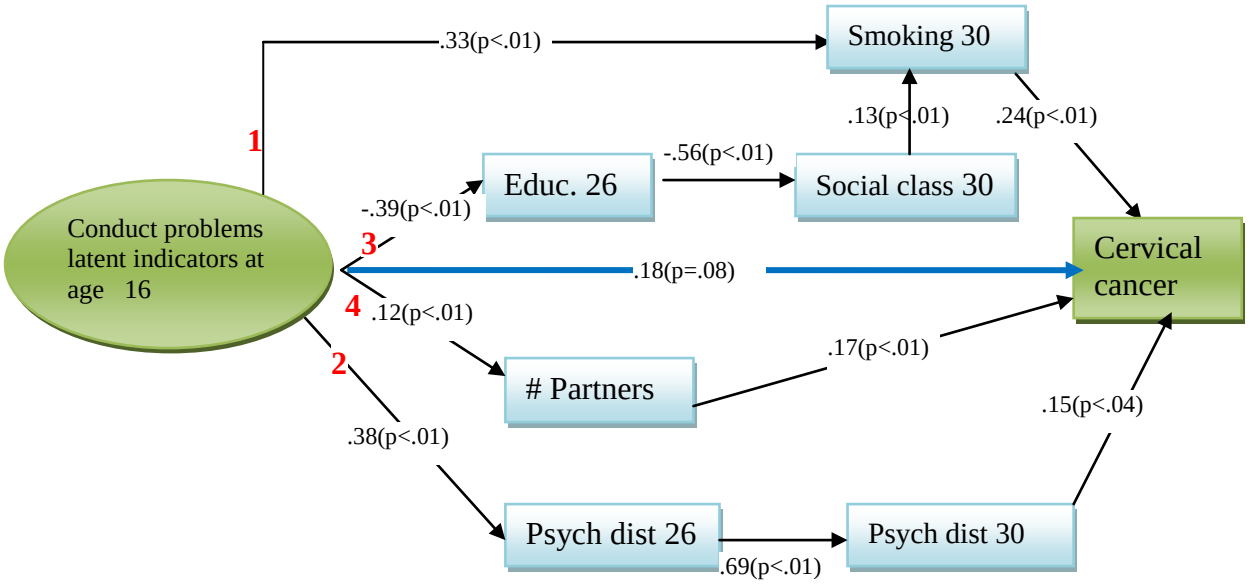


Figure 5-4: direct and indirect effects (standardized coefficients and significance p-values) of the latent psychological variables on the risk of cervical cancer between age 17 and 30 years in the BCS70.

The coefficients shown on the figure are for the conduct problems at age 16 years. RMSEA (Root Mean Square Error of Approximation) estimate = 0.03, CFI = 0.96, TLI = 0.97. Number of partners used as a continuous measure. The arrows are indicative rather than implying a chronological, directional relationship.

Possible mediation effect

Figure 5-4 presents the path estimates for the direct and indirect effects of childhood psychological factors on the risk for cervical cancer between age 17 and 30 years. The estimates shown are for the effects of conduct problems at home assessed by the mother at age 16 years. Even though there was no direct effect between conduct problems measured at age 16 and the subsequent development of cervical cancer after age 16, all the indirect path coefficients were significant showing that all its effects are mediated by other mid life behavioural and psychological factors. Table 5-28 presents the direct and

indirect effects (standardized coefficients and significance p-values) of a subset of the latent psychological variables on the risk of cervical cancer between ages 16 and 30 years. All the age 10 children's development scale measures did not show any significant direct or indirect effect and their results have been omitted from the table. None of the childhood psychological factors had a direct effect on cervical cancer when the possible mediators were introduced in the model. However, a few of the variables (shown in Table 5-28) had significant total effect on cervical cancer despite not having a direct effect.

Table 5-28: Direct and indirect effects (standardized coefficients and significance p-values) of the latent childhood psychological factors on the risk of cervical cancer in the BCS70.

	Direct Effect		Specific Indirect Effect								Tot. Indirect		Total Effect		
			Path 1[1]		Path 2[2]		Path 3[3]		Path 4[4]						
	Est.	Sig.	Est.	Sig.	Est.	Sig.	Est.	Sig.	Est.	Sig.	Est.	Sig.	Est.	SE	Sig.
Age 5 (Rutter A)															
Hyperactive	0.08	0.27	0.04	<0.01	0.04	0.01	0.01	<0.01	0.01	0.03	0.09	<0.01	0.18	(0.07)	0.01
Emotional problems	0.06	0.40	-0.02	0.03	0.02	0.01	0.01	<0.01	0.002	0.54	0.01	0.33	0.07	(0.07)	0.30
Conduct problems	0.06	0.44	0.06	<0.01	0.04	0.01	0.01	<0.01	0.01	0.01	0.12	<0.01	0.18	(0.07)	0.01
Age 10 School (Self completion)															
Locus of control	0.01	0.81	-0.10	<0.01	-0.06	0.01	-0.01	0.05	-0.02	<0.01	-0.19	<0.01	-0.18	(0.09)	0.03
Self esteem	-0.06	0.74	-0.12	<0.01	-0.05	0.08	-0.004	0.07	-0.03	<0.01	-0.21	<0.01	-0.26	(0.12)	0.03
Age 16 (Rutter A)															
Hyperactive	0.15	0.13	0.07	<0.01	0.043	0.04	0.01	<0.01	0.004	0.32	0.08	<0.01	0.30	(0.08)	<0.01
Emotional problems	0.12	0.17	0.02	0.01	0.051	0.01	0.01	<0.01	0.001	0.64	0.08	<0.01	0.20	(0.08)	0.01
Conduct problems	0.18	0.08	0.08	<0.01	0.04	0.04	0.01	<0.01	0.02	0.88	0.15	<0.01	0.32	(0.08)	<0.01

1 Through adult smoking behaviour at age 30.

2 Through mid life psychological distress at age 26 and age 30.

3 Through education achievement at age 26, social class at age 30 and adulthood smoking behaviour at age 30.

4 Through the number of cohabiting or marriage partners from age 16 to age 30.

Chapter 6

Cancer: Discussion and Conclusion

This section examined whether there is a temporal relationship between psychological factors measured in early life and the development of cancer in middle age and whether such associations can be explained by pre-existing physical, social, and environmental confounding factors. Further, an existing theoretical model of the link between psychological factors and cancer onset was tested to see whether such associations are mediated by biological, behavioural, social, and cognitive pathways. This enabled us to test not only the direct association between childhood psychological factors with later cancer onset but also possible pathways with potential intermediaries or confounding factors. This was achieved by testing for both the direct and indirect effects using structural equation models.

When examined separately in the univariable models, the presence of most of the childhood emotional and behavioural difficulties were associated with elevated risk of both cervical cancer and overall cancer. Their effect persisted, though diminished when potential childhood confounders were introduced in the model. However, their direct effects were eliminated when the adulthood social and health risky behaviours were introduced in the model as mediators. Thus, this study found no evidence that early life psychological factors are associated with the development of cancer after adjusting for the other known risk factors for cancer. This is in line with other large prospective studies that have found no association between neuroticism and other psychological distress and the risk of being diagnosed with cancer during the later years of follow-up after adjusting for other potential confounders (Nakaya *et al.*, 2003; Hansen *et al.*, 2005; Surtees *et al.*, 2010). However, most of the studies that have investigated the role of psychological distress in cancer onset have used the adulthood psychological measures (Garssen, 2004), unlike in this study where childhood psychological measures have been used.

Although there was no direct effect of the early life psychological factors in predicting cancer risk in the presence of the well known risk factors, these factor contributed to an elevated risk of cancer indirectly through different pathways. The first pathway explored the effect of each psychological factor on cancer risk, mediated by effect of mid-teenage

smoking behaviour at age 16 and smoking at age 42 years. This is predominantly a behavioural pathway since the effects of the psychological factors are mediated by risky smoking behaviour in mid-teenage which would continue to adulthood. This can be explained by the findings from studies that have associated psychological factors such as stress and associated distress or depression, low self esteem, and externalised locus of control with the initiation of smoking and with maintenance of the behaviour (Bonaguro and Bonaguro, 1987; Covey and Tam, 1990; Byrne *et al.*, 1995). This would eventually lead to higher risk of cancer since smoking is an established risk factor for cancer (Stewart and Kleihues, 2003). Paths 3 and 4 in our models are predominantly social and behavioural pathways whereby adverse childhood behavioural maladjustment, adjusted for the potential childhood confounding factors, influences adulthood education as well as socioeconomic position, which may foster risky health behaviour such as smoking and alcohol consumption, thereby increasing the risk for cancer.

Another pathway and the one that had the most significant effects was the one through adulthood psychological factors, in which the childhood psychological problems continue into adulthood and their effect over the life course increase the risk of cervical and overall cancer. This pattern shows the continuities over time in individual emotional and behavioural difficulties. Other studies have found that childhood emotional and behavioural difficulties especially the conduct disorder predicts depression and anxiety in adulthood (Moffitt *et al.*, 2002; David M. Fergusson, 2005; Colman *et al.*, 2009). The continuities from the adulthood psychological distress to cancer risk may be explained by the substantial biological plausibility of the association between psychological factors and the onset of cancer, primarily via alteration of the endocrine and the immune systems that has been demonstrated in many studies.

Even though there was no direct effect of the childhood psychological factors, this does not imply that they do not have an impact on the cancer risk. A more realistic measure would be the total effect of these variables which were found to significantly increase the risk of cancer onset, especially among the 16-year old measures.

Results also suggest that later psychological problems at age 16 may be more deleterious than earlier ones at ages seven and 11. A possible explanation is that psychological problems during adolescence may be particularly disturbing, since this is a time of major developmental transformations and life choices for youth including a choice and

decisions to leave school (Feldman and Elliott, 1992). A second reason may be the closer proximity to the young adulthood psychological factors and risky behaviours, and thus a greater likelihood of continuity. Another explanation could be the result of accumulation of psychological distress over the life course, where by age 16 the effects will be more pronounced as compared to the earlier ages.

Strengths and limitations

This study benefits from the use of two general population based cohorts of individuals followed from birth to adult life, representing a rare source of prospectively collected childhood data that can be linked with adult disease outcome. Since the childhood psychological factors were recorded before cancer onset, this provides firmer evidence regarding the temporal sequence between these factors and cancer onset. In addition, the use of such prospectively recorded data would limit the problem of recall bias. Also, a major strength of this study was the ability to consider a wide range of factors that might confound or mediate the relationship between psychological factors and cancer onset. These included physical, social, and environmental factors thought to be etiologically important such as smoking, alcohol use, BMI, family history of cancer, education, and adulthood social class besides other childhood measures.

Loss to follow up of those from disadvantaged groups is a common limitation of birth cohort studies. However, this may not be a major problem in this study based on the comparisons on several variables of the achieved sample with the target sample. However, as in all long-term cohort studies, the results were affected by missing data in terms of item non-response. This was of particular concern because the complete-records analyses would discard a lot of information thus reducing the statistical power. We dealt with the potential biases of such analyses by adopting two approaches, namely full information maximum likelihood and multiple imputation procedure. Both the methods rely on an assumption that the data are missing at random. To make such an assumption plausible, we used a very elaborate imputation model when generating the multiply-imputed datasets. These included all the variables considered in the analysis as well as those thought to be predictive of missingness of the key psychological measures which include data on parental and family characteristics, maternal education, abnormal health conditions in childhood, being overweight in childhood, child cognitive ability, not having a biological father present, being in special education, and neighbourhood type.

Overall, for most of the variables, the results obtained from the complete-records approach and the multiple imputation approach were similar in terms of conclusion.

In addition, the results drawn from the analysis of the two cohorts provides firmer evidence since such association are unlikely to be by chance. The use of advanced statistical methodologies appropriate for the analysis of this type of longitudinal data is also a major strength of this study.

The main weakness of this study, however, is the reliance on self reported illnesses which was not medically confirmed. The epidemiology of self reported illnesses may differ from that defined with operational diagnostic criteria. Similarly, participants who did not report the diagnosis may have been misclassified. Secondly, the two cohorts considered are still relatively young and would not be expected to have fully developed conditions like cancer which manifest themselves in earnest through middle-adulthood and into late-adulthood. As a result, the number of the individual cancers were still too few to permit an in depth examination of the site-specific relationships of psychological factors with cancer thus restricting us to analysing only one cancer site and an analysis based on all sites.

In spite of the above limitations, this study makes an important contribution in our knowledge of the pathways through which childhood psychological factors might influences young adult cancer onset. The study highlights the potentially complex roles of psychological distress in cervical cancer and overall cancer onset and demonstrates the relevance of the proposed theoretical model to understanding such relationships.

In conclusion, the overall picture that emerges from this study suggests that there is no significant direct effect of childhood psychological factors on cancer development but suggests an indirect effect through two major pathways- adulthood psychological distress which may exert its effects through the possible weakened immune system, and risky health behaviours, particularly cigarette smoking.

Future data availability and possibly linkage with the national cancer registries to confirm the cancer cases will undoubtedly prove helpful in the understanding of these relationships. Therefore, some of the unresolved issues in our analyses may be resolved in the later sweeps as the cohort ages.

SECTION III

TYPE 2 DIABETES MELLITUS

Chapter 7

Literature Review for Type 2 Diabetes Risk Factors

7.1. Introduction

Diabetes mellitus is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia (high blood glucose) with disturbances of carbohydrate, fat and protein metabolism resulting from impairment of insulin secretion, resistance to insulin action, or both (World Health Organization, 1999). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), diminished quality of life, and huge health care and personal costs (World Health Organization, 2006).

The clinical diagnosis of diabetes is often prompted by symptoms such as increased thirst and urine volume (polyuria), recurrent infections, unexplained weight loss, blurring of vision, and, in severe cases (when it leads to the development of ketoacidosis or a non–ketotic hyperosmolar state), drowsiness, stupor and coma (World Health Organization, 1999). The requirements for diagnostic confirmation for a person presenting with severe symptoms and gross hyperglycaemia differ from those of an asymptomatic person with blood glucose values found to be just above the diagnostic cut-off value. The diagnosis of diabetes in an asymptomatic subject is made on the basis of repeated confirmation of abnormal blood glucose value, either fasting, from a random (casual) sample, or from the oral glucose tolerance test (OGTT). For clinical purposes, an OGTT to establish diagnostic status need only be considered if casual blood glucose values lie in the uncertain range (i.e. between the levels that establish or exclude diabetes) and fasting blood glucose levels are below those which establish the diagnosis of diabetes.

An alternative to blood glucose estimation or the OGTT has long been sought to simplify the diagnosis of diabetes. Glycated haemoglobin (HbA_{1c}), reflecting average glycaemia over a period of weeks, was thought to provide such a test. In spite of giving equal or almost equal sensitivity and specificity to glucose measurement, HbA_{1c} is not currently

considered a suitable standard diagnostic test for diabetes or intermediate hyperglycaemia by WHO (World Health Organization, 2006). This is because it is not widely available in many parts of the world and given that its results can be influenced by several factors including anaemia, abnormalities of haemoglobin, pregnancy and uraemia. However, several researchers have argued for its diagnostic utility (Perry *et al.*, 2001). Most of the studies have recommended an HbA_{1c} cut-off point of > 6.1% as the optimum cut-off point (Bennett *et al.*, 2007); however, there is an argument for population-specific cut-off points since the optimum cut-offs vary by ethnic group, age, gender, and population prevalence of diabetes.

Pathophysiology and classification of diabetes

Several pathogenetic processes are involved in the development of diabetes. These include processes which destroy the beta-cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action wherein insulin is unable to move glucose into the cells where it can be used. Plasma glucose levels are regulated by the beta-cells of the pancreatic islets, which sense glucose levels in extracellular fluid and respond to raised levels by secreting insulin. Insulin lowers plasma glucose by stimulating uptake of glucose from blood and by suppressing production of glucose by the lever. Failure to keep plasma glucose down to normal levels implies that either the secretion of insulin is inadequate, or that there is a resistance to the action of insulin in lowering plasma glucose.

The classification of diabetes encompasses: clinical stages reflecting that diabetes progresses through several clinical stages during its natural history; aetiological types of diabetes mellitus resulting from improved understanding of the causes of diabetes mellitus; and other categories of hyperglycaemia (World Health Organization, 1999). Type 2 diabetes mellitus (T2DM), the commonest form of diabetes generally characterised by an older age onset, results from defect(s) in insulin secretion, almost always with a major contribution from insulin resistance. When one develops insulin resistance over time, the pancreas becomes unable to produce enough insulin to overcome the resistance. The consequence of this is an abnormal rise in blood sugar after meals, which ultimately impairs and possibly destroys the insulin-producing pancreatic beta-cells, thereby stopping insulin production completely and causing full-blown diabetes.

Type 1 diabetes, previously termed as insulin-dependent diabetes, on the other hand encompasses the majority of cases which are primarily due to pancreatic islet beta–cell destruction and are prone to ketoacidosis for which neither aetiology nor a pathogenesis is known (idiopathic) and its diagnosis is made most commonly in childhood. In Type 1 diabetes the "insulin is required for survival" to prevent the development of ketoacidosis, coma and death.

Other types of diabetes include gestational diabetes, defined as any degree of glucose intolerance with onset or first recognition during pregnancy regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy; and a group of other types of diabetes caused by specific genetic defects of beta-cell function or insulin action, diseases of the pancreas, or drugs or chemicals (American Diabetes Association, 2006).

Incidence and prevalence

Recent estimates indicate that the prevalence of diabetes for all age-groups worldwide was 2.8% in the year 2000 and is projected to rise to 4.4% in 2030 (Wild *et al.*, 2004). The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. However, these figures could be higher in some regions; for example, there is a greater diversity of diabetes prevalence in Europe partly explained by differences in known risk factors for T2DM at the population level in European countries (Rathmann and Giani, 2004). For Germany, a prevalence of 4.1% was estimated in the year 2000 corresponding to 2.6 million people (Rathmann *et al.*, 2003). In England, an epidemiological model was used to estimate the prevalence of total diabetes mellitus (diagnosed and undiagnosed) for all persons to be 4.4% in 2001, with T2DM estimated to affect 2,002,000 persons (92.3%) and Type 1 diabetes 166,000 persons (7.7%) (Merrick *et al.*, 2006). Other estimates from the UK show that diabetes prevalence increased from 2.8% in 1996 to 4.3% in 2005, with the incidence increasing from 2.71 (2.58–2.85)/1000 person-years to 4.42 (4.32–4.53)/1000 person-years during the same period (Gonzalez *et al.*, 2009).

There are a number of well known and established risk factors for diabetes but still they do not explain all the variance in the population. It is therefore important to identify other novel risk factors including the psychosocial factors that can lead to development

of new preventive measures. This chapter reviews the evidence that the risk of T2DM in adult life may be set by psychological factors operating early in the life course of an individual. After a review of the main and well established risk factors, much attention is directed to psychological factors influencing the onset and course of diabetes. A number of pathways through which psychological factors may cause T2DM are also reviewed.

The literature searches for the association between psychological factors and T2DM were conducted using Medline, Embase, PsycINFO, and Cochrane Library up to January 2010 together with the reference lists from the relevant review articles and meta-analyses. The main search strategy was a combination of the medical subject headings "Diabetes Mellitus" or "Diabetes Mellitus, Type 2," and "psycho* or stress or depress* or anxiety or personality or affective* or emotion". To be included, the article had to be in English language and on human subjects and mainly on prospective designs; however, a few cross-sectional studies with large sample size were included.

7.2. Known Risk Factors for Type 2 Diabetes

Despite the complexity in the pathogenesis of diabetes, a number of factors that increase the risk for the disease have been identified. Risk factors for T2DM are quite diverse and include both non-modifiable factors, and modifiable (lifestyle or environmental) factors. These are summarised in Figure 7-1. Both genetic and environmental factors are involved in the development of T2DM; first, you must inherit a predisposition to the disease, then something in your environment must trigger diabetes (Hamman, 1992). Non-modifiable risk factors for T2DM include family history (genetic predisposition), age, race or ethnicity, history of gestational diabetes, and low birth weight. Modifiable or lifestyle risk factors include amongst others increased body mass index (BMI), physical inactivity, poor nutrition, hypertension, smoking, and alcohol consumption.

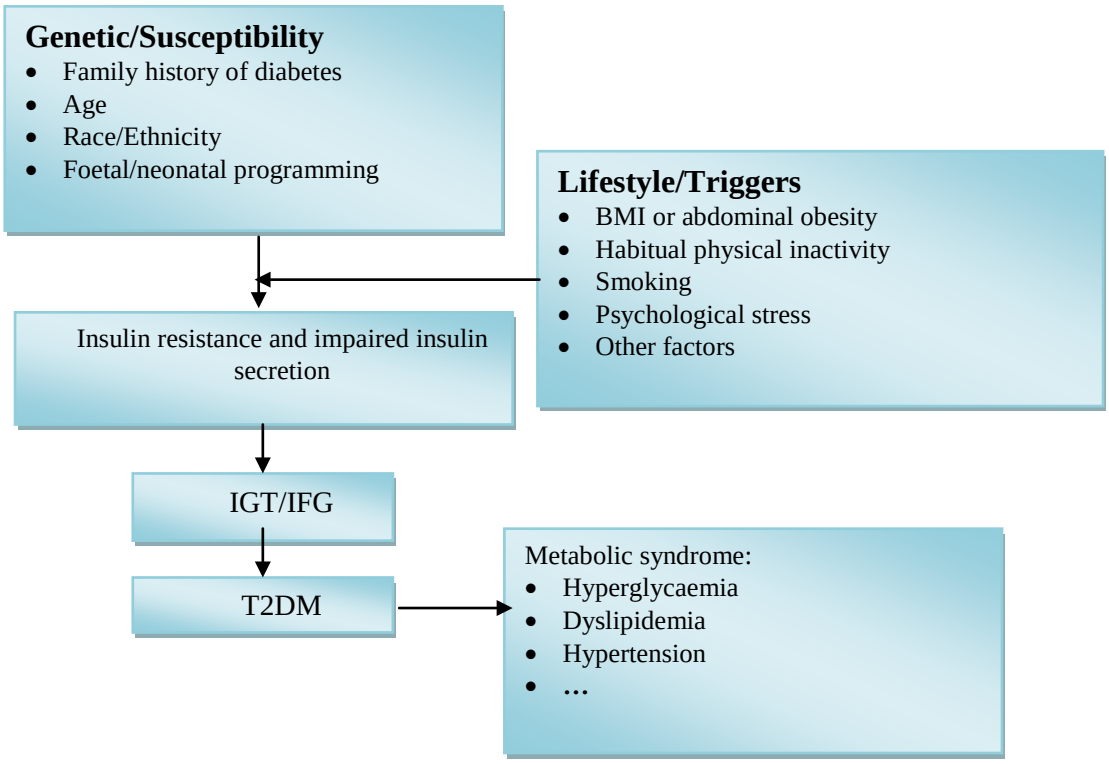


Figure 7-1: Risk factors for developing T2DM and the metabolic abnormalities associated with insulin resistance.
Diabetes and the metabolic syndrome develop when environmental trigger factors, such as obesity, cause insulin resistance and impaired insulin secretion in genetically or otherwise susceptible people. IGT = Impaired glucose tolerance; IFG = Impaired fasting glycaemia.

7.2.1. Non-modifiable factors

Genetics

Several lines of evidence suggest that T2DM has a substantial inherited component: twin studies have demonstrated higher concordance rates for T2DM in monozygotic than in dizygotic twins (Barnett *et al.*, 1981; Newman *et al.*, 1987; Kaprio *et al.*, 1992); family studies have revealed that first degree relatives of individuals with T2DM are at a much higher risk of developing the disease than individuals without a positive family history of the disease (Florez *et al.*, 2003; Gloyn, 2003; Hansen, 2003); gene mapping studies scanning the entire genome have demonstrated the participation of different chromosomal regions conferring susceptibility to develop diabetes (susceptibility loci) (Tusié Luna, 2005); and marked differences in the prevalence among various racial groups (Zimmet *et al.*, 1983; Knowler *et al.*, 1990). Thus, it is clear that T2DM has a strong genetic component.

Recently, there have been considerable progress in defining the predisposing genes for adults with T2DM using thousands of cases and controls and a collaborative genome-wide approach. However, the progress in identification of specific genetic variants predisposing to the disease has been limited, partly due to the complexity of the inheritance pattern where multiple genes are involved each contributing only a small amount. Only a small proportion of T2DM cases (5–10%) are caused by the alteration of a single gene, the monogenic (Bell and Polonsky, 2001). In contrast to the monogenic forms of diabetes which are usually expressed in all individuals carrying the mutation (complete penetrance), environmental factors play an important role in favouring or delaying the development of polygenic T2DM. In polygenic T2DM, the genes involved in the development of the disease (susceptibility genes) exert only a partial effect, thereby the sole effect of a single gene is not enough to cause diabetes (Tusié Luna, 2005). Only the additive effect of these genes, in certain combinations, confers genetic susceptibility and the disease develops only when the environmental risk factors favouring its expression are present.

Important discoveries have been made in dissecting the genes involved in rare monogenic forms of T2DM: maturity-onset-diabetes-of-the-young (MODY), which has become a paradigm for genetic studies of T2DM (Hansen, 2003; Moore and Florez, 2008; Grant *et al.*, 2009). The identification of diabetes susceptibility genes not only allows a better understanding of the many features that contribute to the pathophysiology but may also lead to progress in preventing diabetes and providing patients with better care. To date, more than 50 candidate genes for T2DM have been studied in various populations worldwide. However, the results for essentially all candidate genes have been conflicting due to the small sample sizes, differences in T2DM susceptibility across ethnic groups, variation in environmental exposures, and gene-environmental interactions.

Recent discoveries made via linkage analyses, candidate gene association studies, and genome-wide association (GWA) scans have unravelled the genetic architecture of complex traits and have greatly improved the understanding of the genetics of T2DM, and many studies have reviewed the candidate genes involved (Sladek *et al.*, 2007; Moore and Florez, 2008; Grant *et al.*, 2009; Stolerman and Florez, 2009). The GWA enable a global search throughout the nuclear genome for variants that are associated with specific phenotypes. Currently, single nucleotide polymorphisms in about 24

different genetic loci have been associated with T2DM (Stolerman and Florez, 2009). Therefore, understanding diabetes as a complex disease with different genetic causes will allow the identification of the most appropriate treatment and prognosis for each patient.

Age

It has long been recognized that the prevalence of T2DM increases with age, in fact, T2DM has been known for years as adult-onset or maturity-onset. In the past, the age of 45 years has been used as important cut-off point in estimating the prevalence of diabetes. Previous studies of the prevalence of diabetes worldwide have found the majority of people with diabetes to be in the age range of 45-64 years in developing countries, and 65 years or older in developed countries (King and Rewers, 1993; King *et al.*, 1998). While it is still true that this age-group maintains a higher risk than younger adults, evidence is accumulating that the onset in those aged under 30 years is increasing and is becoming an evolving epidemic (Alberti *et al.*, 2004; Bloomgarden, 2004). T2DM has already been reported in children in a number of countries, including UK where cases have been reported in adolescents aged 13 to 15 years (Drake *et al.*, 2002). In a study reporting the age- and sex-specific prevalence of diabetes in 13 studies from nine European countries (The Decode Study Group, 2003), the age-specific prevalence of diabetes rose with age up to the seventh and eight decades in both men and women in each study population. In most of the studies, the prevalence was <10% in subjects younger than 60 years of age and between 10 and 20% at 60–79 years of age. The rising cases of T2DM in young adults and children are blamed on current lifestyle patterns resulting to excess body weight and less physical activity.

Ethnicity

Significant racial/ethnic disparities exist in the prevalence of diabetes within the UK and the US, with racial and ethnic minorities disproportionately affected by T2DM and its complications. African-Caribbean or South Asian people who live in the UK are about three to five times more likely to have diabetes than the white European population (Nazroo, 1997). Similarly, African Americans and other ethnic minority groups suffer disproportionately from T2DM and its complications than do white Americans (Egede and Dagogo-Jack, 2005). Compared with the prevalence rate of diabetes in white Americans, the relative increase in the prevalence of T2DM is approximately one and-a-

half-fold in African Americans, two-and-a half-fold in Hispanic-Americans, three- to four-fold in Asian-Americans and Pacific Islanders, and ten-fold or greater in certain Native American ethnic groups (Dagogo-Jack, 2003). The exact reasons for the ethnic and racial differences in the incidence and prevalence of T2DM are not known with certainty. Both genetic susceptibility and acquired environmental factors (including cultural, behavioural and socioeconomic) are thought to contribute to the ethnic disparities in diabetes and its complications (Dagogo-Jack, 2003). Racial/ethnic factors can influence dietary behaviours and physical activity via multiple pathways that include genetic variations in risk among populations, cultural variations in the practice of self-regulation, familial beliefs and attitudes about diet and exercise and the accompanying dietary practices, community-level differences in risks and in access to resources, and national policies that result in the unequal distribution of access to healthy environments (Castro *et al.*, 2009). Other theories for the racial variation have been proposed, for example, from an eco-developmental perspective, cultural variables assessed at one level (e.g., family level dietary practices) may interact with other types of variables examined at other levels (e.g., the availability of healthy foods within a low-income neighbourhood), thus prompting the need for a clear analysis of these systemic relationships as they may increase risks for disease. Therefore, the need exists for models that aid in "mapping out" these relationships (Castro *et al.*, 2009).

Birthweight

Several studies have found an association between low birth weight and T2DM, the so-called "small baby syndrome hypothesis". In a recent meta-analysis of 14 studies involving a total of 132,180 persons (Harder *et al.*, 2007), both low birthweight (<2,500 g compared with a birth weight of ≥2,500 g) and high birth weight (>4,000 g compared with a birth weight of ≤4,000 g) were associated with increased risk of T2DM, with an OR of 1.32 (95% CI: 1.06- 1.64) and 1.27 (95% CI: 1.01- 1.59), respectively. Similar results were obtained in a recent systematic review of 31 studies with 6,090 diabetes cases and 152, 084 individuals (Whincup *et al.*, 2008).

Several mechanisms, both genetic and environmental, have been proposed to account for the association between low birthweight and T2DM (Forouhi *et al.*, 2004). The predominant explanation for this association has been the so-called foetal origins hypothesis, which suggests that foetal malnutrition induces adaptive changes in foetal

glucose metabolism such as impaired development of β-cells leading to impaired insulin secretion, that become lasting, thereby contributing to an increased risk of T2DM in adult life (Hales *et al.*, 1991; Forouhi *et al.*, 2004). The effect of preterm birth as a possible mediator of the association between low birthweight and T2DM has also been investigated. A recent cohort study investigating separately the contribution from both the poor foetal growth and preterm birth (Kaijser *et al.*, 2009) found both the factors as important contributors to the risk of T2DM in adult life. The underlying programming mechanisms seem to involve both the prenatal and postnatal factors where the effects of prenatal factors are modified by subsequent growth (Forouhi *et al.*, 2004; Kaijser *et al.*, 2009). Moreover, there may be potential effect of confounding especially by BMI and socioeconomic status in the relationship between birthweight and T2DM.

Gestational diabetes mellitus

Gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with its onset or first recognition during pregnancy, has been shown to induce long-term effects in offspring. Offspring of mothers with GDM are at increased risk of developing T2DM. In studies of the Pima Indians, a population with a very high prevalence of T2DM, it has been reported that the adult offspring of women with GDM have a markedly increased risk for diabetes (Pettitt *et al.*, 1991; Dabelea and Pettitt, 2001). In another study among the Danish population, where the prevalence of T2DM in children and young adults is generally low, the offspring of women with GDM had an almost 8-fold increased risk of diabetes/pre-diabetes after correction for other confounders (Damm, 2009). A host of other studies as summarised in a recent review (Simeoni and Barker, 2009) have added to the accumulating evidence of the lifelong consequences of diabetes in pregnancy in the risk T2DM in offspring. The mechanisms are not well known: one of the explanations for such association is the consequences of GDM on the anthropometric and metabolic alteration. Glucose crosses the placenta and maternal hyperglycaemia during pregnancy results in increased glucose concentrations in the foetus leading to excess foetal growth (Dabelea and Pettitt, 2001; Simeoni and Barker, 2009). It could also be a consequence of the long-term effects of in-utero exposure to a continuous range of high glucose concentrations throughout pregnancy (Simeoni and Barker, 2009).

Women with gestational diabetes have also been found to have an increased risk of developing T2DM in later life. In a recent systematic review and meta-analysis of 20 prospective cohort studies involving 675,455 women and 10,859 T2DM events, (Bellamy *et al.*, 2009) women with GDM had an increased risk of developing T2DM compared with those who had a normoglycaemic pregnancy (RR 7·43, 95% CI= 4·79–11·51). These findings have been supported by studies in another review (Simmons, 2009). Thus there is an accumulating body of consistent evidence from epidemiological studies of an association between GDM and future risk of T2DM.

7.2.2. Modifiable factors

Several modifiable or lifestyle factors affect the incidence of T2DM. Among the well known modifiable factors are obesity and weight gain, physical inactivity, poor nutrition, smoking, and alcohol use.

Obesity, physical inactivity and, sedentary lifestyle

Obesity has been consistently shown to be one of the strongest risk factor for development of diabetes (Colditz *et al.*, 1995; Hu *et al.*, 2001b; Costacou and Mayer-Davis, 2003; Yan *et al.*, 2006; Vazquez *et al.*, 2007). Evidence of this association comes from various sources: the prevalence of T2DM increases in proportion with the level of obesity in the population; and the risk of T2DM increases exponentially with an increase in various obesity measures. Epidemiological studies have demonstrated that different anthropometric measures for obesity such as body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-stature ratio (WSR) are strong and independent predictors of T2DM, however, there has not been any consensus on which measure is the best predictor. Several cohort studies that have compared different anthropometric measurements with regard to diabetes risk prediction from different populations suggest that anthropometric measurements that describe central fat distribution, in particular waist circumference, may be superior to measurements of general adiposity (Kaye *et al.*, 1991; Wei *et al.*, 1997; Stevens *et al.*, 2001; Rosenthal *et al.*, 2004; Schulze *et al.*, 2006). However, other studies have not confirmed these observations with some finding equal predictive powers (Wang *et al.*, 2005; Janghorbani and Amini, 2009; Nyamdorj *et al.*, 2009) and others have found BMI to be a better predictor (Tulloch-Reid *et al.*, 2003). Despite these inconsistent results in comparing the

anthropometric measures it should be noted that the BMI and WC are very highly correlated and likely to behave similarly in diabetes prediction. Besides, studies that found differences in their predictive power found very minimal differences, which were not significant based on the pooled estimates from a meta analysis (Vazquez *et al.*, 2007), thus, these three obesity indicators may have similar associations with incident diabetes.

The mechanisms linking obesity, insulin resistance and T2DM are complex and not fully understood. A prevalent theory is that being overweight causes cellular changes that lead to insulin resistance. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance (Kahn *et al.*, 2006). However, most obese, insulin-resistant individuals do not develop hyperglycaemia, which requires contribution from both insulin resistance and islet β-cell dysfunction. Thus, obesity alone is neither a necessary nor sufficient condition for the development of T2DM. Under normal conditions, the pancreatic islet β-cells increase insulin release sufficiently to overcome the reduced efficiency of insulin action, thereby maintaining normal glucose tolerance (Perley and Kipnis, 1966; Kahn *et al.*, 2006). For hyperglycaemia to exist in Type 2 diabetes, β-cell dysfunction has to be present (Kahn, 2001); probably the ß-cell work harder than normal in case of insulin resistance to keep blood sugar levels regulated, thereby causing the cells to gradually fail. Abnormalities in β-cell function are therefore critical in defining the risk and development of T2DM. Islet β-cell failure in T2DM occurs when islets are unable to sustain β-cell compensation for insulin resistance (Prentki and Nolan, 2006).

Other mechanisms have also been proposed: resistin, a putative adipocyte-derived signalling polypeptide, has been implicated in the pathogenesis of obesity-mediated insulin resistance and T2DM, at least in rodent models, but its relevance to human diabetes is yet to be confirmed (Kusminski *et al.*, 2005). Besides being a major risk factor for T2DM, obesity also makes a significant contribution to the morbidity and mortality associated with T2DM, largely through its contribution to cardiovascular disease.

Epidemiologic evidence also strongly supports the role of exercise in preventing obesity and T2DM. Consistent findings from various studies show that lower levels of physical

activity increase a person's risk for diabetes. Prospective cohort studies have shown that increased physical activity, independent of other risk factors, has a protective effect against the development of T2DM. A recent review of 10 prospective cohort studies investigating moderate-intensity physical activity and diabetes in a total of 301,221 participants and 9,367 incident cases has provided evidence that people who achieve recommended levels of even moderate activity such as brisk walking are about 30% less likely (RR= 0.69, 95% CI= 0.58–0.83) to develop diabetes than their inactive counterparts even after adjusting for BMI (Jeon *et al.*, 2007). There is additional evidence that as frequency and intensity of physical activity increase, the risk of incident diabetes decreases (Perry *et al.*, 1995). A recent review assessing the effects of exercise or exercise and diet for preventing T2DM in participants with impaired glucose tolerance or the metabolic syndrome, however, did not find sufficient data on exercise alone for diabetes prevention (Orozco *et al.*, 2008).

Physical activity, besides leading to weight loss, has a beneficial effect on insulin sensitivity and glucose tolerance in normal as well as insulin resistant populations. Just like insulin, exercise leads to the activation of glucose transport, which perhaps explains why humans with insulin resistance can increase muscle glucose transport in response to an acute bout of exercise (Goodyear and Kahn, 1998). Insulin or exercise, utilizing different signalling pathways, can induce a rapid increase in glucose uptake by translocation of pre-existing GLUT4 glucose transporters from endosomal compartments to surface membranes (Sato, 2000; Khayat *et al.*, 2002; Zorzano *et al.*, 2005).

Studies have also found a link between sedentary behaviours such as excessive television watching or prolonged computer use and T2DM. Findings from two prospective cohort studies, the Nurses' Health Study and the Health Professionals' Follow-up Study, indicate that as the number of hours of sedentary behaviour increase per day or per week, the risk of diabetes increases independently of any reduction in physical activity (Hu *et al.*, 2001a; Hu *et al.*, 2003). After adjusting for age, smoking, alcohol use, and other covariates in the Nurses' Health Study, the relative risks of T2DM across increasing quintiles of MET-h/wk were 1.0, 0.78, 0.65, 0.58, and 0.51 (p for trend < 0.001). Another study, the Black Women's Health Study in the USA (Krishnan *et al.*, 2009), also found that television watching was associated with an increased T2DM risk among 45,668 black women aged 21–69 years; during 10 years of follow-up with 2,928 incident cases, the incidence rate ratio was 1.86 (95% CI= 1.54-2.24) for ≥5 hours relative to <1 hour of

television per day, independent of physical activity. These findings suggest the importance of reducing sedentary behaviour in preventing T2DM.

Diet

Diet and lifestyle modification such as increased physical activity are widely considered as the primary means to control weight and reduce obesity. These strategies to reduce obesity also have a beneficial effect on the prevalence of T2DM, as excess adiposity (particularly central adiposity) is a strong risk factor for the condition. Besides its role in weight loss, the dietary strategies that preserve β-cell function by improving insulin sensitivity (improve glucose and lipid metabolism) and reducing the degree of postprandial glycaemia (unusual amount of blood glucose following a meal), or insulinemia (insulin demand), are likely to be beneficial in diabetes prevention considering the mechanisms of diabetes development (Brand-Miller, 2004; Buyken *et al.*, 2010).

Epidemiological evidence suggests that several dietary patterns, particularly those that have abundant plant food content, low in fat (particularly saturated fat), and high in fibre, wholegrain foods and other complex carbohydrates are effective in reducing the risk of developing diabetes (Marshall *et al.*, 1991; Williams *et al.*, 1999; Schulze *et al.*, 2007; Tonstad *et al.*, 2009; Wyness, 2009). Additionally certain individual food groups and components of the diet, such as high intake of monounsaturated fatty acids, fruits, vegetables, whole grain cereals, dietary fibre, fish, and a low intake of high-caloric soft drinks, beer, red meat, poultry, and processed meat, have been found to be protective against the development of diabetes in many populations (Heidemann *et al.*, 2005; Kastorini and Panagiotakos, 2009). However, studies examining the generalisability of dietary patterns have suggested that dietary patterns that predict T2DM risk in different populations may not be generalisable to different populations (Imamura, Fumiaki *et al.*, 2009).

There is however, some confusion on the role of diet when we consider the mechanisms of diabetes development. While replacing saturated fat with carbohydrate can improve insulin sensitivity and glucose tolerance, it can also increase postprandial hyperglycaemia and insulin demand, particularly in persons with insulin resistance (Brand-Miller, 2004). As a result of such confusion, it has been argued that the most

evidence-based dietary strategy for prevention of T2DM would involve alternative dietary approaches that reduce postprandial glycaemia and insulinaemia, without adverse effects on other risk factors (Buyken *et al.*, 2010). Since the level of postprandial glycaemia is dictated by both the quality and quantity of carbohydrate, the concept of glycaemic load (GL), defined as the product of the carbohydrate content per serving of food and its glycaemic index (GI), should be taken into consideration. Low-GI and/or low-GL diets have been shown to be independently associated with a reduced risk of diabetes in many studies. In a recent systematic review of 37 prospective cohort studies of GI and GL (Barclay *et al.*, 2008), significant positive associations were found in fully adjusted models of validated studies for T2DM (GI RR = 1.40, 95% CI= 1.23-1.59; GL RR = 1.27, 95% CI= 1.12-1.45) for the comparison between the highest and lowest quintiles of GI and GL.

Adherence to a healthy dietary pattern, like the Mediterranean diet, has also been found to exert a beneficial role regarding the development of diabetes (Champagne, 2009). The Mediterranean diet is characterised by high consumption of plant based foods which are rich in fibre and antioxidants such as fruits, vegetables, breads and cereals, fish, olive oil, beans, legume nuts, and seeds, and low consumption of meat products. Consumption of such a diet leads to high ingestion of dietary fibre, antioxidants, magnesium and unsaturated fatty acids (Schröder, 2007; Champagne, 2009). Such diets rich in fibre, antioxidants or polyphenols, lead to delayed gastric emptying and increased oxidative capacity, thus resulting to prevention of insulin resistance and pancreatic β-cell dysfunction. Additionally, this diet is characterized by a low degree of energy density overall, which might be particularly important for the prevention of weight gain.

Several mechanisms are thought to be responsible for the inverse association between the Mediterranean diet and the risks of the metabolic syndrome and T2DM or its complications. These involve the indirect effects through prevention of weight gain, and direct effect through prevention of insulin resistance and beta cell dysfunction (Schröder, 2007).

Thus diet is a viable preventive option for T2DM together with a lifestyle that includes sufficient physical activity. Healthy Mediterranean-style diets and low-GI/GL diets could now be recommended in place of conventional low-fat diets.

Cigarette smoking

Smoking has been shown to be an independent risk factor for T2DM in different populations. Results from both prospective cohort studies (Manson *et al.*, 2000; Wannamethee *et al.*, 2001; Will *et al.*, 2001; Foy *et al.*, 2005; Patja *et al.*, 2005; Cho *et al.*, 2009; Cullen *et al.*, 2009; Yeh *et al.*, 2010) and large population based cross-sectional studies (Beziaud *et al.*, 2004) show an enhanced risk of T2DM in current smokers as compared to non-smokers. Nicotine, acknowledged as the major pharmacologically active chemical in tobacco, has been shown to be responsible for the association between cigarette smoking and development of diabetes (Xie *et al.*, 2009).

In a recent systematic review and meta-analysis of 25 prospective cohort studies with 1.2 million participants and 45,844 incident cases of diabetes (Willi *et al.*, 2007), current smoking was associated with 44% increased risk of developing diabetes (RR =1.44 , 95% CI= 1.31-1.58), with the highest risk among the heavy smokers. The increased risk of diabetes observed in smokers remained significant on adjustment for potential confounders including BMI at baseline, alcohol use, race, amount of exercise, educational level and dietary intakes of fats and carbohydrate. Previous reviews of both cross-sectional and prospective studies have also shown consistent results of enhanced risk of T2DM in smokers as compared to non-smokers (Muhlhauser, 1994; Haire-Joshu *et al.*, 1999). However, a few prospective studies have not found such association, for example, prospective data from the British Regional Heart Study did not find any evidence after adjusting for other risk factors (Perry *et al.*, 1995).

Smoking cessation has been found to increases diabetes risk in the short term, possibly owing to cessation-related weight gain, but in the long term, the benefits of giving up smoking outweigh the adverse effects of early weight gain (Wannamethee *et al.*, 2001; Yeh *et al.*, 2010).

In sum, previous data on smoking and risk of diabetes and the evidence linking smoking with insulin resistance, have thus provided substantial evidence incriminating cigarette smoking as a cause of T2DM. However, there are still concerns about residual confounding, given that the effects of smoking on factors such as central obesity and on taste perception and diet may mediate (in part) the effect of smoking on risk of diabetes.

Alcohol consumption

Moderate alcohol intake has been found to be protective against the incidence of diabetes in both men and women in a number of cohort studies. In recent systematic review involving 20 cohort studies (Baliunas *et al.*, 2009), a U-shaped relationship was found for both sexes. Compared with lifetime abstainers, the RR for T2DM among men was most protective when consuming 22 g/day of alcohol (RR= 0.87, 95% CI= 0.76–1.00), but became deleterious at just over 60 g/day alcohol (RR= 1.01, 95% CI= 0.71–1.44]). Among women, consumption of 24 g/day alcohol was most protective (RR= 0.60 95% CI= 0.52–0.69) and became deleterious at about 50 g/day of alcohol (RR=1.02, 95% CI= 0.83–1.26). Previous studies and reviews have found similar relationship even after adjusting for possible confounders including age, BMI and smoking status (Wei *et al.*, 2000; Conigrave and Rimm, 2003; Howard *et al.*, 2004; Carlsson *et al.*, 2005; Koppes *et al.*, 2005; Djousse *et al.*, 2007; Seike *et al.*, 2008; Imamura, F. *et al.*, 2009; Kawamoto *et al.*, 2009). However, conflicting results have been found regarding high alcohol intake, but majority of the studies have found out that heavy alcohol intake is associated with an increased risk (Hodge *et al.*, 2006; Wandell *et al.*, 2007; Seike *et al.*, 2008). Therefore, like many other chronic diseases, there is a delicate balance between the harmful and beneficial effects of alcohol on the incidence of diabetes.

7.2.3. Other risk factors

There are a number of other factors that can increase the risk of developing T2DM. Emerging evidence suggests that exposure to environmental irritants, such as persistent organic pollutants, is associated with increased insulin resistance, the metabolic syndrome, and diabetes (Jones *et al.*, 2008). Women with polycystic ovary syndrome who are overweight have also been found to be at an increased risk of developing diabetes (De Leo *et al.*, 2004; Diamanti-Kandarakis *et al.*, 2008).

There are mixed findings concerning the roles of childhood cognitive ability on the risk of self-reported T2DM later in life. Studies using the British birth cohorts have given conflicting results: while Olsson *et al.* (2008) reported that impaired cognitive function (IQ at age 11 years) may precede clinical onset of T2DM at age 42 years in the 1958 NCDS, Batty *et al.* (2007) found no such association in the 1970 birth cohort.

Research has also shown that breastfeeding for at least two months is associated with between 10 to 40% reduction in the risk for the baby developing diabetes later in life. A recent systemic review of the published studies (Owen *et al.*, 2006) concluded that breastfeeding in infancy is associated with a reduced risk of T2DM, with marginally lower insulin concentrations in later life, and with lower blood glucose and serum insulin concentrations in infancy. This may be in part due to its effects in prevention of obesity in later life. Published analyses and reviews of the obesity research (Dewey, 2003; Harder *et al.*, 2005; Owen *et al.*, 2005a; Owen *et al.*, 2005b) have shown that to varying degrees, breastfeeding has a protective effect against later obesity and overweight, although residual confounding may exist.

A few studies have examined the association between age at menarche and menstrual pattern and the risk of diabetes. Such association might be expected since a higher BMI is associated with earlier menarche; however, studies have given conflicting results. In a study using two large prospective data, the Nurses' Health Study-NHS and NHS II (He *et al.*, 2010), early menarche was associated with increased risk of T2DM in adulthood with stronger association among younger women. Associations were substantially attenuated after additional control for updated time-varying BMI. However, other studies have not found such an association in postmenopausal women (Cooper *et al.*, 2000; Saquib *et al.*, 2005).

Observations that parity, particularly five or more live births, might be associated with T2DM were made several decades ago (Pyke, 1956), and since then, a number of studies have attempted to determine the nature of such relationship, and establish the cause of it. The results of these studies have been conflicting with some indicating positive relationships even after controlling for obesity (Kritz-Silverstein *et al.*, 1989; Hanley *et al.*, 2002; Nicholson *et al.*, 2006), whereas other have found no association upon adjustment for other potential confounders (Boyko *et al.*, 1990; Collins *et al.*, 1991; Manson *et al.*, 1992). It is reasonable to suggest that parity should be associated with diabetes risk, as increasing parity is generally associated with postpartum weight retention (Scholl *et al.*, 1995; Rosenberg *et al.*, 2003), development of obesity and central obesity (Boyko *et al.*, 1990; Manson *et al.*, 1992) and impaired insulin sensitivity (Branchtein *et al.*, 1997). All these parallel the mechanisms underlying the development of diabetes.

7.3. Psychological Factors and Diabetes

Several lines of evidence suggest that psychological factors, mainly depression, and T2DM are associated, and that such association is bi-directional: psychological distress may occur as a result of diabetes, but may also be a risk factor for the onset of T2DM. This section examines the latter association by reviewing the literature on the evidence and possible mechanisms and pathways that may explain such an association.

7.3.1. Empirical evidence linking psychological factors and T2DM

Speculation regarding the role of psychological factors in the onset and course of diabetes has been ongoing for long. This dates back to 1684, when the English physician Thomas Willis suggested that diabetes resulted from sadness or prolonged sorrow and other depressions and disorders (Willis, 1971; Rubin and Peyrot, 2002). Since then, a number of studies have investigated the relationship between depressive disorder and T2DM. This has been occasioned by the extensive evidence that diabetes and depressive disorder occur together more often than would be expected by chance association (Gavard *et al.*, 1993). Numerous studies, both cross-sectional and longitudinal, have demonstrated that depression and its associated symptoms constitute a major risk factor for the onset of T2DM, independent of other conventional risk measures and may also accelerate the onset of diabetes complications (Everson-Rose *et al.*, 2004; Golden *et al.*, 2004; Carnethon *et al.*, 2007; Engum, 2007; Golden *et al.*, 2008), thus giving some indication of a direct effect of depression preceding the diagnosis of T2DM.

Despite the paucity of prospective studies, especially those from the general population, on the relationship between diabetes and depressive disorders, earlier studies that have examined the temporal relationship of depression and incident diabetes have yielded similar findings of positive association. Eaton and colleagues (1996) using the data from Epidemiologic Catchment Area (ECA) Program survey at the East Baltimore site concluded that a major depressive disorder was associated with almost two-fold increased incidence of T2DM during 13 years of follow-up (RR= 2.23; 95% CI= 0.90-5.55). A more recent analysis of the association in the same study population after 23 years of follow-up (Mezuk *et al.*, 2008b) also found similar results and concluded that risk of T2DM associated with major depressive disorder persists over the life course and is independent of the effects of health behaviours, BMI, and family history. Another

study of a cohort of employed Japanese men followed for eight years (Kawakami *et al.*, 1999) reached a similar conclusion. Both these studies had a common limitation of small numbers of incident diabetes thus limited power. Other recent longitudinal studies (Carnethon *et al.*, 2007; Engum, 2007; Toshihiro *et al.*, 2008) have also yielded similar results.

Several reviews and meta-analyses of longitudinal studies examining the association between psychological factors and T2DM have also found an increased risk of diabetes in psychologically distressed individuals. Earlier review of past studies on the effect of emotion on diabetes (Greydanus and Hofmann, 1979) indicated that there is a notable degree to which psychological factors seem to influence the course of diabetes. Though these earlier studies did not show the role of stress in the precipitation of the onset of diabetes, these factors profoundly affected the metabolic control of the diabetic.

More recent reviews have continued to support the relationship. Knol *et al*. (2006) reviewed and performed a meta-analysis of nine longitudinal studies examining the relationship between depression and T2DM in adults up to the year 2005. Their results revealed that depressed adults have a 37% increased risk of developing T2DM (Pooled RR using random effects model = 1.37, 95% CI = 1.14-1.63). Similar results were obtained by Cosgrove *et al.* (2008) with the pooled "fully adjusted" relative risk estimate from the three highest quality longitudinal studies of 1.25 (95% CI= 1.02–1.48). Another meta-analysis of 13 studies of depression predicting onset T2DM (Mezuk *et al.*, 2008a), concluded that depression is associated with a 60% increased risk of T2DM (RR=1.60, 95% CI= 1.37-1.88).

Thus, the replication of results in various studies with such diverse populations and diverse methods amounts to a strong pattern of evidence of association. However, the results are far from conclusive as some prospective studies (Saydah *et al.*, 2003; Hildrum *et al.*, 2009) have failed to support the etiologic relationship between depression and diabetes, while others have found the association only in populations with low educational attainment (Carnethon *et al.*, 2003).

The gender differences in the association between psychological distress and T2DM have also yielded inconsistent findings. Some studies have found the association only in men (Eriksson *et al.*, 2008; Kato *et al.*, 2009) and young men of age 20-50 (van den Akker *et*

al., 2004); in contrast, associations between depressive symptoms and T2DM have been reported in prospective studies of women (Arroyo *et al.*, 2004; Everson-Rose *et al.*, 2004). The studies that have found the relationship only in men have argued that the gender differences could be as a result of different coping strategies between men and women. While women communicate symptoms of distress and depression, men are more unwilling to admit such feelings and tend to cope through drinking, drug use and other risky behaviours that may increase the risk of diabetes (Eriksson *et al.*, 2008). Thus if men under-report symptoms of psychological distress, it might be that when they finally report symptoms they have already become severe and are affecting the neuroendocrine stress systems.

In summary, much evidence suggests that psychological factors may predict the onset of T2DM, and this association may not be attributable solely to the adoption of adverse health behaviours. However, the pathophysiologic mechanism for this association remains unclear.

7.3.2. Mechanisms and pathways through which psychological factors might affect the onset of Type 2 diabetes

Empirical evidence suggests that psychological factors such as stress and depression have a modest association with T2DM but the mechanisms remain unclear. There are several possible models and explanations that have been suggested to explain such an association. As presented in Figure 7-2, the primary candidates for mediating pathways are the biological mechanisms involving dysregulation of the hypothalamus–pituitary–adrenal (HPA), sympathetic nervous system (SNS), and sympathetic adrenal medullary (SAM) systems; and the negative health behaviours such as poor diet, smoking, and physical inactivity. Other possible explanations include the hypotheses that there could be a common underlying aetiological mechanism to both the conditions, and that the early symptoms of diabetes may be confused with that of depression.

Direct Biological Pathways

Increased release of counter-regulatory hormones in the stress response

The effects of stress on glucose metabolism are mediated by a variety of counter-regulatory hormones that are released in response to stress and that result in elevated

blood glucose levels and decreased insulin action. Insulin, an anabolic hormone, increases glucose utilization to support protein and triglyceride synthesis and glycogen storage. In contrast, the catabolic counter-regulatory hormones such as cortisol, epinephrine and norepinephrine, growth hormone, and glucagon, increase glucose production through proteolysis, lipolysis, glycogenolysis, and gluconeogenesis (Musselman *et al.*, 2003). In response to psychological stress, the brain stimulates release of the counter-regulatory hormones which counteract the hypoglycaemic action of insulin by raising blood levels of glucose (Surwit and Schneider, 1993; Sapolsky *et al.*, 2000; Musselman *et al.*, 2003). As a consequence of increased release of counter-regulatory hormones and diminished cellular glucose uptake, patients with major depression may exhibit insulin resistance (Nathan *et al.*, 1981; Winokur *et al.*, 1988). Thus enhanced release of counter-regulatory hormones in response to psychological stress may be a possible link between psychological distress and diabetes.

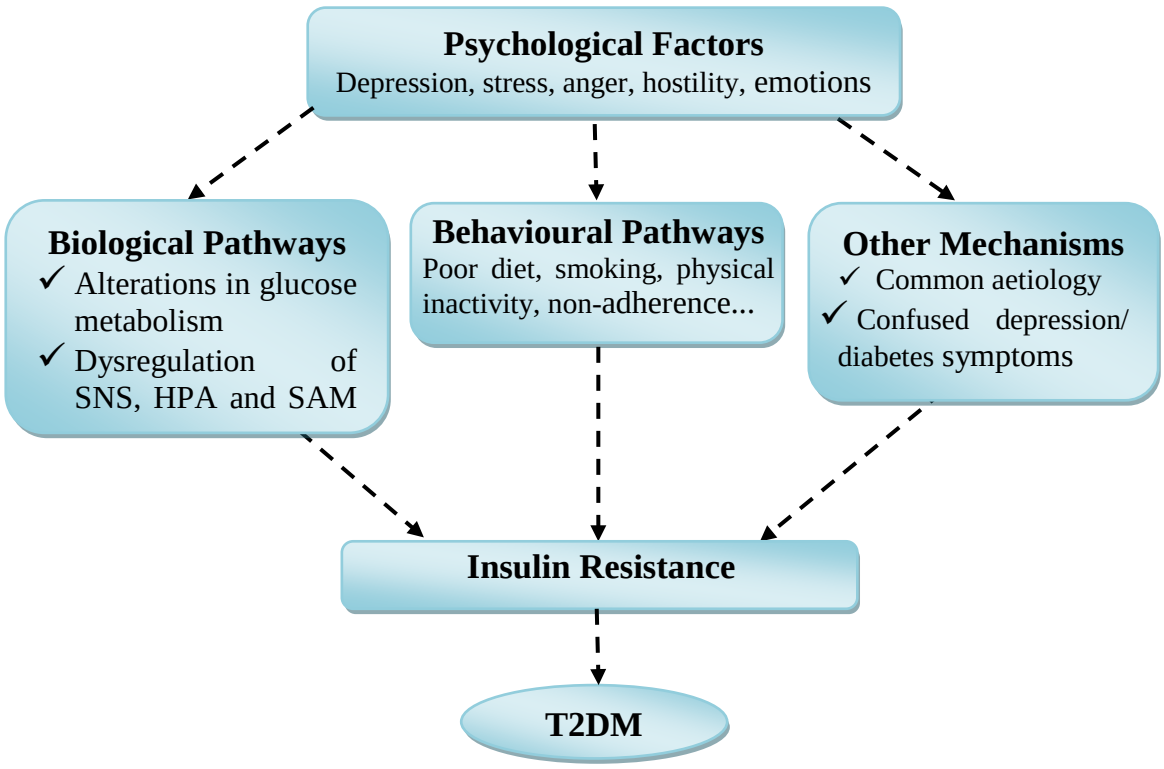


Figure 7-2: Possible pathways linking psychological factors and diabetes. HPA = hypothalamic-pituitary-adrenal axis; SNS = sympathetic nervous system; SAM = sympathetic adrenal medullary system.

Hypothalamic, sympathetic and immune dysregulation

The mechanism behind a relation between psychological distress and T2DM is also believed to involve a direct effect of depression and prolonged stress on the entire neuroendocrine system by activation of the central sympathetic nervous system and the HPA axis (Björntorp, 2001; Golden, 2007). Activation of the HPA axis causes excessive cortisol production that induces insulin resistance and contributes to diabetes risk. Recent research also suggests that immune dysregulation may be another core mechanism for the association between psychological factors and chronic diseases including T2DM (Kiecolt-Glaser and Glaser, 2002).

Negative Health Behaviours

The development of diabetes in people with depression may be related to the behaviours associated with depression rather than the depression itself. Depression is known to be associated with health behaviours that are likely to increase the risk of T2DM such as increased smoking, alcohol consumption, and unhealthy eating, and with diminished physical activity. Previous research indicates that health behaviours such as sedentary lifestyle and poor diet that lead to weight gain are more prevalent among depressed persons (Wurtman and Wurtman, 1995). This in turn can lead to obesity and insulin resistance, increasing the risk of developing T2DM. In fact, it has been suggested that the major link between stress and diabetes is central adiposity in which case stress causes a more central distribution of fat, which in turn causes diabetes (Björntorp, 1988, 1991).

It has also been estimated that about 37% of the association between depressive symptoms and diabetes could be explained by health behaviours and baseline BMI (Carnethon *et al.*, 2003). Smoking, which itself is emerging as a risk for T2DM, has also been found to be significantly associated with depressive symptoms (Haire-Joshu *et al.*, 1994). Results from meta-analyses of the effects of depression on patient adherence have also demonstrated a significant association between depression and treatment non-adherence in patients with diabetes (Dimatteo *et al.*, 2000; Gonzalez *et al.*, 2008). Overall, these studies provide some indication that negative health behaviours such as smoking, poor diet, and physical inactivity may be a plausible link between psychological factors and the onset of T2DM.

Other Pathways

Common underlying aetiological mechanism for psychological factors and T2DM

Another possible explanation for an association between psychological factors (e.g. depression) and T2DM is that diabetes is not caused by depression; rather there is a common underlying aetiological mechanism to both conditions (Cosgrove *et al.*, 2008). In this case, depression and diabetes might both be consequences of some other process such as genetic background or environmentally caused vulnerability established early in life. For instance, factors operating early in the life course such as birth weight and other in-utero exposures are known to increase the risk of developing both depression and diabetes. In addition, obesity and factors such as low socioeconomic status might be confounders in the association, thus leading to both depression and diabetes. If this is the case, resolving depression will not reduce diabetes risk.

Symptoms of diabetes confused with depression

A further explanation is that diabetes is preceded by symptoms such as tiredness and malaise that may be confused with depression when using a screening questionnaire. This confusion can however, be avoided if the data on psychological measures are collected long before the diagnosis of T2DM.

Weight gain due to depression medication

Some of the medications used to treat depression can induce weight gain and obesity (Allison *et al.*, 1999; Parsons *et al.*, 2009), which could predispose depressed individuals to the risk of T2DM.

In summary, there is good evidence of an association between psychological factors especially stress and depression and subsequent development of T2DM. Intensive research has been devoted to finding explanations and possible mechanisms for such an association and several mechanisms have been proposed. There is now mounting evidence that the risk of T2DM in adult life may be set by factors operating early in the life course of an individual. Thus it is vital to assess the effects of psychological factors early in life and the subsequent onset of T2DM later in life. This study seeks to unveil

such an association using two population-based British birth cohort studies, the NCDS and BCS70.

7.4. Diabetes in the NCDS and BCS70

At ages 33 and 42 years in the NCDS and age 30 years in the BCS70, the cohort members were asked whether they had ever or had been told they had diabetes, what kind of diabetes they had (insulin dependent, that is controlled by injection; non-insulin dependent, that is controlled by diet or tablets; or some other kind of diabetes), their age when they first had diabetes, whether they had diabetes in the last 12 months, and whether they had seen a doctor in the past 12 months about their diabetes. Participants reporting that they had or had been told they had "non-insulin-dependent diabetes that is controlled by diet or tablets" were classified as having Type 2 diabetes in this study.

A medical examination and record review at age 16 years also gave confirmed or suspected cases of diabetes by age 16. At age 45 in the NCDS, the participants completed a survey in which the nurse collected information on currently prescribed medication (through direct observation of packaging) from which oral antidiabetes drugs were identified.

As part of biomedical survey in the NCDS, the biochemical analyses of blood samples included measures of Glycosylated haemoglobin (HbA_{1c}) on whole citrated blood by ion exchange high performance liquid chromatography, using the Tosoh A1c 2.2 Glycohemoglobin Analyser HLC-723GHb (Gibb *et al.*, 1999). Results were standardized to the A_1c assay used in the Diabetes Control and Complications Trial (Marshall *et al.*, 2002).

Outcome measures

A diagnosis of Type 2 diabetes after age 16 years, identified by age at onset, was the main dependent variable. Those with confirmed or suspected diagnoses of diabetes (Type 1 or 2) by age 16 years, those with gestational diabetes, as well as those with Type 1 diabetes or insufficient information on diabetes, were excluded from all analyses. Another outcome considered in the NCDS was a measure of glucose metabolism in midlife; in this case, the measures of HbA_{1c} at 45 years, categorised as a binary variable

using a cut-off of 6% (Barr *et al.*, 2002; Bennett *et al.*, 2007). In line with other previous studies (Thomas *et al.*, 2007), those with Type 2 diabetes were assumed to have $HbA_{1c} \geq 6\%$ since the treatment for diabetes is known to lower the HbA_{1c}.

Predictors

Several prenatal and childhood factors were identified from the literature that have been shown to be associated with Type 2 diabetes later in life including birthweight, breastfeeding status, mother's age at delivery, parity, smoking during pregnancy, eclampsia, social class of the mother's husband, parent's education, child's cognitive ability, and smoking status at age 16. To control for genetic predisposition to Type 2 diabetes, we used information on whether first degree relatives (parent or sibling) had diabetes. A host of other potential mediating factors were also considered including mid-life psychological distress, alcohol consumption, and educational achievement by age 23, physical exercise, dietary factors (consumption of fruits, salads), and measures of obesity (BMI, WC).

7.5. Analytical Methods

The association between various childhood psychological factors and incident of self reported Type 2 diabetes after age 16 years was investigated using a series of discrete-time survival models. The relative risks (and 95% CIs) of incident diabetes in the discrete time-to-event models were estimated by the odds ratios in logistic regressions, adjusted for the rare outcome event. Both the results of complete case analyses and those from 10 multiply-imputed datasets were presented and compared.

For the HbA_{1c} outcome, logistic regression for the categorical indicator for $HbA_{1c} \geq 6\%$ was used. The criteria for model selection and adjustment for possible confounding variables is as described in Section 4.7. Initially, the bivariate association between the outcome measure and potential confounding variables was investigated. This was followed by a series of multivariable models evaluating the influence of early-life psychological factors on incident T2DM adjusted for all the other significant variables. All covariates were evaluated as potential effect modifiers by using first-order interaction terms between each covariate and depressive symptom categories. A significant ($p < 0.05$) change in the maximum likelihood χ^2 value following removal of the interaction

term from the model indicated statistical interaction. When there was evidence of effect modification, the interaction term was retained in the model.

To investigate the extent to which established risk factors including BMI, smoking status, diet and physical exercise may explain the association between childhood depressive symptoms and incident diabetes, a series of structural equation models were fitted taking into account the temporal nature of the variables. Previous studies using this same cohort (Thomas *et al.*, 2007; Thomas *et al.*, 2008) have found that the associations between several prenatal factors and glucose metabolism are largely mediated through adult adiposity. We hypothesized that, as illustrated in Figure 7-3, early life psychological factors will influence Type 2 diabetes either directly (path 1), or that their effect will be mediated through adulthood obesity (path 2), adulthood psychological distress (path 3) or through educational attainment and social class in adulthood (path 4). We tested this hypothesis through a series of structural equation models for each of the childhood psychological measure and adjusting for all the possible confounders. Apart from BMI which was modelled as a continuous measure, all the other variables were modelled as discrete time-varying covariates.

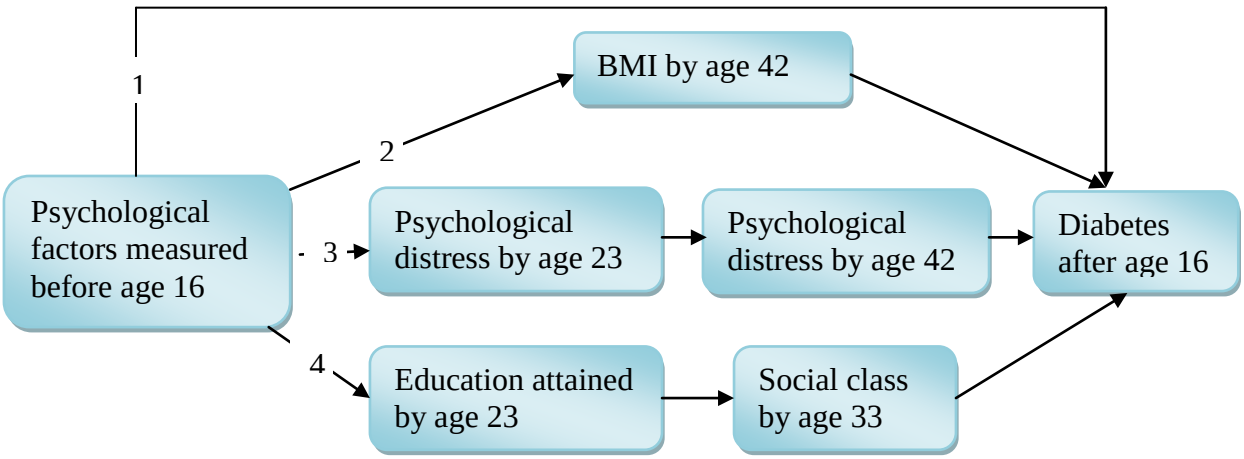


Figure 7-3: Hypothesized relationship between early life psychological factors and Type 2 diabetes in adulthood.
Psychological factors measured before age 16 may influence Type 2 diabetes through different pathways: 1) by having a direct effect; 2) through increased adiposity which increases the risk of diabetes; 3) through a cumulative effect whereby childhood behavioural maladjustments lead to psychological distress in adulthood which in turn increases the risk of T2DM; and 4) through lack of proper educational achievement, leading to manual social class, and higher risk of T2DM.

Chapter 8

Type II Diabetes Risk in Mid-life: Results

8.1. Self Reported Diabetes at age 42 years

8.1.1. Sample characteristics

Out of the original 18,558 participants from birth, 11,419 had some data during the 6th follow-up at age 42 years in the NCDS. Information on diabetes was obtained from 11,376 participants. Participants reporting Type 1 diabetes (n = 75) or other type of diabetes (n = 25) or who reported Type 2 diabetes before age 17 years (n = 4) were excluded, leaving 11, 272 individuals for the analyses with 93 cases (51 males and 42 females) of Type 2 diabetes. The median age at diagnosis was 38 years (inter-quartile range 32.5-40 years); age at diagnosis was unknown for one participant. Because the number of diabetic participants was relatively small, and given that there was no significant sex interaction with psychological factors, the results are presented for sexes combined.

In the BCS70, out of the original sample of 18,732 participants from birth, 11,226 had some data during the 1999/2000 follow-up at 30 years of age. Information on diabetes was obtained for 11,211 participants. There were 109 reported cases of diabetes, with 61 reporting Type 1 diabetes, 25 reporting Type 2 diabetes, and 23 other kinds of diabetes. Since the reported number of cases for Type 2 diabetes in the BCS70 was quite few for any meaningful analysis, only the results for NCDS have been presented.

The percentage of missing data for each covariate is presented in Tables 8-1 to 8-4 which also show the main body of results. Childhood psychological measures had a substantial amount of missing data (12-26%), with the highest percentage at age 26 when there was a change of response from parents to participant themselves. There were also considerable amount of missing data for the other variables; the least percentage being among the measures at age 42 years. Analysis has therefore been done based on 10 multiply-imputed datasets to reduce any bias due to missing data and results compared to those of complete cases in all the models.

8.1.1. Univariable models

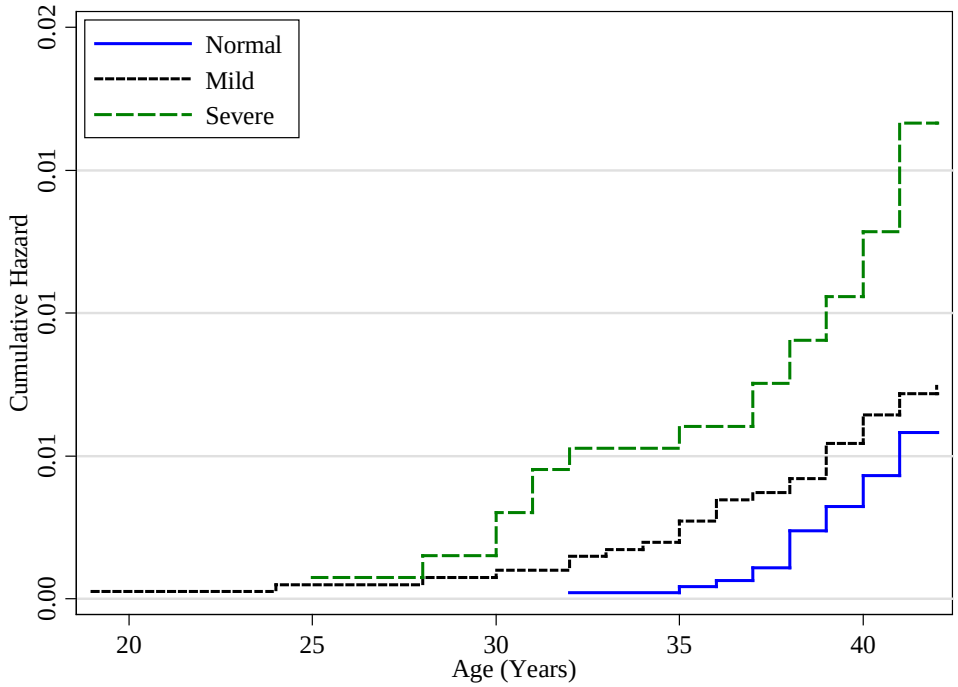
Early life psychological factors

As a preliminary analysis to visualise the effects of childhood psychological factors on Type 2 diabetes risk, Nelson-Aalen cumulative hazard function, that is the cumulative probability of being diagnosed with Type 2 diabetes by a certain age, was plotted for each of the categories of the behavioural scores. The equality of the survivor functions was formally tested by log-rank test. Most of the Rutter subscales did not show any clear difference between those with severe behavioural problems and those considered normal based on the cumulative graphs and a formal test using log-rank test, and their graphs have not been presented. However, the results for the discrete-time survival models are presented for all the psychological measures.

Figures 8-1 and 8-2 present sample plots for the conduct and emotional problems subscales of the BSAG scale at ages 7 and 11 years. There were clear difference in the cumulative hazard of developing Type 2 diabetes among those considered normal and those with severe and mild behavioural problems for conduct problems at age 7 (log-rank test $\chi^2_{(2)}$=15.45, p<0.001), emotional problems at age 7($\chi^2_{(2)}$=11.02, p=0.0064) conduct problems at age 11 ($\chi^2_{(2)}$=10.25, p=0.006), and emotional problems at age 11 ($\chi^2_{(2)}$=13.33, p=0.001).

The cumulative hazard plots were roughly parallel after age 33, indicating that the behavioural problems effect on Type 2 diabetes risk was constant over time. Hence the age-adjusted risk ratios (RRs) estimated by the logistic regression model may roughly represent the overall effects of behavioural problems over the entire age span analysed in this study. Those with severe conduct and emotional problems had consistently higher rates of reporting Type 2 diabetes at both ages 7 and 11 years.

a)



b)

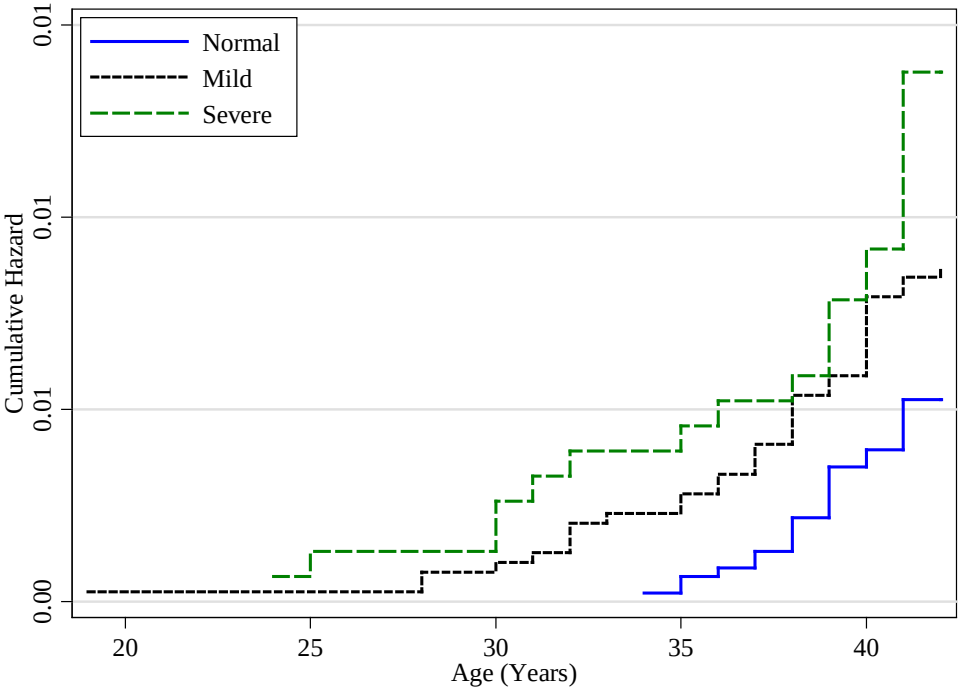
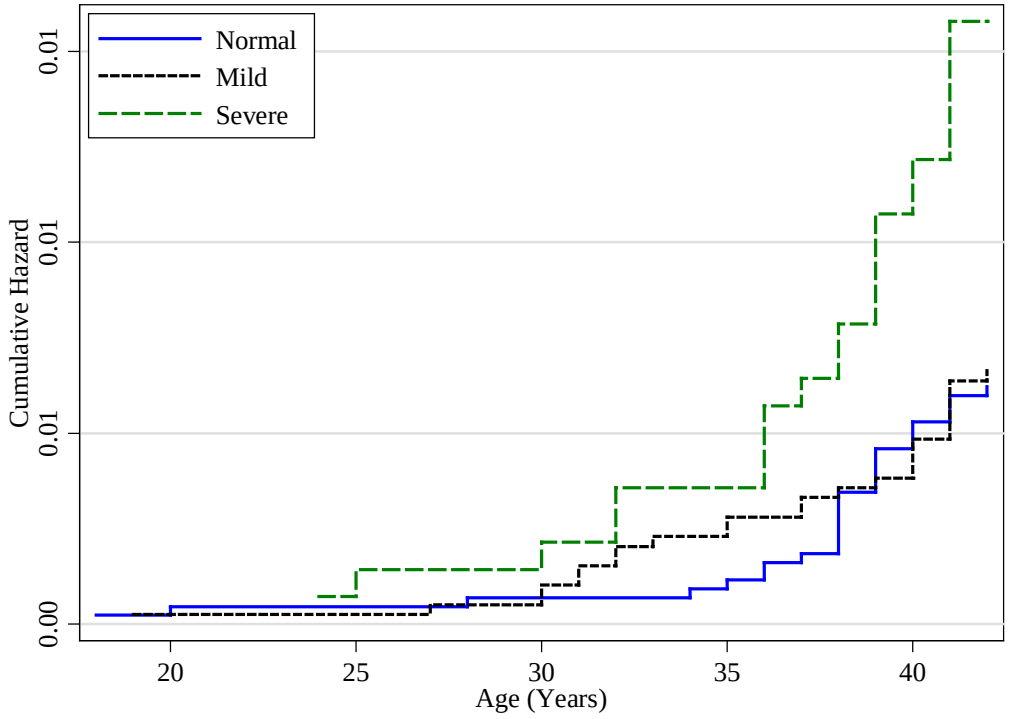


Figure 8-1: Sample cumulative hazard function, that is, cumulative probability of being diagnosed with diabetes by a given age, by categories of teacher assessed (a) conduct and (b) emotional problems of BSAG scale by age 7 years.

a)



b)

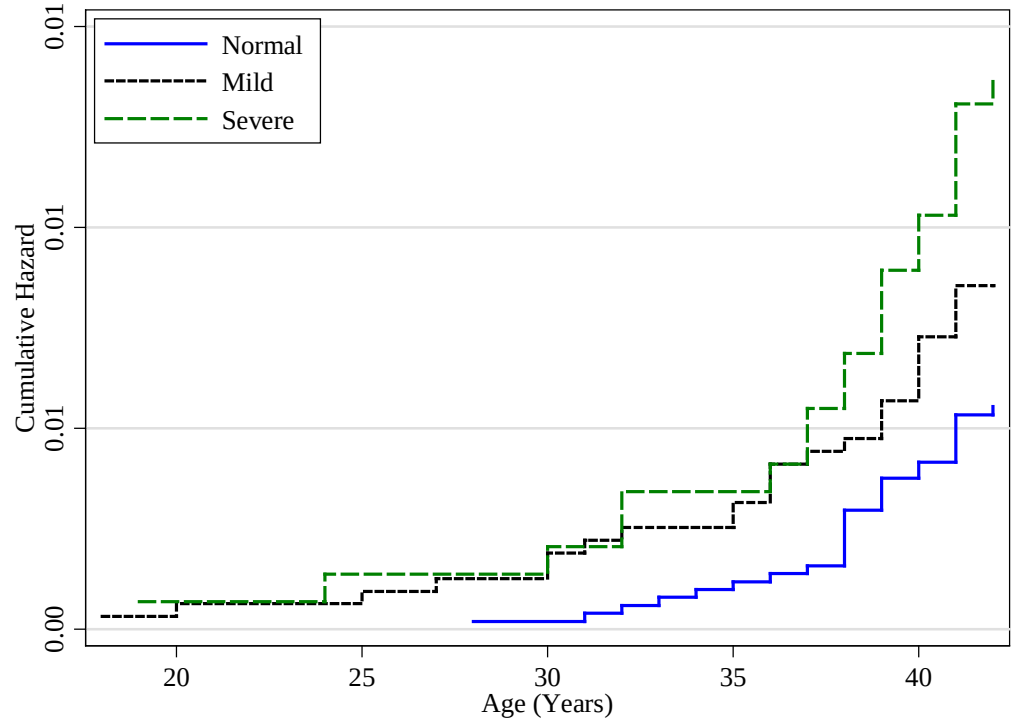


Figure 8-2: Sample cumulative hazard function, that is, cumulative probability of being diagnosed with diabetes by a given age, by categories of teacher assessed (a) conduct and (b) emotional problems of BSAG scale by age 11 years.

Table 8-1 presents the number of those who reported and who did not report Type 2 diabetes for each of the childhood psychological measure as well as the bivariate relationships between early life psychological factors and Type 2 diabetes at age 42 years. All the childhood psychological measures reported by the mother did not show any significant relationship with T2DM. Conversely, the measures reported by the teacher showed significant association with T2DM, with those who showed worse under-reaction or emotional problems and conduct or over-reaction behaviours at both age 7 and 11 having higher risk of Type 2 diabetes in mid life. The total Rutter score for the teacher's scale also showed significant association with Type 2 diabetes, though none of its subscales was significant.

Perinatal and childhood social and environmental factors

The relationship between a number of perinatal and childhood social, health and environmental measures and T2DM were assessed in order to test whether they could confound the relationship between early life psychological factors and diabetes. Of the variables that were considered (Table 8-2), only birthweight and the two cognitive measures at age seven (arithmetic and reading scores) were significantly associated with T2DM after age 16. Those with birthweight of >3.5 kg (as compared to birthweight up to 3 kg), and those with higher scores in arithmetic and reading had a reduced risk of T2DM. Mother's education was significant in the complete cases results but lost its significance in the MI data. Family history of diabetes did not show any significant association with diabetes probably due to the small number of those who reported having diabetes and also had family history of diabetes.

Mid-life psychological factors

Table 8-3 presents the results for the bivariate relationship between the mid-life psychological factors and self reported T2DM in mid life. Psychological distress at age 23 did not show any significant association with T2DM. This could be probably a result of the small number of participants who reported both being depressed as well as having T2DM at that age. However, both the psychological factors at age 42 (Malaise inventory and GHQ12) were significantly associated with Type 2 diabetes in the age-adjusted model.

Table 8-1: Effect of childhood psychological factors (age-adjusted odds ratios and 95% CI) on self reported diabetes in mid-life in the NCDS.

				Age-adjusted OR (95% CI)					
				Complete Cases			MI[4]		
	N_D[1]	N_{ND}[2]	% M[3]	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	82	9,785	12.5	1.01	(0.95 , 1.08)	0.65	1.01	(0.95 , 1.08)	0.71
Hyperactive	82	9,777	12.5	1.01	(0.84 , 1.21)	0.92	1.01	(0.82 , 1.23)	0.96
Emotional problems	82	9,784	12.5	0.96	(0.83 , 1.10)	0.56	0.96	(0.84 , 1.10)	0.57
Conduct Problem	82	9,782	12.5	1.05	(0.91 , 1.21)	0.51	1.05	(0.91 , 1.21)	0.53
Child Behaviour at School (BSAG)									
Emotional problems	80	9,948	11.0	1.07	(1.03 , 1.11)	<0.01	1.06	(1.03 , 1.10)	<0.01
Conduct problems	80	9,948	11.0	1.05	(1.02 , 1.09)	<0.01	1.06	(1.03 , 1.09)	<0.01
Miscellaneous Nervous Syndrome	80	9,947	11.0	1.46	(0.96 , 2.21)	0.08	1.46	(1.00 , 2.14)	0.05
At Age 11									
Child Behaviour at Home (Rutter A)									
Total Score	76	9,507	15.0	1.05	(0.99 , 1.12)	0.12	1.04	(0.99 , 1.10)	0.14
Hyperactive	76	9,506	15.0	1.14	(0.96 , 1.36)	0.12	1.15	(0.98 , 1.35)	0.09
Emotional problems	76	9,506	15.0	1.04	(0.91 , 1.20)	0.56	1.02	(0.89 , 1.17)	0.74
Conduct Problem	76	9,504	15.0	1.09	(0.93 , 1.26)	0.29	1.09	(0.93 , 1.28)	0.30
Child Behaviour at School (BSAG)									
Emotional problems	76	9,623	14.0	1.09	(1.04 , 1.13)	<0.01	1.09	(1.05 , 1.13)	<0.01
Conduct problems	76	9,623	14.0	1.08	(1.05 , 1.11)	<0.01	1.08	(1.05 , 1.11)	<0.01
Miscellaneous Nervous Syndrome	76	9,623	14.0	2.03	(1.39 , 2.95)	<0.01	2.02	(1.44 , 2.85)	<0.01
At Age 16									
Child Behaviour at Home (Rutter A)									
Total Score	65	8,273	26.0	1.00	(0.93 , 1.07)	0.91	0.99	(0.92 , 1.07)	0.80
Hyperactive	65	8,265	26.1	1.12	(0.85 , 1.46)	0.42	1.11	(0.88 , 1.41)	0.36
Emotional problems	65	8,271	26.0	0.94	(0.79 , 1.12)	0.49	0.92	(0.76 , 1.13)	0.44
Conduct Problem	65	8,269	26.1	1.10	(0.92 , 1.33)	0.29	1.09	(0.92 , 1.30)	0.32
Child Behaviour at School (Rutter B)-Total score			22.1						
Well adjusted	45	7,372							
With behavioural disorder	21	1,343		2.56	(1.52 , 4.31)	<0.01	2.12	(1.25 , 3.60)	0.01
Subscales									
Neurotic	66	8,685	22.4	1.19	(1.00 , 1.41)	0.04	1.15	(0.97 , 1.36)	0.11
Antisocial	66	8,690	22.3	1.09	(0.97 , 1.22)	0.16	1.09	(0.98 , 1.21)	0.13

1 Diabetes cases- those who reported having diabetes by age; 2 With no diabetes cases reported at age 42 years
3 Percentage of missing data for each va;4 Analysis based on combined results of 10 multiple-imputed datasets
* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

Table 8-2 : Effect of perinatal and childhood social, health and environmental factors on self reported diabetes in midlife in the NCDS.

				Age-adjusted OR (95% CI)					
				Complete Cases			MI[4]		
Variable (Reference category)	N_D[1]	N_{ND}[2]	% M[3]	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Sex (Male)	51	5,505	0.0						
Female	42	5,674		0.80	(0.53 , 1.20)	0.28	0.80	(0.53 , 1.21)	0.29
Family history of diabetes(No)	77	9,441	13.6						
Yes	2	219		1.42	(0.35 , 5.80)	0.62	1.48	(0.39 , 5.63)	0.56
Mother's age at delivery(<21)	13	1,555	5.3						
22-25	19	2,727		0.83	(0.41 , 1.69)	0.61	0.86	(0.42 , 1.78)	0.69
26-30	27	3,360		0.96	(0.49 , 1.87)	0.91	1.01	(0.50 , 2.07)	0.97
31+	25	2,954		1.01	(0.52 , 1.98)	0.97	1.03	(0.52 , 2.01)	0.94
Maternal smoking during preg.(No)	48	7,161	5.2						
Smoker	36	3,441		1.56	(1.01 , 2.41)	0.04	1.48	(0.96 , 2.28)	0.08
Parity (No prev aft 28wks)	23	3,981	5.2						
1 After 28wks	27	3,299		1.42	(0.81 , 2.48)	0.22	1.30	(0.75 , 2.26)	0.35
2 after28wks	16	1,644		1.68	(0.89 , 3.20)	0.11	1.53	(0.83 , 2.84)	0.18
3+ after 28wks	18	1,676		1.86	(1.00 , 3.45)	0.05	1.74	(0.95 , 3.17)	0.07
HBP/proteinuria or eclampsia(None)	50	6,835	5.2						
Toxaemic/eclampsia/proteinuria	34	3,765		1.23	(0.80 , 1.91)	0.35	1.24	(0.80 , 1.92)	0.33
Social class of father (Non-manual)	23	3,724	8.5						
Manual	61	6,511		1.52	(0.94 , 2.45)	0.09	1.52	(0.95 , 2.44)	0.08
Birthweight (up to 3 kg)	29	2,777	5.6						
up to 3.5 kg	34	3,865		0.84	(0.51 , 1.39)	0.50	0.85	(0.50 , 1.42)	0.53
> 3.5 kg	21	3,918		0.51	(0.29 , 0.90)	0.02	0.53	(0.30 , 0.93)	0.03
Breastfed (No)	33	2,986	13.1						
Under 1 month	16	2,395		0.60	(0.33 , 1.10)	0.10	0.66	(0.37 , 1.20)	0.17
Over 1 month	33	4,335		0.69	(0.42 , 1.12)	0.13	0.72	(0.44 , 1.17)	0.18
Mother's educ: at sch after16 (No)	70	7,807	5.5						
Yes	13	2,762		0.52	(0.29 , 0.95)	0.03	0.57	(0.32 , 1.03)	0.06
Father's educ: at sch after 16 (No)	63	7,140	15.4						
Yes	18	2,318		0.88	(0.52 , 1.49)	0.63	0.86	(0.50 , 1.48)	0.59
Child's cognitive skills at age 7									
Arithmetic	80	9,923	11.3	0.89	(0.81 , 0.97)	0.01	0.89	(0.82 , 0.96)	0.01
Reading	83	9,939	11.1	0.95	(0.92 , 0.97)	<0.01	0.95	(0.92 , 0.97)	<0.01
Smoking at age 16 (Non-smoker)	41	5,507	24.5						
Smoker	24	2,937		1.10	(0.66 , 1.82)	0.72	1.09	(0.69 , 1.71)	0.72
Child in care by age 11 (No)	73	9,139	15.9						
Yes	1	272		0.46	(0.06 , 3.32)	0.44	0.94	(0.13 , 6.69)	0.95

1 Diabetes cases- those who reported having diabetes by age 42 years; 2 With no diabetes cases reported at age 42 yea
3 Percentage of missing data for each variable; 4 Analysis based on combined results of 10 multiple-imputed datasets

Mid-life social, environmental, and lifestyle factors

The age-adjusted odds ratios (95% CI) for the relationship between a number of early adulthood social, environmental, and lifestyle risk factors and T2DM are presented in

Table 8-4. The percentage prevalence of those who reported diabetes by age 42 by the categories of these variable are also presented. Higher education achievement and regular physical exercise had a significant protective effect on T2DM. On the other hand, obesity and being in manual social class had a significant positive effect on diabetes risk. Alcohol consumption by age 23 years, daily consumption of fruits, and smoking by age 42 years did not show any significant association.

Table 8-3: Effect of midlife psychological factors on self reported diabetes in midlife in the NCDS.

				Age-adjusted OR (95% CI)					
			%	Complete Cases			MI[4]		
	N_D[1]	N_{ND}[2]	M[3]	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological distress at 23 (Malaise)			16						
Normal	67	8,795							
Depressed	9	655		1.89	(0.94 , 3.78)	0.07	1.88	(0.98 , 3.58)	0.06
Psychological distress at 42 (Malaise)			0.9						
Normal	69	9,627							
Depressed	24	1,455		2.32	(1.46 , 3.69)	<0.01	2.31	(1.45 , 3.68)	<0.01
GHQ12 at 42 years	93	11,084	0.8	1.04	(1.01 , 1.08)	0.01	1.04	(1.01 , 1.08)	0.01

1 Diabetes cases- those who reported having diabetes by age 42 years; 2 With no diabetes cases reported at age 42.
3 Percentage of missing data for each variable; 4 Analysis based on combined results of 10 multiple-imputed datasets

8.1.2. Mutually adjusted model for self reported diabetes

Among the possible confounding variables tested in a series of multivariable models to evaluate their influence on the effect of early-life psychological factors on incident T2DM, only maternal smoking during pregnancy, and childhood cognitive ability (arithmetic and reading scores) were significant in the multivariable model and were adjusted for in the mutually adjusted model. Since the arithmetic and reading scores were highly correlated, only the reading score was included in the final model since it was more highly significant in the bivariate case. None of the covariates evaluated showed a significant first-order interaction with each the depressive symptom categories showing no potential effect modifiers.

Table 8-4: Effect of mid-life social, environmental, and lifestyle factors on self reported diabetes in midlife in the NCDS.

				Age-adjusted OR (95% CI)					
			%	Complete Cases			MI[4]		
	N_D[1]	N_{ND}[2]	M[3]	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Alcohol consumption at age 23			15.4						
None	26	2,357							
Light	17	2,375		0.66	(0.36 , 1.21)	0.18	0.56	(0.25 , 1.24)	0.15
Medium/Heavy	33	4,725		0.63	(0.38 , 1.06)	0.08	0.52	(0.25 , 1.07)	0.08
Educational level at age 23			19.3						
No qualification	22	1,119							
CSE 2-5/equiv nvq1	10	1,189		0.44	(0.21 , 0.93)	0.03	0.50	(0.23 , 1.09)	0.08
O level/equiv nvq2 & Higher	39	6,715		0.29	(0.17 , 0.50)	<0.01	0.33	(0.20 , 0.55)	<0.01
Social class at age 33			19.5						
I /II/III: Proff/manager/non-manual	28	5,525							
III: Skilled manual	22	1,784		2.44	(1.39 , 4.26)	<0.01	2.32	(1.33 , 4.07)	<0.01
IV or V: Partly/ Unskilled	19	1,701		2.22	(1.24 , 3.97)	0.01	2.09	(1.24 , 3.53)	0.01
Smoking at age 42			0.0						
Never smoked	34	4,998							
Used to smoke	30	2,808		1.57	(0.96 , 2.56)	0.07	1.57	(0.96 , 2.56)	0.07
Current smokers	29	3,371		1.27	(0.77 , 2.08)	0.35	1.27	(0.77 , 2.08)	0.35
Drinking problem at age 42 (CAGE)			1.4						
No	77	9,583							
Yes	15	1,440		1.33	(0.76 , 2.31)	0.31	1.32	(0.76 , 2.29)	0.33
Physical Exercise at age 42			0.0						
No	34	2,880							
Yes	59	8,296		0.60	(0.39 , 0.92)	0.02	0.60	(0.39 , 0.92)	0.02
BMI at age 42									
Normal	14	5,273	2.6						
Overweight	32	3,934		2.99	(1.60 , 5.61)	<0.01	2.96	(1.58 , 5.52)	<0.01
Obesity	43	1,688		9.24	(5.06 , 16.90)	<0.01	9.08	(5.03 , 16.38)	<0.01
Fruit Consumption			0.0						
Never/occasional(<1 day a wk)	20	2,206							
1-6 days a week	47	5,675		0.90	(0.53 , 1.52)	0.70	0.90	(0.53 , 1.52)	0.70
1 0r more a day	26	3,295		0.86	(0.48 , 1.55)	0.63	0.86	(0.48 , 1.55)	0.63

1 Diabetes cases- those who reported having diabetes by age 42 years; 2 With no diabetes cases at age 42.

3 Percentage of missing data for each variable

4 Analysis based on combined results of 10 multiple-imputed datasets

After adjusting for age at diagnosis, mother's smoking status during pregnancy, and reading ability, both outwardly (overreaction or conduct problems) and inwardly (undereaction or emotional problems) expressed behaviours as assessed by the teacher at ages 7 and 11 were still significantly associated with self reported diabetes at 42 years (Table 8-5). There was a 4% increase in the risk of diabetes for every unit increase in the behavioural score as reported by the teacher at age seven. For the age 11 measures, there

was a 6% and 7% increase in the risk of T2DM for each unit increase in the conduct and emotional problems score, respectively.

Table 8-5: Effect of childhood psychological factors on self reported diabetes in midlife in the NCDS, with adjustment for age at diagnosis and other confounders[1].

	Age and confounders-adjusted OR(95% CI)[1]					
	Complete Cases			MI[2]		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	1.00	(0.93 , 1.06)	0.90	1.00	(0.94 , 1.07)	0.98
Hyperactive	0.97	(0.79 , 1.19)	0.79	0.99	(0.81 , 1.20)	0.92
Emotional problems	0.97	(0.85 , 1.11)	0.62	0.96	(0.84 , 1.09)	0.51
Conduct Problem	0.98	(0.85 , 1.14)	0.80	1.00	(0.86 , 1.16)	0.97
Child Behaviour at School (BSAG)						
Emotional problems	1.05	(1.01 , 1.09)	0.01	1.04	(1.01 , 1.08)	0.02
Conduct problems	1.04	(1.01 , 1.07)	0.01	1.04	(1.01 , 1.07)	0.01
Miscellaneous Nervous Syndrome	1.36	(0.91 , 2.03)	0.13	1.32	(0.88 , 1.97)	0.18
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	1.04	(0.97 , 1.10)	0.26	1.03	(0.98 , 1.09)	0.26
Hyperactive	1.11	(0.94 , 1.31)	0.22	1.11	(0.95 , 1.30)	0.21
Emotional problems	1.06	(0.91 , 1.22)	0.47	1.02	(0.89 , 1.18)	0.76
Conduct Problem	1.03	(0.88 , 1.21)	0.72	1.05	(0.90 , 1.22)	0.52
Child Behaviour at School (BSAG)						
Emotional problems	1.07	(1.02 , 1.12)	<0.01	1.07	(1.03 , 1.12)	<0.01
Conduct problems	1.06	(1.02 , 1.10)	<0.01	1.06	(1.02 , 1.09)	<0.01
Miscellaneous Nervous Syndrome	1.84	(1.24 , 2.74)	<0.01	1.80	(1.23 , 2.65)	<0.01
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.98	(0.92 , 1.04)	0.54	0.97	(0.90 , 1.05)	0.48
Hyperactive	1.07	(0.79 , 1.44)	0.68	1.05	(0.82 , 1.35)	0.69
Emotional problems	0.95	(0.78 , 1.16)	0.62	0.91	(0.74 , 1.12)	0.37
Conduct Problem	1.01	(0.84 , 1.22)	0.88	1.03	(0.86 , 1.23)	0.75
Child Behaviour at School (Rutter B)						
Total Score						
Well adjusted						
With behavioural disorder	2.13	(1.20 , 3.79)	0.01	1.71	(0.95 , 3.07)	0.08
Subscales						
Neurotic	1.11	(0.93 , 1.33)	0.26	1.06	(0.87 , 1.29)	0.55
Antisocial	1.02	(0.90 , 1.16)	0.73	1.02	(0.90 , 1.16)	0.78

1 Adjusted for the effect of maternal smoking, and reading score

2 Analysis based on combined results of 10 multiple-imputed datasets

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment

8.1.3. Mediating effect for self reported diabetes

Table 8-6 presents the results of the hypothesised relationship (in Figure 7-3) between early life psychological factors latent indicators and Type 2 diabetes. The estimated path coefficients represent standardized regression coefficients on latent and observed variables' variances. Such standardized coefficient represents the amount of change in an outcome variable per standard deviation unit of a predictor variable. The comparative fit index measures of the model global fit were close to one (0.97–0.98) for all the models and the RMSEA value ranged from 0.025 to 0.057 which is well below the recommended 0.06 cut-off that indicates good model fit, implying that the model fitted the data well.

For simplicity of the table, the estimates for the specific relationship between each variable along the pathway have been omitted; only the specific indirect effects on diabetes through other variables, the total indirect effect, and the total effect for both the direct and indirect effects, as obtained by the product of coefficients have been presented.

All the Rutter behavioural sub-scales at age 7 were not directly associated with diabetes in mid life. Although the hyperactive and conduct problems at age 7 had significant indirect effects, the magnitude of their indirect effects was not strong enough to have a significant total effect. Emotional problems at age 7 only had an indirect effect through adulthood psychological distress. Although the emotional and conduct problems as assessed by the teacher at age 7 were not directly associated with diabetes in mid-life, they had indirect effects through all the pathways, so that both their total indirect and the total effect on diabetes were significant. All the age 11 behavioural problems reported by the parents were also not directly associated with diabetes. Even though their total indirect effects were significant, the total effects were not significant, except for the hyperactive behaviours.

Both the emotional and conduct problems assessed by the teacher through the BSAG scale at age 11 were directly associated with Type 2 diabetes in mid life. This shows that their effects on diabetes were not mediated by obesity, adulthood psychological measures, education attainment or social class. All the age 16 behavioural problems did not show a direct association with diabetes, neither was there a total effect except for the neurotic behaviour as reported by the teacher. However, all their indirect effects were significant. This shows that their effect were all mediated through adulthood obesity

(path 2), adulthood psychological distress (path 3) and through educational attainment and social class in adulthood (path 4).

Table 8-6: Direct and indirect effect of the latent childhood psychological factors on self reported diabetes in midlife in the NCDS with adjustment for possible confounders and mediators

	Direct Effect			Specific Indirect Effect						Total Indirect			Total Effect		
				Path 2[1]		Path 3[2]		Path 4[3]							
	Est	95% CI	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	95% CI	Sig.	Est	95% CI	Sig.
Age 7(Rutter A)															
Hyperactive	-0.06	(-0.19, 0.06)	0.31	0.03	<0.01	0.03	<0.01	0.03	<0.01	0.08	(0.06, 0.11)	<0.01	0.02	(-0.10, 0.14)	0.73
Emotional problems	-0.06	(-0.16,0.04)	0.23	-0.01	0.11	0.01	0.01	-0.002	0.30	0.004	(-0.01,0.02)	0.46	-0.06	(-0.16,0.04)	0.27
Conduct problems	-0.04	(-0.16,0.08)	0.52	0.03	<0.01	0.03	<0.01	0.04	<0.01	0.09	(0.06,0.12)	<0.01	0.05	(-0.06,0.17)	0.37
Age 7 (BSAG)															
Emotional problems	0.07	(-0.01,0.16)	0.07	0.01	<0.01	0.02	<0.01	0.04	<0.01	0.07	(0.04,0.10)	<0.01	0.14	(0.07,0.22)	<0.01
Conduct problems	0.06	(-0.02,0.13)	0.16	0.02	<0.01	0.02	<0.01	0.03	<0.01	0.07	(0.05,0.09)	<0.01	0.12	(0.05,0.19)	<0.01
Age 11 (Rutter A)															
Hyperactive	0.03	(-0.08,0.15)	0.60	0.03	<0.01	0.03	<0.01	0.04	<0.01	0.09	(0.06,0.12)	<0.01	0.12	(0.01,0.23)	0.03
Emotional problems	-0.04	(-0.14,0.07)	0.48	0.001	0.83	0.02	<0.01	0.01	0.02	0.03	(0.01, 0.05)	<0.01	-0.01	(-0.11,0.09)	0.90
Conduct problems	-0.01	(-0.14,0.11)	0.85	0.03	<0.01	0.03	<0.01	0.04	<0.01	0.10	(0.06,0.13)	<0.01	0.08	(-0.03,0.20)	0.14
Age 11 (BSAG)															
Emotional problems	0.09	(0.01,0.17)	0.02	0.02	<0.01	0.02	<0.01	0.04	<0.01	0.08	(0.05,0.11)	<0.01	0.17	(0.09,0.24)	<0.01
Conduct problems	0.08	(0.01,0.16)	0.03	0.03	<0.01	0.02	<0.01	0.03	<0.01	0.08	(0.05,0.11)	<0.01	0.16	(0.09,0.23)	<0.01
Age 16 (Rutter A)															
Hyperactive	0.02	(-0.14,0.17)	0.82	0.03	<0.01	0.04	<0.01	0.05	<0.01	0.11	(0.07,0.16)	<0.01	0.13	(-0.01,0.27)	0.06
Emotional problems	-0.13	(-0.28,0.02)	0.09	0.01	0.14	0.05	<0.01	0.02	<0.01	0.08	(0.04,0.11)	<0.01	-0.06	(-0.19,0.08)	0.43
Conduct problems	-0.02	(-0.16,0.11)	0.72	0.03	<0.01	0.04	<0.01	0.05	<0.01	0.12	(0.07,0.16)	<0.01	0.09	(-0.02,0.21)	0.12
Age 16 (Rutter B)															
Neurotic	0.05	(-0.09,0.18)	0.50	0.02	<0.01	0.03	<0.01	0.04	<0.01	0.09	(0.05,0.13)	<0.01	0.14	(0.02, 0.25)	0.03
Antisocial	-0.01	(-0.15,0.13)	0.89	0.02	<0.01	0.03	<0.01	0.06	<0.01	0.11	(0.06,0.16)	<0.01	0.10	(-0.02,0.22)	0.10

1 Through BMI (kg/m^2) at age 42

2 Through adulthood psychological distress at age 23 and age 42

3 Through education achievement at age 23, and social class at age 33

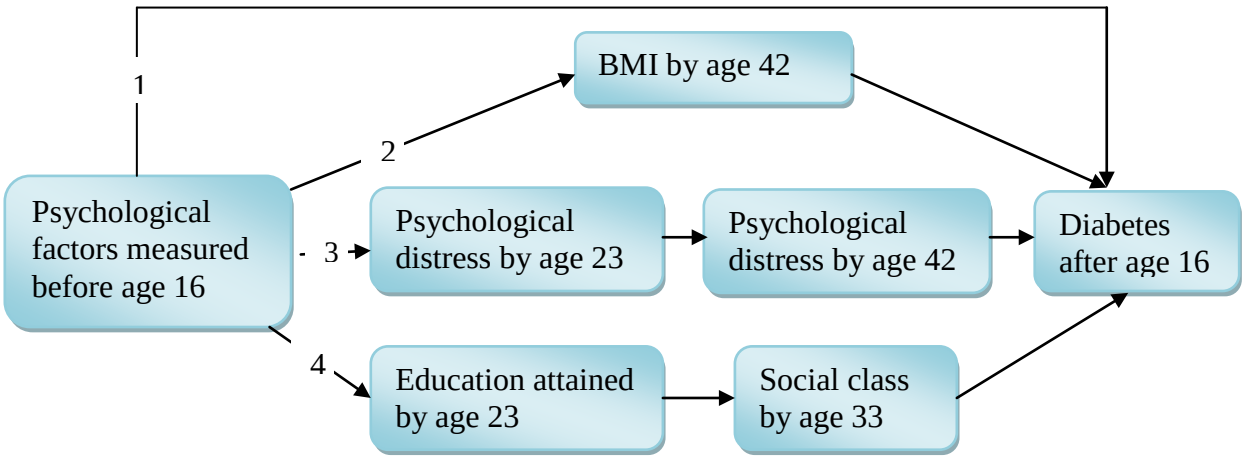


Figure 8-3: The hypothesized relationship (taken from Figure 7-3 for easy reference to the table) between early life psychological factors and Type 2 diabetes in adulthood.

8.2. Elevated Glycosylated Haemoglobin ($HbA_{1c} \geq 6$) and/or T2DM

8.2.1. Unadjusted bivariate models

Of the 9,377 subjects who had some information at age 45 years in the biomedical survey, 1,151(12.3%) had no blood received at the lab and a further 303(3.2%) had no HbA_{1c} recorded, leaving 7,923 (84.5%) subjects for analysis. About 5.6% (*n* = 364) of the analysed sample had $HbA_{1c} \geq 6$ and/or T2DM, with men having a higher percentage (5.5%, *n* = 218) as compared to females (3.7%, *n* = 146). The distribution of the cases of $HbA_{1c} \geq 6$ and/or T2DM for all the variables are shown in Tables 8-7 to 8-10.

Childhood psychological factors

Table 8-7 presents the unadjusted results from logistic regression analyses (*n* = 7,923) of the relationships between childhood psychological factors and $HbA_{1c} \geq 6$ and/or T2DM. As with the self reported diabetes, both the emotional and conduct problems reported by the teacher at age 7 and 11 were significantly associated with $HbA_{1c} \geq 6$ and/or T2DM. Also both neurotic and antisocial behaviours reported by teacher at age 16 (Rutter B) were significantly associated with the prevalence with $HbA_{1c} \geq 6$ and/or T2DM. Among the behavioural problems reported by the mother, only conduct problems at both age 7 and 11 and the total Rutter score were significantly associated with $HbA_{1c} \geq 6$ and/or T2DM.

Perinatal and childhood social and environmental factors

Unlike in the self reported diabetes case where only a few childhood factors were significantly associated with T2DM, most of the variables assessed were significantly associated with $HbA_{1c} \geq 6$ and/or T2DM. Being a female, being born by an older mother, higher birthweight, being born by an educated mother and having high scores in reading and arithmetic had a protective effect on $HbA_{1c} \geq 6$ and/or T2DM. Conversely, those who had family history of diabetes, those whose mothers were smokers during pregnancy, those whose fathers were in manual social class, and those who were smokers by age 16 had a significantly higher risk of $HbA_{1c} \geq 6$ and/or T2DM (Table 8-8).

Table 8-7: Effect of childhood psychological factors on prevalence with HbA1c ≥ 6 and or Type 2 diabetes in midlife in the NCDS.

	N_D[1]	N_{ND}[2]	% M[3]	Complete Cases OR	(95% CI)	Sig	MI[4] OR	(95% CI)	Sig
At Age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	316	6,641	12.2	1.02	(0.99 , 1.06)	0.16	1.02	(0.99 , 1.05)	0.27
Hyperactive	316	6,634	12.3	1.07	(0.97 , 1.19)	0.15	1.07	(0.97 , 1.17)	0.19
Emotional problems	316	6,640	12.2	0.98	(0.91 , 1.05)	0.52	0.97	(0.90 , 1.04)	0.39
Conduct Problem	316	6,638	12.2	1.08	(1.01 , 1.16)	0.03	1.08	(1.00 , 1.16)	0.04
Child Behaviour at School (BSAG)									
Emotional problems	318	6,753	10.8	1.05	(1.03 , 1.07)	<0.01	1.05	(1.02 , 1.07)	<0.01
Conductl problems	318	6,753	10.8	1.04	(1.02 , 1.06)	<0.01	1.04	(1.02 , 1.06)	<0.01
Miscellaneous Nervous Syndrome	318	6,752	10.8	1.35	(1.07 , 1.71)	0.01	1.34	(1.06 , 1.68)	0.01
At Age 11									
Child Behaviour at Home (Rutter A)									
Total Score	310	6,505	14.0	1.03	(1.00 , 1.06)	0.09	1.04	(1.01 , 1.07)	0.02
Hyperactive	310	6,505	14.0	1.06	(0.97 , 1.15)	0.22	1.08	(0.98 , 1.18)	0.11
Emotional problems	310	6,504	14.0	1.00	(0.93 , 1.08)	0.96	1.01	(0.95 , 1.09)	0.69
Conduct Problem	310	6,503	14.0	1.10	(1.02 , 1.19)	0.01	1.13	(1.05 , 1.21)	<0.01
Child Behaviour at School (BSAG)									
Emotional problems	310	6,550	13.4	1.05	(1.03 , 1.08)	<0.01	1.05	(1.02 , 1.08)	<0.01
Conductl problems	310	6,550	13.4	1.05	(1.03 , 1.07)	<0.01	1.04	(1.03 , 1.06)	<0.01
Miscellaneous Nervous Syndrome	310	6,550	13.4	1.29	(0.96 , 1.73)	0.09	1.26	(0.94 , 1.69)	0.12
At Age 16									
Child Behaviour at Home (Rutter A)									
Total Score	271	5,744	24.1	1.02	(0.99 , 1.06)	0.20	1.03	(1.00 , 1.06)	0.07
Hyperactive	271	5,740	24.1	0.99	(0.84 , 1.16)	0.90	1.08	(0.94 , 1.25)	0.29
Emotional problems	271	5,743	24.1	1.07	(0.99 , 1.16)	0.10	1.04	(0.96 , 1.12)	0.35
Conduct Problem	271	5,743	24.1	1.07	(0.97 , 1.18)	0.17	1.07	(0.98 , 1.17)	0.14
Child Behaviour at School (Rutter B) total score			20.6						
Well adjusted	233	5,165							
With behavioural disorder	61	835		1.60	(1.22 , 2.18)	<0.01	1.60	(1.19 , 2.15)	<0.01
Subscales for Rutter B									
Neurotic	292	5,985	20.8	1.12	(1.04 , 1.24)	0.01	1.12	(1.03 , 1.23)	0.01
Antisocial	292	5,988	20.7	1.07	(1.01 , 1.14)	0.02	1.07	(1.01 , 1.14)	0.02

1Those with HBA1c ≥6 and/or Type 2 diabetes by age 45 years; 2 With HBA1c <6 and no diabetes at age 45 years
3 Percentage of missing data for each variable; 4 Analysis based on combined results of 10 multiple-imputed datasets
* For all the psychological measures, higher scores indicate worse conditions of hehavioural maladjustment.

Table 8-8: Effect of perinatal and childhood social and environmental factors on HBA1c ≥6 and/or Type 2 diabetes in mid-life for the NCDS.

				Complete Cases			MI[4]		
Variable (Reference category)	N_D[1]	N_{ND}[2]	% M[3]	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Sex (Male)	218	3,758	0.0						
Female	146	3,801		0.66	(0.54 , 0.82)	<0.01	0.66	(0.54 , 0.82)	<0.01
Family history of diabetes (No)	296	6,409	13.2						
Yes	17	156		2.42	(1.45 , 4.04)	<0.01	2.25	(1.38 , 3.68)	<0.01
Mother's age at delivery (<21)	62	1,011	5.2						
22-25	93	1,831		0.83	(0.59 , 1.15)	0.26	0.83	(0.60 , 1.16)	0.28
26-30	101	2,350		0.70	(0.51 , 0.97)	0.03	0.71	(0.52 , 0.98)	0.04
31+	79	1,981		0.65	(0.46 , 0.91)	0.01	0.67	(0.48 , 0.93)	0.02
Maternal smoking during preg. (No)	205	4,894	5.2						
Smoker	130	2,285		1.36	(1.09 , 1.70)	0.01	1.34	(1.07 , 1.67)	0.01
Parity (No prev aft 28wks)	134	2,644	5.2						
1 After 28wks	92	2,294		0.79	(0.60 , 1.04)	0.09	0.79	(0.60 , 1.05)	0.10
2 after28wks	50	1,145		0.87	(0.62 , 1.21)	0.40	0.90	(0.64 , 1.26)	0.54
3+ after 28wks	59	1,094		1.07	(0.78 , 1.46)	0.68	1.07	(0.78 , 1.46)	0.69
HBP/proteinuria or eclampsia (none)	205	4,659	5.2						
Toxaemic/eclampsia/proteinuria	130	2,519		1.17	(0.94 , 1.47)	0.16	1.17	(0.94 , 1.47)	0.16
Social class of father (Non-manual)	92	2,577	8.4						
Manual	235	4,356		1.51	(1.18 , 1.93)	<0.01	1.47	(1.15 , 1.88)	<0.01
Birthweight (up to 3kg)	107	1,844	5.6						
up to 3.5 kg	119	2,635		0.78	(0.60 , 1.02)	0.07	0.79	(0.60 , 1.03)	0.08
> 3.5 kg	108	2,669		0.70	(0.53 , 0.92)	0.01	0.71	(0.54 , 0.94)	0.02
Breastfed (No)	102	1,972	12.8						
Under 1 month	81	1,565		1.00	(0.74 , 1.35)	0.99	0.99	(0.74 , 1.34)	0.97
Over 1 month	132	3,060		0.83	(0.64 , 1.09)	0.18	0.86	(0.66 , 1.13)	0.28
Mother's educ: at sch after 16 (No)	269	5,196	5.4						
Yes	65	1,963		0.64	(0.49 , 0.85)	<0.01	0.64	(0.48 , 0.84)	<0.01
Father's educ: at sch after16 (No)	238	4,768	14.9						
Yes	65	1,669		0.78	(0.59 , 1.04)	0.09	0.77	(0.59 , 1.00)	0.05
Child's cognitive skills at age 7									
Arithmetic	316	6,725	11.1	0.92	(0.88 , 0.96)	<0.01	0.92	(0.88 , 0.96)	<0.01
Reading	318	6,757	10.7	0.96	(0.95 , 0.98)	<0.01	0.96	(0.95 , 0.98)	<0.01
Smoking at 16 (Non-smoker)	171	3,862	22.6						
Smoker	110	1,991		1.25	(0.98 , 1.60)	0.08	1.30	(1.03 , 1.65)	0.03
Child in care by age 11 (No)	297	6,261	14.9						
Yes	9	176		1.13	(0.57 , 2.24)	0.72	1.18	(0.57 , 2.43)	0.66

1Those with HBA1c ≥6 by age 45 years; 2 With HBA1c <6 and no Type 2 diabetes at age 45 years
3 Percentage of missing data for each variable; 4 Analysis based on combined results of 10 multiple-imputed datasets

Mid-life psychological factors

Only psychological distress at age 42 was significantly associated with the prevalence of HbA1c ≥ 6 and/or T2DM (Table 8-9). Both the Psychological distress at age 23 and the GHQ12 score did not show any significant association with $HbA_{1c} \geq 6$ and/or T2DM.

Table 8-9: Effect of midlife psychological factors on HBA1c ≥6 in midlife in the NCDS

	N_D[1]	N_{ND}[2]	% M[3]	Complete Cases OR (95% CI)	Sig	MI[4] OR (95% CI)	Sig
Psychological distress at 23 yrs (Malaise)			13.5				
Normal	281	6,112					
Depressed	24	433		1.23 (0.80 , 1.88)	0.35	1.27 (0.84 , 1.91)	0.25
Psychological distress at 42 yrs (Malaise)			3.6				
Normal	297	6,416					
Depressed	57	870		1.42 (1.06 , 1.91)	0.02	1.38 (1.03 , 1.85)	0.03
GHQ12 at 42 years	354	7,286	3.6	1.01 (0.98 , 1.03)	0.68	1.00 (0.98 , 1.03)	0.73

1Those with HBA1c ≥6 by age 45 years; 2 With HBA1c <6 and no Type 2 diabetes at age 45 years

3 Percentage of missing data for each variable; 4 Based on combined results of 10 multiple-imputed datasets

Mid-life social, environmental, and lifestyle factors

The age-adjusted odds ratios (95% CI) for the relationship between a number mid-life social and lifestyle risk factors and the prevalence with $HbA_{1c} \geq 6$ and/or T2DM are presented in Table 8-10. As in the self reported diabetes, higher education attainment and regular physical exercise had a significant protective effect on T2DM. In contrast, obesity (both BMI and waist circumference), being in manual social class, and smoking by age 42 had a significant positive effect on the prevalence with $HbA_{1c} \geq 6$ and/or T2DM. BMI had the highest unadjusted effect with the odds of those who were obese almost 9 times the odds of those with normal weight (OR = 8.73, 95% CI = 6.43-11.84) Alcohol consumption by age 23 years and daily consumption of fruits by age 42 years did not show any significant association.

8.2.2. Mutually adjusted model for HBA1c ≥ 6 and/or T2DM

A number of possible confounding factors that were found significant in the univariable model were tested in a series of multivariable models to evaluate their influence on the effect of early-life psychological factors on the prevalence with HbA1c ≥ 6 and/or T2DM. Majority of the significant confounders in the bivariate model were highly correlated with each other, and so among the correlated ones, only one was maintained in the final model. Arithmetic and reading scores were highly correlated with each other and with the social class of the mother's husband, with those whose fathers were in the non-manual class having higher scores. Also reading and arithmetic score as well as the social class of the mother's husband highly predicted the smoking status by age 16. The

social class at birth was also highly correlated with the mother's education attainment. After a series of model selection procedures, the final model was the one adjusted for sex, family history of diabetes, social class of the father, and maternal smoking. There were no interaction effects between any of the covariates evaluated and the childhood behavioural problems showing no potential effect modifiers.

Table 8-10: Effect of midlife social, environmental, and lifestyle factors on HBA1c ≥6 in midlife in the NCDS.

	N_D[1]	N_{ND}[2]	%	Complete Cases			MI[4]		
			M[3]	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Alcohol consumption at age 23			13.5						
None	74	1,565							
Light	71	1,651		0.91	(0.65 , 1.27)	0.58	1.14	(0.67 , 1.94)	0.64
Medium/Heavy	160	3,329		1.01	(0.76 , 1.34)	0.93	1.24	(0.72 , 2.15)	0.44
Educational level at age 23			16.6						
No qualification	57	673							
CSE 2-5/equiv nvq1	46	819		0.66	(0.44 , 0.99)	0.05	0.67	(0.44 , 1.01)	0.06
O level/equiv nvq2 & Higher	194	4,822		0.47	(0.35 , 0.64)	<0.01	0.48	(0.36 , 0.64)	<0.01
Social class at age 33			16.3						
I /II/III: Proff/manager/non-man.	155	3,946							
III: Skilled manual	71	1,254		1.45	(1.08 , 1.93)	0.01	1.44	(1.11 , 1.88)	0.01
IV or V: Partly/ unskilled	69	1,136		1.55	(1.16 , 2.08)	<0.01	1.62	(1.21 , 2.18)	<0.01
Smoking at age 41			3.2						
Never smoked	129	3,368							
Ex/occasional smoker	109	2,213		1.29	(0.99 , 1.67)	0.06	1.29	(0.99 , 1.67)	0.06
Current smokers	115	1,737		1.73	(1.34 , 2.24)	<0.01	1.73	(1.34 , 2.24)	<0.01
Drinking problem at age 42			4.4						
No	306	6,313							
Yes	42	915		0.96	(0.69 , 1.33)	0.79	0.94	(0.68 , 1.31)	0.71
Physical exercise at age 42			3.2						
No	112	1,778							
Yes	242	5,539		0.69	(0.55 , 0.87)	<0.01	0.69	(0.54 , 0.87)	<0.01
BMI at age 42			0.5						
Normal	44	2,701							
Overweight	98	3,153		1.90	(1.32 , 2.72)	<0.01	2.39	(1.75 , 3.27)	<0.01
Obesity	218	1,671		7.94	(5.71 , 11.03)	<0.01	8.73	(6.43 , 11.84)	<0.01
Sex specific waist circumference			0.5						
Normal abdominal fat	109	5,090							
Severe abdominal fat	252	2,436		4.82	(3.83 , 6.06)	<0.01	4.82	(3.83 , 6.06)	<0.01
Fruit consumption			3.2						
Never/occasional(<1 day a wk)	78	1,356							
1-6 days a week	172	3,801		0.78	(0.60 , 1.03)	0.08	0.78	(0.60 , 1.03)	0.08
1 or more a day	104	2,161		0.84	(0.62 , 1.13)	0.24	0.84	(0.62 , 1.13)	0.24

1Those with HBA1c ≥6 by age 45 years; 2 With HBA1c <6 and no Type 2 diabetes at age 45 years

3 Percentage of missing data for each variable; 4 Analysis based on combined results of 10 multiple-imputed datasets

Table 8-11: Effect of childhood psychological factors on HBA1c ≥ 6 or/and Type 2 diabetes in midlife in the NCDS with adjustment for confounders[1].

	Confounders-adjusted OR(95% CI)[1]					
	Complete Cases			MI[2]		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	1.01	(0.98 , 1.04)	0.57	1.01	(0.98 , 1.05)	0.52
Hyperactive	1.04	(0.93 , 1.15)	0.51	1.05	(0.95 , 1.15)	0.35
Emotional problems	0.97	(0.90 , 1.05)	0.48	0.97	(0.90 , 1.04)	0.40
Conduct problem	1.03	(0.95 , 1.12)	0.43	1.04	(0.97 , 1.12)	0.29
Child Behaviour at School (BSAG)						
Emotional problems	1.05	(1.02 , 1.07)	<0.01	1.04	(1.01 , 1.06)	<0.01
Conduct problems	1.03	(1.01 , 1.05)	<0.01	1.03	(1.01 , 1.05)	<0.01
Miscellaneous Nervous Syndrome	1.33	(1.04 , 1.70)	0.02	1.24	(0.98 , 1.57)	0.08
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	1.02	(0.99 , 1.06)	0.20	1.03	(1.00 , 1.06)	0.08
Hyperactive	1.04	(0.95 , 1.15)	0.39	1.05	(0.96 , 1.16)	0.28
Emotional problems	1.00	(0.93 , 1.08)	0.96	1.02	(0.95 , 1.09)	0.66
Conduct problem	1.07	(0.98 , 1.16)	0.11	1.09	(1.01 , 1.17)	0.03
Child Behaviour at School (BSAG)						
Emotional problems	1.05	(1.03 , 1.08)	<0.01	1.04	(1.02 , 1.07)	<0.01
Conduct problems	1.04	(1.02 , 1.06)	<0.01	1.04	(1.02 , 1.06)	<0.01
Miscellaneous Nervous Syndrome	1.33	(0.97 , 1.82)	0.07	1.19	(0.88 , 1.61)	0.25
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	1.01	(0.97 , 1.05)	0.72	1.02	(0.99 , 1.05)	0.14
Hyperactive	0.92	(0.76 , 1.11)	0.37	1.05	(0.90 , 1.21)	0.54
Emotional problems	1.07	(0.99 , 1.17)	0.11	1.05	(0.97 , 1.13)	0.20
Conduct problem	1.04	(0.93 , 1.16)	0.51	1.05	(0.96 , 1.16)	0.27
Child Behaviour at School (Rutter B) total score						
Well adjusted						
With behavioural disorder	1.72	(1.26 , 2.35)	<0.01	1.47	(1.09 , 1.98)	0.01
Subscales for Rutter B						
Neurotic	1.17	(1.06 , 1.30)	<0.01	1.13	(1.04 , 1.24)	0.01
Antisocial	1.07	(1.01 , 1.14)	0.03	1.04	(0.98 , 1.11)	0.16

1 Adjusted for the effect of sex, family history of diabetes, social class of the father, and maternal smoking

2 Analysis based on combined results of 10 multiple-imputed datasets

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

In the fully confounder adjusted model, both outwardly (overreaction/conduct problems) and inwardly (undereaction/emotional problems) expressed behaviours as assessed by the teacher were still significantly associated with the prevalence with $HbA_{1c} \geq 6$ and/or

T2DM (Table 8-11). There was a 4% increase in the odds of the prevalence with $HbA_{1c} \geq 6$ and/or T2DM for every unit increase in the emotional problem scores as reported by the teacher at age seven and a 3% increase for the outwardly expressed behaviour. For the age 11 measures, there was a 4% increase in the odds of prevalence with $HbA_{1c} \geq 6$ and/or T2DM for each unit increase in both the teacher reported conduct and emotional problem scores, showing that children with more behavioural problems were at a higher risk of having elevated HbA_{1c} and/or Type 2 diabetes later in life. Those with any behavioural disorder by age 16 (Rutter B teacher scale) were also significantly at risk of $HbA_{1c} \geq 6$ and/or T2DM (OR= 1.47, 95% CI= 1.09-1.98) later in life. Only the neurotic component of the Rutter B scale was significant after adjusting for the confounders.

8.2.3. Possible mediating effect

Table 8-12 presents the results of the hypothesised relationship (in Figure 7-3) between early life psychological factors latent indicators and the prevalence with $HbA_{1c} \geq 6$ and/or T2DM. Both the comparative fit index and the RMSEA value showed a good model fit for all the models. Only the specific indirect effects on the prevalence with $HbA_{1c} \geq 6$ and/or T2DM through other variables, the total indirect effect, and the total effects, for both the direct and indirect effects, as obtained by the product of coefficients have been presented in the table.

Children who showed extreme inwardly expressed behaviour (emotional problems) as assessed by the teacher at both age 7 and age 11 were at a higher risk of having elevated HbA_{1c} and/or diabetes later in life and this effect was not mediated by any of the factors tested. For every standard deviation increase in the these behavioural scores, there was a 6% and 7% increase, respectively, in the standard deviation for prevalence with $HbA_{1c} \geq 6$ and/or Type 2 diabetes in midlife. There was also an indirect effect through obesity in adulthood (path 2) and through educational attainment and social class at age 33.

All the other psychological factors were not directly associated with elevated HbA_{1c} and/or diabetes. However, there were significant total indirect effects through other pathways except for the emotional problems at age 7. The magnitude of indirect effect of teacher reported conduct problems at age 7 and 11, mother reported conduct problems at age seven, and antisocial and neurotic problems at age 16 were high enough such that there were significant total effects for these measures.

Table 8-12: Direct and indirect effects of the latent childhood psychological factors on $HbA_{1c} \geq 6$ and/or self reported Type 2 diabetes in midlife in the NCDS with adjustment for possible confounders and mediators.

	Direct Effect			Specific Indirect Effect						Total Indirect			Total Effect		
				Path 2[1]		Path 3[2]		Path 4[3]							
	Est	95% CI	Sig.	Est	Sig.	Est	Sig.	Est	Sig.	Est	95% CI	Sig.	Est	95% CI	Sig.
Age 7(Rutter A)															
Hyperactive	-0.01	(-0.09, 0.07)	0.82	0.05	<0.01	0.01	0.07	0.02	<0.01	0.07	(0.06, 0.11)	<0.01	0.07	(-0.01, 0.14)	0.09
Emotional problems	-0.06	(-0.12,0.01)	0.10	0.00	0.53	0.01	0.05	-0.001	0.53	0.001	(-0.01,0.02)	0.86	-0.06	(-0.12,0.01)	0.11
Conduct problems	0.01	(-0.07,0.08)	0.86	0.05	<0.01	0.01	0.09	0.02	<0.01	0.08	(0.06,0.10)	<0.01	0.09	(0.02,0.16)	0.01
Age 7 (BSAG)															
Emotional problems	0.06	(-0.01,0.12)	0.03	0.02	<0.01	0.01	0.09	0.02	<0.01	0.05	(0.03,0.07)	<0.01	0.11	(0.06,0.17)	<0.01
Conduct problems	0.02	(-0.04,0.07)	0.50	0.04	<0.01	0.01	0.07	0.02	<0.01	0.06	(0.05,0.08	<0.01	0.08	(0.03,0.14)	<0.01
Age 11 (Rutter A)															
Hyperactive	-0.03	(-0.10,0.05)	0.50	0.06	<0.01	0.01	0.08	0.02	<0.01	0.09	(0.07, 0.12)	<0.01	0.07	(-0.01,0.14)	0.06
Emotional problems	-0.05	(-0.11,0.02	0.15	0.003	0.57	0.01	0.03	0.001	0.48	0.02	(0.00, 0.03	0.05	-0.03	(-0.09,0.03)	0.35
Conduct problems	0.01	(-0.07, 0.08)	0.86	0.06	<0.01	0.01	0.11	0.02	<0.01	0.09	(0.07,0.11)	<0.01	0.10	(0.03,0.16)	0.01
Age 11 (BSAG)															
Emotional problems	0.07	(0.01,0.12)	0.02	0.03	<0.01	0.01	0.11	0.02	<0.01	0.06	(0.04,0.08)	<0.01	0.12	(0.07,0.18)	<0.01
Conduct problems	0.05	(-0.01,0.10)	0.09	0.04	<0.01	0.01	0.09	0.02	<0.01	0.07	(0.05,0.09)	<0.01	0.11	(0.06,0.16)	<0.01
Age 16 (Rutter A)															
Hyperactive	-0.04	(-0.15,0.07)	0.46	0.06	<0.01	0.02	0.13	0.03	<0.01	0.11	(0.07,0.11)	<0.01	0.07	(-0.02,0.16)	0.12
Emotional problems	0.02	(-0.06,0.11)	0.62	0.01	0.33	0.02	0.08	0.01	<0.01	0.03	(0.01,0.06)	0.01	0.05	(-0.03,0.14)	0.18
Conduct problems	-0.03	(-0.11,0.06)	0.51	0.05	<0.01	0.02	0.11	0.03	<0.01	0.10	(0.06,0.13)	<0.01	0.07	(-0.01,0.14)	0.07
Age 16 (Rutter B)															
Neurotic	0.05	(-0.03,0.13)	0.24	0.03	<0.01	0.01	0.18	0.03	<0.01	0.07	(0.04,0.10)	<0.01	0.12	(0.04, 0.19)	<0.01
Antisocial	0.01	(-0.08,0.09)	0.87	0.04	<0.01	0.01	0.12	0.03	<0.01	0.09	(0.05,0.12)	<0.01	0.09	(0.02,0.17)	0.01

1 Through BMI (kg/m^2) at age 42

2 Through adulthood psychological distress at age 23 and age 42

3 Through education achievement at age 23, and social class at age 33

In contrast to the self reported diabetes results, there were no significant indirect effects through the mid-life psychological distress for all the childhood psychological measures except for the emotional problems reported by the mother at age 11. This shows the lack of continuities in the psychological measures over the life course in affecting the disease in mid life. The path through BMI had the highest magnitude effect for all the measures, showing that children with behavioural problems are more likely to be obese in mid life thus increasing their risk of having elevated HbA_{1c} or diabetes.

Chapter 9

Type 2 Diabetes in Mid-life: Discussion and Conclusions

Using this prospective nationwide representative birth cohort data, social adjustment at school as measured by the BSAG scale at age 7 and 11 and behavioural problems as reported by the teacher at age 16 were significantly associated with both the self reported Type 2 diabetes at age 42 years and the prevalence with $HbA_{1c} \geq 6$ and/or T2DM. Subjects who by age 7 or 11 showed severe conduct and emotional problems had significantly higher risk of T2DM in mid life. The total Rutter score for the teacher's scale, implying behavioural difficulties at school, also showed significant association with Type 2 diabetes, though none of its subscales was significant.

In a mutually adjusted structural equations model and taking into account the temporal nature of the predictor variables, both conduct and emotional problems assessed by the teacher through the BSAG scale at age 11 were directly associated with Type 2 diabetes in mid life. Thus their effects on diabetes were not completely mediated by obesity, adulthood psychological measures, education attainment or social class. Findings also revealed that children who showed extreme inwardly expressed behaviour (emotional problems) as assessed by the teacher at both age 7 and age 11 were at a higher risk of having elevated HbA_{1c} and/or diabetes later in life and this effect was not mediated by any of the factors tested.

Investigation of home behaviour, which reflected the parental view of the child's behaviour, gave a different picture. None of the parental subscales at either age 7, 11 or 16 significantly predicted self reported Type 2 diabetes. Only the conduct problems at age 7 and 11 and the total Rutter score were significantly associated with $HbA_{1c} \geq 6$ and/or T2DM. This discrepancy in the finding may be due to the greater tendency of parents, rather than teachers, to over-protect their children concerning the adverse behavioural difficulties. The evidence regarding discrepancy between parent's and teacher's behaviour rating has been observed in many studies. Just by the fact that the rating is done by different individuals, one encounters the expected problems of bias which characterise tasks requiring human judgements of other humans. For the example of the NCDS, only a correlation of 0.21 was obtained between the total score of the BSAG and a home behaviour scale completed by the mother (Lambert and Hartsough,

1973). Although in the extreme case it can be argued that the factors or the ratings represent the teacher's view and not the true characteristic of the child, it is unlikely that a teacher's perception of the child is a wholly projection of himself (Ghodsian, 1977), therefore it is reasonable to consider these as the child's behaviour through the eyes of the teacher.

Despite not having any direct association with T2DM, the parents' identified behavioural difficulties still had indirect effects through mid life psychological factors, mid life educational attainments and social class, and through adulthood obesity. The magnitude of such indirect effects was quite strong for some behavioural problems such that there were significant total effects for these measures.

There was a significant indirect effect for both the teacher assessed and the parent identified behavioural problems through adulthood psychological factors. Through this pathway, the childhood behavioural difficulties were significantly associated with adulthood psychological distress which in turn increased the risk for self reported T2DM and prevalence with $HbA_{1c} \geq 6$ and/or T2DM. Such continuities over time in individual emotional and behavioural difficulties and their effects on T2DM can be explained by the increase in blood glucose levels and decreased insulin action occasioned by a variety of counter-regulatory hormones that are released in response to stress. Studies have found that in response to psychological stress, the brain stimulates release of the counter-regulatory hormones which counteract the hypoglycaemic action of insulin by raising blood levels of glucose (Surwit and Schneider, 1993; Sapolsky *et al.*, 2000; Musselman *et al.*, 2003). As a consequence of increased release of counter-regulatory hormones and diminished cellular glucose uptake, patients with major depression may exhibit insulin resistance (Nathan *et al.*, 1981; Winokur *et al.*, 1988).

Comparison with other studies

There is not much literature on the association between childhood psychological factors and mid-life diabetes. One previous study using the NCDS data (Thomas *et al.*, 2008) examined how different stressful emotional or neglectful childhood adversities are related to adiposity and glucose control in mid adulthood and found out that some childhood adversities increase the risk of obesity in adulthood and thereby increasing the risk for Type 2 diabetes. The same authors (Thomas *et al.*, 2007; Thomas *et al.*, 2008),

using the 1958 NCDS also investigated the roles of psychological factors in childhood and glucose metabolism in mid life and found that associations for several prenatal factors including stressful emotional experiences in childhood were largely mediated through adult adiposity. This study has found similar results with the teacher reported conduct and emotional behavioural problems in childhood. In addition, this study adds a new finding of the cumulative effect of childhood psychological factors to mid life psychological distress and ultimately increased risk for T2DM and prevalence with $HbA_{1c} \geq 6$ and/or T2DM.

For some time, research on psychological factors and diabetes has focused on adulthood psychological factors and there is no indication of whether the disease occurs before or after the psychological factors are measured. Despite the paucity of prospective studies, especially those from the general population, on the relationship between diabetes and depressive disorders, this study confirms the results of a few studies that have examined the temporal relationship of adulthood depression and incident diabetes later in life. Eaton and colleagues (1996) found that a major depressive disorder was associated with almost two-fold increased incidence of T2DM during a 13 years of follow-up. A more recent analysis of the association in the same study population after 23 years of follow-up (Mezuk *et al.*, 2008b) also found similar results and concluded that risk of T2DM associated with major depressive disorder persists over the life course and is independent of the effects of health behaviours, BMI, and family history. Another study of a cohort of employed Japanese men followed for eight years (Kawakami *et al.*, 1999) reached a similar conclusion. Other recent longitudinal studies (Carnethon *et al.*, 2007; Engum, 2007; Toshihiro *et al.*, 2008) have also yielded similar results. Similar to this current study, these studies also suffer from common limitation of small numbers of incident diabetes thus limited power. Thus, large prospective studies followed over a long period of time are required to confirm these findings.

Strengths and limitations

The major strengths of this study include its longitudinal design, large sample, objective measures for glucose metabolism, BMI and WC, prospectively collected data on psychological factors, and rich data on other childhood circumstances. The other advantage is that the psychological factors were measured before the diagnosis of

diabetes thus ruling out the possibility of the observed association being a result of reciprocal association.

A main limitation of the study is the lack of glucose tolerance tests because of practical limitations. However, HbA_{1c}, despite not being currently considered a suitable standard diagnostic test for diabetes or intermediate hyperglycaemia by WHO reflects average glycaemia over a period of weeks and is a good predictor of microvascular and macrovascular outcomes when compared with the oral glucose tolerance test (Perry *et al.*, 2001). Even though the diagnosis of Type 2 diabetes up to age 42 relied on self report which was not medically confirmed, subjects who were using prescriptions for diabetes were confirmed by research nurses during the biomedical survey.

The study is also limited by the lack of complete information on first-degree relatives with diabetes in the 1958 Birth Cohort. The only information available was collected once when the study participants were 7 years of age, supplemented by whether either of their parents had a diabetes-related cause of death.

As with all longitudinal studies, sample attrition had occurred over time, and although cross-sectional comparisons showed only small biases by childhood psychological measures, larger biases as well as loss of information and statistical power were apparent when complete data were examined for this study, and we, therefore, used multiple imputation to minimize any bias associated with missing data.

This study was confined to Type 2 diabetes with early onset (by 42 years of age) and HbA_{1c} by 45 years of age; therefore, extrapolation to older ages must be done cautiously. At age 42, the cohort is still relatively young and would not be expected to have fully developed conditions like diabetes which manifest themselves in earnest through middle-adulthood and into late-adulthood.

Despite these limitations, this study adds to our knowledge of the possible pathways through which childhood behavioural problems may increase the risk of Type 2 diabetes and glucose metabolism in mid life.

Conclusions

The findings from this study suggest that some childhood behavioural problems, particularly the conduct problems or overreaction behaviours in school, significantly increase the risk of Type 2 diabetes and glucose metabolisms in mid life either directly, cumulatively over the life course, or by increasing the risk for obesity in adulthood and thereby increasing the risk for Type 2 diabetes. However, the study demonstrated no independent effects of parent's reported behavioural problems with Type 2 diabetes.

More research using large prospective cohort studies with larger number of incident diabetes is required to confirm these findings.

SECTION IV

ADULT-ONSET ASTHMA

Chapter 10

Literature Review for Asthma Risk Factors

10.1. Introduction

Asthma, a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, is a serious global health problem with an estimated 300 million affected individuals, both children and adults of all ages (Masoli *et al.*, 2004; Braman, 2006). The chronic inflammation causes an associated increase in airway hyper-responsiveness (the tendency of airways to narrow excessively in response to triggers that have little or no effect in normal individuals) that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning (Braman, 2006). These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Mechanisms of asthma

The pathogenetic mechanisms underlying the many variants of asthma are complex, but airway inflammation is well recognised as the central focus in the pathogenesis of asthma and development of disease severity, and as the target of therapy (Busse, 1999). The airway inflammation in asthma is persistent even though symptoms are episodic, and the relationship between the severity of asthma and the intensity of inflammation is not clearly established (Cohn *et al.*, 2004). Approximately 80% of asthmatics experience the allergic asthma (Cohn *et al.*, 2004). The mechanisms regulating the allergic responses in the airways are complex, involving antigen presenting cells and T lymphocytes, which process antigens and orchestrate the response, and mast cells and eosinophils as effector cells (Djukanovic, 2000). Abundant evidence also points to a proinflammatory role for structural cells, including epithelial and endothelial cells, and smooth muscle. The mechanisms of inflammation central to the pathophysiology of these atopic disorders overlap and involve a cascade of events that include the release of immunologic mediators triggered by both immunoglobulin-E (IgE)-dependent and independent mechanisms (Wright *et al.*, 2005). Airway obstruction in bronchial asthma is mainly caused by contraction of bronchial smooth muscle, edema of the airway walls, mucous

plugging of the bronchioles, and irreversible changes in the lungs known as remodelling (Global Initiative for Asthma-GINA, 2008).

Diagnosis of asthma

A clinical diagnosis of asthma is suggested by its symptoms. Episodic symptoms after an incidental allergen exposure, seasonal variability of symptoms and a positive family history of asthma and atopic disease are also helpful diagnostic guides (Bateman *et al.*, 2008). Physical examination usually follows; the most usual abnormal physical finding being wheezing on auscultation, a finding that confirms the presence of airflow limitation. However, in some people with asthma, wheezing may be absent or only detected when the person exhales forcibly, even in the presence of significant airflow limitation. The diagnosis of asthma in early childhood (≤ 5 years) is challenging and has to be based largely on clinical judgment and an assessment of symptoms and physical findings. For older children and adults, a careful history and physical examination, together with the demonstration of reversible and variable airflow obstruction, preferably by pulmonary function tests such as spirometry will in most instances confirm the diagnosis of asthma (Bateman *et al.*, 2008). Spirometry measures the forced expiratory volume in one second (FEV_1), the forced vital capacity (FVC), and the Tiffeneau parameters (FEV_1/VC). For patients with symptoms consistent with asthma but normal lung function, measurements of airway responsiveness to methacholine, histamine, mannitol, adenosine monophosphate or exercise challenge may help to establish a diagnosis of asthma (Cockcroft, 2003). The presence of allergies in asthma patients (identified by skin testing or measurement of specific IgE in serum) can help to identify risk factors that cause asthma symptoms in individual patients.

Prevalence of asthma and asthma symptoms

The true prevalence of asthma is difficult to determine due to the lack of a single objective diagnostic test, different methods of classification of the condition, and differing interpretation of symptoms in different countries. However, based on the application of standardised methods to the measurement of the prevalence of asthma and wheezing illness in children (Masoli *et al.*, 2004) and adults (Urrutia *et al.*, 2007), the global prevalence ranges from 1–18% of the population in different countries. Estimates suggest that the prevalence has been increasing globally by 50% every decade (Masoli *et*

al., 2004). In Western Europe, almost 30 million individuals now have asthma and the prevalence rate has doubled over the last decade as indicated in the European Lung White Book (Loddenkemper *et al.*, 2003). In the UK, one estimate suggests that 3.4 million people, with one of every seven children aged 2-15 years (1.5 million) and one of every 25 adults (1.9 million), have asthma symptoms requiring treatment (Loddenkemper *et al.*, 2003).

Asthma and other respiratory conditions are now a significant cause of ill health and pose substantial public health problems in terms of primary care contacts, hospital admissions, loss of productivity and premature deaths. In the UK, there was an increase in the patients' consultation rates for asthma between 1971 and 1991 in all age groups, but marked in the youngest children (0-4 years) in whom the rates increased seven-fold (Loddenkemper *et al.*, 2003). Since then, there has been a gradual decrease in the incidence of the asthma episodes presenting to general practitioners. Fluctuations in asthma death rates have been observed in the UK since 1958 as illustrated in the data available, with the peak in 1988 at just over 2,000. Since then asthma deaths have began to fall, but are still currently around 1,500 per year for England and Wales (Loddenkemper *et al.*, 2003). The majority of asthma deaths occur in those aged over 45 years, with around 40% of deaths occurring in the 75+ age group.

Research into asthma

Although understanding of many aspects of asthma has improved over the past decades, the fundamental causes of the disorder and the reasons for its increased prevalence remain largely unknown. Many plausible hypotheses have been tested to understand the reason behind the increasing prevalence and severity of the disease. Among the factors that have been associated with the increase in asthma prevalence is the rise in atopic sensitization, a parallel increase in other allergic conditions (e.g. eczema and rhinitis), environmental factors (indoor air, outdoor air, tobacco smoking, nutrition, and respiratory infections) and host factors (genetic, gender effects, lung function). However, the focus on traditional genetic and environmental risk factors has not fully explained these trends in increased prevalence. As a result, advances in the field of psychoneuroimmunology (Ader *et al.*, 1995) and the epidemiological evidence regarding important interaction between psychosocial factors and development of disease have

provided fresh insight into means by which psychosocial stressors may influence the development and expression of inflammatory diseases.

Through the use of longitudinal studies, many researchers have examined the risk factors for the development as well as persistence, remission or relapse of asthma from infancy, through childhood to middle-age in the British population (Anderson *et al.*, 1986; Anderson *et al.*, 1987; Jones, 1996; Strachan *et al.*, 1996; Butland and Strachan, 2007). These studies have provided a useful understanding of the major risk factors of childhood asthma; however, few studies have investigated the adult-onset wheezing. The birth cohort studies have also suggested that events and exposure *in utero*, in early infancy, and during the pre-school years play a major role in the development of asthma. A life course approach to the epidemiology of asthma therefore seems appropriate.

This section examines the direct and indirect contribution of the childhood psychological factors in the development of asthma. Using longitudinal data from the two British birth cohort studies, this study investigates whether early life behavioural and emotional difficulties have a causal role in the aetiology of adult wheezing illness. A review of the literature is undertaken to determine the current state of knowledge in the risk factors involved in the development of asthma so that all such known and putative risk factors are properly adjusted for. After a review of the host and environmental factors, a comprehensive review of the roles of psychological factors is considered. The major databases searched were Medline, PsycINFO, and PubMed up to October 2009 together with the reference lists from the relevant review and articles. For the review of the psychological factors, the search was restricted to mainly prospective cohort studies investigating the influence of psychosocial factors on atopic disorders. The main search strategy was “asthma or atop* or allerg*”- aetiology in combination with “psycho* or stress or depress* or anxiety or emotions or personality or affective*”.

10.2. Factors Influencing the Development and Expression of Asthma

There are a number of risk factors for the development of asthma, including genetic and environmental components. According to the Global Initiative for Asthma (GINA) report (2008), the risk factors can be divided into those that cause the development of asthma and those that trigger asthma symptoms; some do both. The former include host factors (which are primarily genetic) and the latter are usually environmental factors. However,

the mechanisms whereby these factors influence the development and expression of asthma are complex and interactive (Holgate, 1999; Ober, 2005).

10.2.1. Host factors

Genetic

It is widely accepted that asthma has a heritable component, and a number of studies have shown an increased prevalence of asthma, and phenotypes associated with asthma among the relatives of asthmatic subjects compared with non-asthmatic subjects (Longo *et al.*, 1987; Dold *et al.*, 1992). However, those genetic studies have shown that asthma does not follow classical patterns of Mendelian inheritance; instead, asthma is inherited as a complex trait and the results from the interaction of multiple genes and the environmental factors play a fundamental role both in the pathogenesis and in the development of the disease.

Since the familial concordance of a disorder can be due to shared environment as well as shared genes, twin studies can help to determine the relative contribution of shared environment and shared genes to a phenotype. Numerous twin studies (Laitinen *et al.*, 1998; Los *et al.*, 2001) have shown a significant increase in concordance among monozygotic twins compared with dizygotic twins, providing evidence for a genetic component. Due to the genetic complexity of asthma, a number of genes are thought to be involved in its pathogenesis (polygenetic inheritance) (Holloway *et al.*, 1999). The different combinations of genes may act in different families (genetic heterogeneity) and the same gene or sets of genes may influence multiple traits (pleiotropy), for example, asthma and eczema (Los *et al.*, 2001). The search for genes linked to the development of asthma has focused on four major areas: production of allergen-specific IgE antibodies (atopy); expression of airway hyper-responsiveness; generation of inflammatory mediators such as cytokines, chemokines, and growth factors; and determination of the ratio between T_H1 and T_H2 immune responses- as relevant to the hygiene hypothesis of asthma (Global Initiative for Asthma-GINA, 2008).

Studies have identified markers and candidate genes on nearly every chromosome that demonstrate linkage or association with asthma or its intermediate phenotypes. Schwartz (2009) has reviewed some of the most reproducible linkages and plausible chromosomal regions. However, the search for a specific gene (or genes) involved in susceptibility to

atopy or asthma continues as results to date have been inconsistent (Holloway *et al.*, 1999).

Obesity

Several studies have reported an association between asthma and obesity (Schachter *et al.*, 2001; Guerra *et al.*, 2002; Weiss and Shore, 2004; Chinn *et al.*, 2006). However, most of these studies are cross-sectional, and some use self-report to define asthma, emphasizing the need for longitudinal, prospective studies. The results of a pooled analysis from three large epidemiological studies (Schachter *et al.*, 2001) showed that after adjusting for atopy, age, sex, smoking history, and family history, severe obesity was a significant risk factor for recent asthma (OR 2.04, $p = 0.048$) and wheeze in the previous 12 months (OR 2.6, $p = 0.001$). The nature of the association between obesity and asthma is still controversial (Elamin, 2004; Apter, 2007)- what remains unclear is whether the association has a biologic cause, whether respiratory symptoms in obese persons are misdiagnosed as asthma, or whether the observed association is due to simultaneously occurring but unrelated factors, such as the growing availability of high-calorie food. Several possible mechanisms have been suggested but no consensus has been reached. The common assumption is that weight gain occurs because many asthmatic patients avoid exercise since physical activity can trigger their symptoms (Westermann *et al.*, 2008). Large prospective studies and randomized population-based studies are therefore needed to determine the prevalence of such an association and the mechanisms that might lead to the association.

Sex

Male sex has been found to be a significant risk factor for asthma in children. Prior to the age of 14, the prevalence of asthma is nearly twice as great in boys as in girls (Horwood *et al.*, 1985; Nicolai *et al.*, 2001). As children get older the difference between the sexes narrows, and by adulthood the prevalence of asthma is greater in women than in men. Becklake and Kauffmann (1999) have given a comprehensive review on some of the observed gender differences in asthma and some of the basic physiological differences that may explain them. One of the reasons for the sex-related difference is that lung size is smaller in males than in females at birth but larger in adulthood. The influence of some environmental risk factors may also be influenced by gender. The influence of obesity on

the development of asthma has also been found to be greater in women than in men (Weiss and Shore, 2004).

10.2.2. Environmental factors

Environmental factors can influence the risk of developing asthma or can cause asthma symptoms or both (e.g. occupational sensitizers). However, there are some important causes of asthma symptoms such as air pollution and some allergens which have not been clearly linked to the development of asthma (Global Initiative for Asthma-GINA, 2008). From current evidence, it appears that in subjects with the appropriate genetic make-up, environmental factors such as infections and allergens can induce a proinflammatory cytokine response that causes airway inflammation and that in turn leads to the initiation and persistence of altered airway function (Busse, 1999). The major environmental factors that have been associated with asthma development and exacerbations are discussed below:

Allergens

Many studies have demonstrated the important role that allergens play not only in the initiation of asthma but also in its persistence. Amongst numerous other factors, exposure to allergens has been related to asthma severity. It is well established that allergen exposure is a secondary cause of asthma in that it can trigger asthma attacks in sensitised asthmatic subjects and prolonged exposure can lead to the persistence of symptoms (Peat *et al.*, 1996; Rosenstreich *et al.*, 1997; Custovic *et al.*, 1998).

Although indoor and outdoor allergens are well known to cause asthma exacerbations, their specific role in the development of asthma is still not fully resolved. Showing the direct relationship between personal allergen exposure and symptoms has always been difficult, in part due to a number of possible confounding factors. Patients are often sensitized and exposed to more than one allergen, and viral infection and medication may obscure the relationship. Furthermore, such relationship between allergen exposure and sensitization depends on the allergen, the dose, the time of exposure, the individual's age, and probably genetics as well.

Birth-cohort studies have shown that sensitization to house dust mite allergens, cat dander, dog dander (Sporik *et al.*, 1990; Sporik *et al.*, 1992; Wahn *et al.*, 1997), and *Aspergillus* (Hogaboam *et al.*, 2005) are independent risk factors for asthma like symptoms in childhood. However, the results from a randomised controlled trial that measured allergen exposure early in life and related it to overall asthma risk after the age of five years (Burr *et al.*, 1993) did not support such finding. Similar findings have been observed in longitudinal studies (Lau *et al.*, 2002). The hypothesised causal mechanism is that allergen exposure produces sensitisation and continued exposure leads to clinical asthma through the development of airways responsiveness and inflammation (Sporik *et al.*, 1990).

Even though the association of allergy and symptoms of asthma has been mainly established in childhood studies, adult studies have also found that asthma is predominantly an allergic condition mediated by IgE. A prospective study of a hundred babies of atopic parents based in Poole, England (Rhodes *et al.*, 2001) found that subjects at risk of atopy, skin sensitivity to hen's egg or cow's milk in the first year are predictive of adult asthma. Another study based on 2,657 subjects carried out by Burrows *et al.* (1989) to investigate the association of self-reported asthma or allergic rhinitis with serum IgE levels concluded that asthma is almost always associated with some type of IgE-related reaction and therefore has an allergic basis. However, recent reviews examining the roles of allergen exposure as a major primary cause of asthma (Pearce *et al.*, 2000; Holt and Thomas, 2005) have found the direct evidence to be relatively weak and far from convincing. This issue remains unresolved as can be demonstrated in the recent reappraisal (Von Hertzen and Haahtela, 2009) and its associated rebuttal (Platts-Mills *et al.*, 2009); therefore, population-based cohort studies are clearly required.

Infections

Viral infections have been implicated in at least three ways to the pathogenesis of asthma: inception, prevention and exacerbations. In early life, viral infections can either increase or remarkably decrease the risk of subsequent asthma. Certain viral infections in infancy such as respiratory syncytial virus (RSV) and parainfluenza virus produce a pattern of symptoms including bronchiolitis that parallel many features of childhood asthma (Sigurs *et al.*, 2000; Gern and Busse, 2002). It has also been proposed that infants who contract RSV bronchiolitis are at an increased risk of developing asthma later in life.

A number of long-term prospective studies of children admitted to the hospital with documented RSV have shown that approximately 40% will continue to wheeze or have asthma into later childhood (Sigurs *et al.*, 2000). However, studies to determine the effect of viral infections on the development of asthma have yielded controversial and conflicting results. Recent epidemiological studies indicate that not all viral infections increase the risk of asthma and, in fact, some may actually reduce the risk of developing allergic diseases and asthma as the child gets older (Stein *et al.*, 1999). Such variability in the studies' results may be attributable to several factors, including the specific viral pathogen, the severity of the illness, the anatomical location of the illness and the age of the affected individual.

The controversial idea that some viral infections might actually protect against the development of allergies and asthma, termed the "hygiene hypothesis", was first suggested by Strachan (1989), who noted that the risk of developing allergies and asthma is inversely related to the number of children in the family using the NCDS data. The hygiene hypothesis of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a "non-allergic pathway", leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this mechanism may explain observed associations between family size, birth order, day-care attendance, and the risk of asthma (Bateman *et al.*, 2008).

In children and adults with existing asthma, viral respiratory infections have been found to be important precipitants for acute episodes of airway obstruction and wheezing. In recent studies using reverse transcription polymerase chain reaction (RT-PCR)-based diagnostic assays (Nicholson *et al.*, 1993; Johnston *et al.*, 1995), the rhinovirus has emerged as the most important cause of these acute episodes and infection. In fact, up to 80% of exacerbations of asthma in children and about half of such episodes in adults are caused by viral infections most of which are attributable to rhinoviruses (Nicholson *et al.*, 1993).

Occupational sensitizers

Occupational asthma (OA) is a type of asthma due to causes and conditions attributable to a particular work environment rather than to stimuli encountered outside the

workplace (Bernstein *et al.*, 2006). Over 300 substances have been associated with OA, most of these have been summarised by Malo and Chan-Yeung (2009). These substances can be classified conveniently into high-molecular-weight (HMW) and low-molecular-weight (LMW) compounds. HMW compounds, which are often from biological sources, generally induce asthma through an IgE-dependent mechanism, whereas many LMW compounds induce asthma through non–IgE-dependent mechanisms. Two types of OA can be distinguished: first, immunologic OA appears after a latency period of exposure necessary for acquiring immunologic sensitization to the causal agent; second, non-immunologic OA, which is far less frequent and characterized by the absence of a latency period, occurs after acute exposure to high concentrations of irritants and has been termed irritant-induced asthma (Bernstein *et al.*, 2006).

Occupational asthma arises predominantly in adults (Bernstein *et al.*, 2006; Malo and Chan-Yeung, 2009) and has become one of the most common forms of occupational lung disease in many industrialized countries, having been implicated in 9% to 15% of cases of adult asthma (Nicholson *et al.*, 2005). OA results from the interactions of host factors, genetic factors, and levels and routes of exposure to an inciting agent. Maestrelli *et al.* (2009) provide a comprehensive review of the currently known mechanisms involved in OA. Some of the occupations associated with a high risk for OA include farming and agricultural work, painting (including spray painting), cleaning work, and plastic manufacturing (Malo and Chan-Yeung, 2009).

Other than the intrinsic physicochemical and immunogenic properties of agents, the most important risk for developing OA is the level and duration of exposure to agents capable of causing OA. The most important method of preventing occupational asthma is elimination or reduction of exposure to occupational sensitizers. Therefore, adoption and enforcement of optimum industrial hygiene measures in the workplace is the only effective means to reduce or completely eliminate ambient levels of known allergens or respiratory irritants (Bardana Jr, 2008).

Outdoor/indoor air pollution

Although extensive evidence shows that ambient air pollution exacerbates existing asthma (Utell and Frampton, 2000), a link with the development of asthma is less well established. This is primarily because few prospective studies with extensive exposure

data have been conducted. The ambient air pollutants that have been studied include particulate matter (PM), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and ozone (O_3). Children raised in a polluted environment have diminished lung function. In a prospective study over eight-year period, Gauderman *et al.* (2004) found that deficits in the growth of FEV_1 were associated with exposure to nitrogen dioxide ($p = 0.005$), acid vapour ($p = 0.004$), particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) ($p = 0.04$), and elemental carbon ($p = 0.007$), even after adjustment for several potential confounders and effect modifiers. However, the relationship of such loss of function to the development of asthma is not known. From a review of five prospective studies evaluating the associations between air pollution and incidence of asthma, Gilmour *et al.* (2006) found that the results from these studies support a modest increase in risk for air pollution in relation to phenotypes relevant to asthma. However, three of these studies with subjects old enough to have a firm diagnosis of asthma shared limitations of uncertainty about when asthma started.

There is also some little evidence of the effects of indoor pollutants (such as smoke and fumes from gas and biomass fuels used for heating and cooling, moulds, and cockroach infestations) and asthma (Gilmour *et al.*, 2006). Fungi are also an important factor in indoor exposures leading to allergic and asthmatic events (Jaakkola and Jaakkola, 2004). Several studies have also shown that home dampness is a significant predictor of respiratory symptoms (Bornehag *et al.*, 2001; Institute of Medicine, 2004).

Tobacco smoking

The evidence implicating smoking and the benefits of smoking cessation have been extensively reviewed (US Department of Health and Human Services-Public Health Service, 1984, 1990), probably not least for patients suffering from asthma. Several deleterious effects have been described in people with asthma because of smoking: accelerated decline in lung function in male and female adults (Gold *et al.*, 1996; Ulrik and Lange, 2001; Kohansal *et al.*, 2009); more severe symptoms (Althuis *et al.*, 1999; Siroux *et al.*, 2000); impairment in quality of life (Thomson *et al.*, 2003); and diminished therapeutic response to steroids (Chalmers *et al.*, 2002; Chaudhuri *et al.*, 2003; Thomson *et al.*, 2003).

Studies investigating whether active smoking is a risk factor for asthma have however produced conflicting results. Oechsli *et al.* (1987) reported from a longitudinal study of a large cohort of white boys and girls (n = 1,445), aged 15 to 17 years, followed since birth that cigarette smoking is not causally related to childhood and adolescent asthma. In line with this observation, another epidemiological prospective study of almost 15,000 Finnish adults (Vesterinen *et al.*, 1988) also concluded that smoking is not a strong risk factor for asthma. In contrast, other longitudinal studies have observed an association between asthma and active smoking in adolescence (Kaplan and Mascie-Taylor, 1997; Rasmussen *et al.*, 2000).

Exposure to tobacco smoke both prenatally and after birth has been found to be associated with measurable harmful effects including a greater risk of developing asthma-like symptoms in early childhood. Prenatal environmental tobacco smoke (ETS), particularly maternal smoking in pregnancy has been found to be a risk factor for wheeze in early life (Lau *et al.*, 2002; Macaubas *et al.*, 2003), with infants of smoking mothers almost 4 times more likely to develop wheezing illnesses in the first year of life (Dezateux *et al.*, 1999). Maternal smoking during pregnancy and children's exposure to ETS have also been found to be among the non-allergic factors associated with an increased risk for development of and enhanced morbidity in persistent asthma or rhinitis or both (Arruda *et al.*, 2005). In contrast, there is little evidence (based on meta-analysis) that maternal smoking during pregnancy has an effect on allergic sensitization (Strachan and Cook, 1998).

Diet

It has been hypothesized that the recent increase in the prevalence of asthma may, in part, be a consequence of changing diet. Four types of dietary constituents have been extensively studied: breast feeding and food avoidance in infancy; antioxidant vitamins, specifically vitamin C; dietary cations, specifically sodium and magnesium; and N3-N6 fatty acids. However, the available data are insufficient to implicate any dietary constituent as a causal risk factor for asthma.

Components of maternal and early life diets have been reported to influence offspring immune function and asthma. Reduced maternal intake of vitamin E, vitamin D, and zinc during pregnancy have been associated with a greater risk of development of asthma and

wheezing symptoms in 5-year-old children (Devereux *et al.,* 2006; Devereux *et al.,* 2007). Recent studies have also revealed that adherence to a Mediterranean diet (Chatzi *et al.,* 2008) and frequent maternal intake of fish (Calvani *et al.,* 2006; Romieu *et al.,* 2007) during pregnancy, are associated with protection from persistent wheeze and atopy in children. The role of breast-feeding in the prevention of allergic disease has been extensively reviewed (Friedman and Zeiger, 2005), and though still remains controversial, in general, studies reveal that infants fed on formulas of intact cow's milk or soy protein have a higher incidence of wheezing illnesses in early childhood compared with those fed on breast milk.

There is also relatively persuasive evidence that use of processed foods and decreased antioxidant (in the form of fruits and vegetables), increased n-6 polyunsaturated fatty acid (found in margarine and vegetable oil), reduced magnesium, and decreased n-3 polyunsaturated fatty acid (found in oily fish) intakes have contributed to the recent increases in asthma and atopic disease (Baker and Ayres, 2000; Fogarty and Britton, 2000; Devereux and Seaton, 2005).

Social environment

Social environment has a marked influence on the outcome of asthma and other treatable diseases. It has long been recognised that there is a strong association between poor socioeconomic status (SES) and both mortality and general practice consultations for adult respiratory disease in Britain (Strachan, 1995). Although much of this may be attributable to social class differences in smoking behaviour, population surveys have shown associations independent of current smoking habits. Findings with respect to SES and asthma prevalence are mixed, with some studies reporting no, positive, or inverse associations. However, most of these studies have been cross sectional in design and have relied on subjective markers of asthma such as symptoms of wheeze, and many have been unable to control adequately for potential confounding factors. One of the prospective cohort study (Hancox *et al.,* 2004) has also reported no significant association between childhood or adult socioeconomic status and asthma prevalence, lung function, or airway responsiveness at any age.

Other aspects of social environment that might have adverse effect on asthma in terms of barriers to quality of care include membership to certain racial and ethnic minority

groups, culture and physical environment (Apter, 2007). Other factors that have been found to be associated with asthma include occupation, housing type, and overcrowding (Kaplan and Mascie-Taylor, 1985).

10.2.3. Other factors

A host of other factors have been found to be associated with both asthma onset and exacerbation. Perinatal environment exposures are thought to influence the immune development and potentially alter the risk for allergic responses to allergens. Evidence suggests that preterm babies have an increased risk of asthma compared with term babies. Jaakkola *et al.* (2006) through a meta-analysis found that preterm birth (gestational age less than 37 weeks) is associated with development of asthma, defined by a physician's diagnosis, hospitalization, patient or parent report, or history of asthma. Based on 19 articles that provided estimates for the meta-analysis, the summary effect estimates for asthma (fixed-effects OR= 1.074, 95% CI= 1.072-1.075, heterogeneity $p < 0.001$; random-effects OR= 1.366, 95% CI= 1.303-1.432) showed an increased risk in relation to preterm delivery, with substantial heterogeneity between study-specific estimates.

A number of authors have examined the relation of incidence of wheezing disease at different age groups in the British cohort studies to a range of perinatal, medical, social, environmental, and lifestyle factors. Among the variables that have been found to be associated with the wheezing disease in these cohorts include: atopy, cigarette smoking (Butland and Strachan, 2007); intake of fresh fruits (Butland *et al.*, 1999); parental age and occupation, housing type, overcrowding, breastfeeding, sex, histories of infections such as pneumonia, hay fever, eczema, whooping cough, recurrent abdominal pain, and migraine (Kaplan and Mascie-Taylor, 1985; Anderson *et al.*, 1986; Anderson *et al.*, 1987; Strachan, 1989; Strachan *et al.*, 1996); and birthweight, adult BMI, and maternal smoking during pregnancy (Lewis *et al.*, 1995; Shaheen, S. *et al.*, 1999).

10.3. Psychological Factors and Asthma

The hypothesis of an association between stress and asthma emerges from a wide range of clinical observations and dates back to the early 20th century; in fact, before the underlying inflammatory basis of asthma was better understood, asthma used to be

known as "asthma nervosa" in early medical texts (Osler, 1901). In a discussion of the diseases of the respiratory system in his medical text book, William Osler (1901, P. 628-632) referred to asthma largely as “a neurotic affection” and noted that in a majority of cases there was a consensus that asthma had a strong neurotic element. Despite more recent published studies supporting the association of asthma and psychological factors, a significant confusion still exists among healthcare providers regarding this psychological component.

Although many studies have suggested that stress and psychosocial factors may affect asthma morbidity, their roles in the genesis, incidence and symptomatology remain controversial because the mechanisms are not well understood. Recent advances in the field of psychoneuroimmunology linking psychosocial stress, the central nervous system, and alternation in the immune and endocrine function (Ader *et al.*, 1995), have provided possible biological pathways through which stress may influence the development and expression of asthma. Asthma and psychological states and traits may mutually potentiate each other through direct psychophysiological mediation, non-adherence to medical regimen, exposure to asthma triggers, and inaccuracy of asthma symptom perception.

10.3.1. Empirical evidence linking psychological factors and asthma

Research documenting an association between psychological stress and asthma continues to grow. Prominent among the psychological factors that have been investigated are stressor exposure such as negative life event and daily stress; psychological distress (internalizing, anxious, or depressive symptom, stress-related personality, family dysfunction, immature coping skills, etc.); poor social support such as social isolation, impoverished and social relationships (Chida *et al.*, 2008).

Perhaps the most convincing evidence for the pivotal role of psychological factors in asthma has been reported by studies showing that psychological stress worsens asthmatic symptoms especially in children. In a study set out to examine whether stressful experiences provoke new exacerbations in children (Sandberg *et al.*, 2004), a group of asthmatic children with verified chronic asthma were prospectively followed up for 18 months. Key measures included asthma exacerbations, high threat life events, and chronic stressors. Using statistical methods capable of investigating short-time lags

between stressful life events and asthma exacerbations, the authors found a significant increase in the risk of a new asthma attack immediately after a stressful event by a factor of 4.69; an increased risk of 1.81 was also found 5–7 weeks after a severe event. The risk was increased further and brought earlier in time, if multiple chronic stressors were present in the child's life (Sandberg *et al.*, 2000; Sandberg *et al.*, 2004). Stress in the form of early parenting difficulties (e.g., excessive parental anxiety, poor coping, and lack of child-care skills) has also been shown to predict the onset of asthma by the age of 3 years in children genetically at risk by being born to asthmatic mothers (Mrazek *et al.*, 1999).

In another study of children predisposed to atopy on the basis of their family history, Wright *et al.* (2004) examined the influence of reported parental caregiver stress in the first 6 months of their child's life on several markers of early childhood immune response (lymphocyte allergen-specific proliferative response, cytokine production, and total IgE expression) when the children were 2–3 years of age. They concluded that increased stress in early childhood was associated with an atopic immune profile in these children predisposed to atopy-asthma.

There is also evidence that stressful life experiences diminish expression of genes encoding the glucocorticoid and the β_2-adrenergic receptors in children with asthma (Miller and Chen, 2006). In 77 children (39 asthmatics, 38 healthy controls), chronic stress was associated with reduced expression of the mRNA of the β_2-adrenergic receptor among children with asthma. In the sample of healthy children, however, the direction of this effect was the opposite. Children with asthma, who simultaneously experienced acute superimposed on chronic stress, exhibited a 5.5-fold reduction in glucocorticoid receptor mRNA, and a 9.5-fold reduction in β_2-adrenergic receptor mRNA compared to children with asthma without similar stressor exposure. These findings suggest that stressful experience diminishes expression of the glucocorticoid and β_2-adrenergic receptor genes in children with asthma, a process that could explain the increased asthma morbidity associated with stress.

Studies have also investigated the role of stress in asthma onset. In a recent systematic review of prospective studies investigating the relationship between psychosocial factors (stressful events, anxiety or depression symptoms, behavioural problems, psychological distress, poor social support) and atopic disorders among children and adults (Chida *et al.*, 2008), both the combined effect of 34 studies (correlation coefficient (r) as combined

size effect = 0.024, 95% CI= 0.014-0.035) and the subgroup meta-analyses on the studies with healthy populations and atopic populations (effects of 0.015 (95% CI, 0.005–0.024) and 0.046 (95% CI, 0.021–0.074), respectively) found that psychosocial factors were involved in both the development and prognosis of atopic disorder. Most of these studies assessed asthma outcomes among children, where the relationship between psychosocial factors and asthma is probably most robust.

There are also reports in the literature relating asthmatic death to depression (Dirks and Kinsman, 1982; Strunk *et al.*, 1985; Miller, 1987). However, most of these are matched case-control studies on children and adolescents. In a systematic review of the psychological risk factors associated with near fatal or fatal asthma, Alvarez and Fitzgerald (2007) based on seven case-controlled studies that met their strict inclusion and exclusion criteria found conflicting results and could not conclude that psychological factors increase the risk of near fatal or fatal asthma.

In sum, with the current data it is not possible to answer affirmatively the question of whether psychological factors are a risk factor for adult-onset asthma. Though empirical evidence obtained from different studies make a strong case for psychosocial stress increasing the risk of asthma and other atopic disorders especially in children. This supports the use of psychological in addition to conventional physical and pharmacological interventions, in the successful prevention and management of atopic disorders.

10.3.2. Pathways and mechanisms through which psychological factors may affect onset of allergy and asthma

Since the evidence linking psychological factors to the expression of asthma and atopy continues to grow, the examination of the underlying mechanisms linking psychological factors to asthma and other allergic phenomena has become an active area of research. There are a number of proposed mechanisms to link psychological factors with asthma including direct psychophysiological mediation such as stress-related changes in immunity and autonomic nervous system function; non-adherence to medical regimen; poor health practices which promote exposure to asthma triggers; and inaccuracy of asthma symptom perception.

Direct psycho-physiological pathway

Several studies on psychological factors and asthma have demonstrated positive results even after controlling for important covariates such as smoking, atopy and socioeconomic status implying that there is a plausible direct biological link. Many models have been proposed to explain the biological mechanisms underlying this phenomenon. Mechanisms linking psychological stress, personality, and emotion to neuroimmunoregulation have been thoughtfully discussed (Cohen and Herbert, 1996; Cohen *et al.*, 1999; Ader, 2007) as summarised in Section 4.2.1. This has been occasioned by advances in our understanding of psychoneuroimmunology and the bidirectional links among the central nervous system (CNS), autonomic nervous system in the periphery, endocrine system, and immune system. The activation of the hypothalamic–pituitary–adrenal (HPA) axis by specific cytokines increases the release of cortisol, which in turn feeds back and suppresses the immune reaction.

The co-existence of chronic inflammation and neural dysfunction has recently drawn attention to the involvement of interaction pathways between the nervous and the immune system in the airways. Rather than stress directly causing the asthma symptoms, it is thought that stress modulates the immune system to increase the magnitude of the airway inflammatory response to allergens and irritants. Intensive research has accumulated over time on the role of stress in asthma onset and these have been well documented (Wright *et al.*, 1998; Nagata *et al.*, 1999; Lehrer *et al.*, 2002; Wright, 2005; Wright *et al.*, 2005; Vig *et al.*, 2006; Veres *et al.*, 2009). All these studies are in agreement that changes in behavioural and emotional states that accompany the perception of, and the effort to adapt to, environmental circumstances are accompanied by complex patterns of neuro-endocrine and immunological changes which in turn lead to increased risk of asthma. The biological pathways for how stress may amplify the risk to asthma triggers include the HPA axis, immune system function, oxidative stress pathway, the sympathetic-adrenal-medullary (SAM) axis, the sympathetic (SNS) and parasympathetic (PNS) arms of the autonomic nervous system, and the modified genetic expression. Wright (2005) has given a comprehensive review on these proposed physiological mechanisms linking stress to asthma.

A potential consequence of stress induced changes in immune response is the suppression of host resistance to infectious agents, particularly agents that cause upper

respiratory disease (Wright *et al.*, 1998). The primary evidence for such effects comes from studies of psychological stress as a risk factor for respiratory infections. Cohen *et al*. (1991) investigated prospectively the relation between psychological stress (negative life events, perceived stress and negative affective measures) and the frequency of documented clinical colds among 394 subjects intentionally exposed to five different upper respiratory viruses. They found out that psychological stress was associated in a dose-response manner with an increased risk of acute infectious respiratory illness, and this risk was attributable to increased rates of infection rather than to an increased frequency of symptoms after infection. Kiecolt-Glaser *et al*. (1996) also showed that down-regulation of the immune response to influenza virus vaccination is associated with a chronic stressor in the elderly. These studies suggest that stress-induced immune-suppression and increased susceptibility to respiratory infection may be factors that influence the onset or exacerbation of asthma and provide us with a possible causal mechanism in the stress-asthma paradigm.

Behavioural and socioeconomic pathways

Although psychological factors alone are not considered sufficient to produce asthma because of lack of an established causal link as well as the complexity of the disease, such factors may be capable of influencing or modifying asthma symptoms. These factors may contribute directly to asthma symptomatology or interact with immunological, allergic, genetic, infectious, or environmental factors. The relationship between psychosocial factors and atopic disorders might be mediated via behavioural and socioeconomic pathways. For example, stress might cause some atopic disease-exacerbating behaviour such as poor diet, lack of exercise, sleep disturbance, frequent smoking, substance abuse and unhygienic living environment.

Social and psychological risk factors are closely related because social factors can increase psychological stress which in turn modulates the immune system. Chronic psychological stress may be exacerbated by socioeconomic status such as poverty, minority ethnicity, and threat of crime and violence, which may eventually alter health outcomes including asthma (Drake *et al.*, 2008).

Health behaviours and non-adherence to medical regimen

The expression of asthma may also be influenced by behavioural stress responses such as self management strategies and adherence to prescribed treatment plans. One of the premises of the self-management approach is the ability to identify accurately symptoms and pulmonary function compromise. There may be direct effects on biological functions- for example, uncontrollable shock on T cells- or lack of perceived control may undermine symptom perception and disease management efforts (Wright *et al.*, 1998).

Poor patient compliance with inhaled medication is known to cause morbidity and mortality in asthma. Psychological factors, mainly depression have been linked to poorer adherence to therapy (Bosley *et al.*, 1995; Smith *et al.*, 2006). Asthmatics with comorbid psychological symptoms have also been found to be more non-compliant (Creer, 1993). Even though most of these findings are from prospective cohort studies, they are limited by the number of participants.

10.3.3. Perinatal and early life factors and asthma in mid life

There is a growing evidence to suggest that atopic disease in adulthood could be manifestations of events in early life (Strachan, 1994; Shaheen, S. O. *et al.*, 1999) or even during foetal life (Piccinni *et al.*, 1993). These evidences, coupled with the growing evidence of the link between psychological factors and the risk of asthma, have led us to investigate in this study whether psychological factors early in life may have an effect on asthma development later in life.

10.4. Asthma in the NCDS and BCS70

In the NCDS, information about current and past asthma or wheezing was obtained as part of a structured questionnaire on medical and other topics administered to parents by health visitors at ages 7, 11, and 16 years, and via interviews to cohort member themselves at ages 23, 33 and 42 years. The form of the questions slightly differed at each age. At age 7, parents were asked whether their child had “ever had attacks of asthma” or “attacks of bronchitis with wheezing”; if positive to either question, the number of attacks in the past 12 months was recorded. At age 11, the parent was asked whether the child had ever had attacks of asthma, wheezing bronchitis, or neither of

these. If attacks had occurred in the past 12 months, their frequency was assessed. At age 16 years the question did not distinguish between asthma and wheezing; parent was asked whether the child "ever had an attack of asthma or wheezy bronchitis". If attacks had occurred in the past 12 months frequency of occurrence was assessed.

As in age 16, the questions did not separate asthma from wheezy bronchitis at the age of 23 years; cohort members were asked whether they had ever had an attack of asthma or wheezy bronchitis since their 16th birthday, and as in earlier sweeps the occurrence of attacks in the past 12 months was recorded. Those who responded positively were also asked whether they take any prescribed medicine to control those attacks. At age 33, subjects were asked whether they had been told that they had asthma, whether these symptoms had occurred at any time in the last 12 months and if so whether they had used an inhaler or any other medicine prescribed by the doctor to treat the asthma or wheezing. At the age of 42 years a checklist was used to identify a number of common conditions including migraine, hay fever, bronchitis, asthma, and allergic rhinitis, followed with questioning directed at the condition on age at which the condition first occurred, and whether the condition has occurred in the last 12 months. In the great majority of cases, continuity with earlier sweeps was maintained through repeat questioning; although suggestions from advisers led to some additions or improvements, for example, the addition of questions on allergic rhinitis.

At ages 44 to 45 years as part of the biomedical survey, blood samples collected by nurses underwent measurement of IgE levels using the HYTEC enzyme immunoassay (Nolte and Dubuske, 1997), with positive and negative controls. Total IgE was assayed on all specimens, and allergen-specific IgE to house dust mite, mixed grasses, and cat fur, were measured on specimens with a total IgE concentration above the median (30kU/L). Lung function was also measured for this sample based on three measures (from up to five attempts) of forced vital capacity (FVC), forced expiratory volume (FEV1) and peak expiratory flow rate (PEFR).

In the BCS70 cohort, information on asthma and wheezing was obtained via parental interviews at ages 5, 10 and 16 years, and through questionnaires to the cohort members at ages 26 and 30 years. At age 5 the parent was asked whether the child had ever wheezed, the particular periods of its occurrence, and the particular wheezing diagnosis-whether asthma, wheezy bronchitis, wheezing with croup or wheezing only. At age 10

the parent was asked whether the child had ever had one or more attacks or bouts in which there was wheezing or whistling in the chest; whether they were thought to be due to asthma, wheezy bronchitis or other causes; whether the child had been seen by a doctor because of these attacks; and whether the child had wheezed within the past 12 months. At age 16 the parents were asked whether the study teenager had ever had any attacks of wheezing or whistling in the chest. If positive, questions on when the attacks had occurred; how many attacks; whether the attacks were thought to be asthma, wheezy bronchitis or other causes; whether the attacks had ever necessitated investigation or treatment; whether the teenager had asthma or wheezy bronchitis the past 12 months; and if so the frequency of its occurrence.

At age 26, a checklist was used to identify a number of common conditions including migraine, hay fever, bronchitis, and asthma since they were age 16 and in the past 12 months. At age 30 the cohort members were asked whether they had ever had or been told they had migraine, hay fever, bronchitis, asthma, or allergic rhinitis. This was followed with questioning directed at the condition on age at which the condition first occurred, and whether the condition has occurred in the last 12 months, or whether they had seen a doctor in the past 12 months about the condition.

Since at some sweeps of data collection (e.g. at 16 and 23 years of age in the NCDS) the questions did not separate asthma from wheezy bronchitis, these variables were combined in the analysis and referred to as wheezing illness. A prospective study comparing selected groups of 7-year-old school children with mild wheezy bronchitis, with moderate wheezy bronchitis, and with asthma, with a control group (Williams and Mcnicol, 1969), showed that if there was any significant difference between the study groups and the controls it was usually present in all these study groups. The author concluded that children with wheezy bronchitis and asthma were from the same population with the same underlying basic disorder; therefore, there is a reasonable clinical and pathological justification for combining the two variables.

10.4.1. Outcome and explanatory variables

Two main outcome variables were considered. The primary outcome was the incidence of wheezing illness between age 17 and 42 years in the NCDS and between age 17 and 30 in the BCS70. Only cases without a history of asthma or wheezy bronchitis at all

previous childhood follow-ups up to age 16 were considered. For both the cohorts, both the fully linked data comprising all those with information at each follow-up, and partially linked data comprising those with missing information at one or more follow-ups, were considered.

The prevalence of wheezing illness at the age of 42 years in the NCDS and at age 30 years in the BCS70 derived from the self reported wheezing occurring at any time over a 12-month period was also considered as a second outcome. All subjects who responded to this question at age 42 in the NCDS and at age 30 in the BCS70 were considered in the analysis. Due to the intermittent nature of asthma symptoms, wheezing occurring at any time within the previous 12 months has been used to define current asthma symptoms in many studies including the European Community Respiratory Health Survey (ECRHS) (Burney *et al.*, 1994; Burney *et al.*, 1996). Such outcome has been found to have a good specificity and sensitivity for bronchial hyper-responsiveness and a diagnosis of asthma in adults and children (Masoli *et al.*, 2004).

The main predictor variables investigated were the psychological measures as described in Section 2.2.2. These included behavioural maladjustments, hostility patterns, personality, and motivational assessment such as self esteem and locus of control. Information was available from birth and follow-ups to 16 years on known risk factors for atopic disease and other perinatal, environmental and socioeconomic factors which might be potential confounders.

From a very large number of other possible confounders, we selected all those that have been associated with asthma or wheezy bronchitis. A vast majority of variables that have been found to be associated with asthma in the NCDS (Anderson *et al.*, 1986; Anderson *et al.*, 1987; Butland *et al.*, 1999; Butland and Strachan, 2007; Marossy *et al.*, 2007; Blakey *et al.*, 2009) and the BCS70 data (Lewis *et al.*, 1996; Shaheen, S. *et al.*, 1999) were considered. These included perinatal and childhood factors (birth weight, gestational age, parity, breast feeding, birth order or rank in the family, parental smoking/ smoking during pregnancy, age of mother at child birth), childhood infections (history of pneumonia, whooping cough, throat or ear infections or tonsillectomy); childhood allergic diseases such as hay fever, eczema and allergic rhinitis; other childhood infections such as measles, upper respiratory illnesses affecting the throat and ears, headaches or migraine; age at menarche, the sharing of household amenities (bathroom,

toilet), crowding, number of children in the household, tenure of accommodation, separation from the mother, being in care or with the absence of one or both biological parents from the household. Others in the BCS70 included a "family history of atopy" defined by the presence of hayfever, eczema, or asthma in either parent or any sibling ascertained at the age-five survey.

The adjustment for the above explanatory variables was necessary since asthma epidemiology is well suited for the life course approach. Evidence has shown that events early in the development of the lung and immune system may influence susceptibility to later infections. The critical periods during which these early influences may operate are poorly defined, but probably include both prenatal and post natal development. The complex relationship between early psychological factors and later lung disease may prove particularly difficult to disentangle and may follow different pathways which all need to be tested.

In order to test whether such associations between psychological factors and wheezing illness could be explained by pre-existing and well established risk factors, a number of explanatory variables were investigated as possible mediators. These included the characteristics that can be measured objectively such as total and specific IgE (atopy), and lung function as well as cigarette smoking, adulthood social class, and sex. In addition the dietary factors such as fresh fruits intake and BMI at age 42 were also tested as possible mediators.

For lung function in the NCDS biometric survey data, the spirometric indices used were the FEV_1, FVC and FEV_1/ FVC ratio. These indices were adjusted for height and sex, and the subjects with the best two lung function readings differing by more than 10% from each other, or those whose values were outside the normal range (standardised residuals greater than 3 SD units from the mean) were excluded from subsequent analyses.

For IgE measurements, those with specific IgE >2000 were re-coded to 2000 while those with IgE <0.35 were re-coded to 0. Those with at least one measurement of specific IgE greater that the lowest threshold of 0.35 kU/L recommended for detection of allergen-specific IgE were classified as atopic. Those with specific IgE between 0.35 and 3.5 kU/L were considered weak to moderate atopic, while those with specific IgE greater

than 3.5 were considered strongly atopic. Since the measurement of specific IgE was done only for those with total IgE >30kU/L, it is possible that some cohort members might have been mistakenly classified as non-atopic rather than atopic.

10.5. Analytical Strategy

In order to estimate the direct and indirect contribution of childhood psychological factors to the risk of wheezing illness, two major analytical methods were used. Logistic regression models were used to calculate the odds ratios and 95% CIs for the association between childhood psychological factors and adult-onset asthma. For both the outcomes, univariable analyses provided the odds ratios and 95% CIs. These were re-examined after adjusting for the effects of other potential risk factors. The approach for fitting the multivariable model was similar to the one described in Section 4.7 for cancer analysis. Since the two outcomes of interest did not involve the element of time to asthma diagnosis, no survival analysis was carried out, but rather logistic regression models.

Structural equation modelling was used to estimate both the direct and indirect effect of the childhood psychological factors in the development of wheezing disease. In order to reduce the measurement error, latent variables were used to represent each of the subscales of the psychological measures rather than using the separately calculated latent variables in regression analyses. As already described in Section 4.7, root mean square error of approximation (RMSEA) and comparative fit index (CFI) were used to assess the model fit. Models were fitted using Mplus (Muthén and Muthén, 1998-2007). Both the maximum likelihood estimation methods to handling missing data and multiple imputation of the predictor variables under MCAR and MAR assumptions were used and the results compared to complete case analysis.

Chapter 11

Adult-onset Asthma: Results

11.1. The NCDS

Sample attrition

Of the original 18,558 cohort members with at least some data since birth in the NCDS, 14,525 (78%) had full information on asthma and wheezy bronchitis provided by parents at the 7-year follow-up. About 62% (n = 11,419) of the cohort members were observed during the sixth follow-up of data collection at age 42. The lost cases were attributable to deaths (5.9%, n = 1,090), temporary emigrants (0.1%, n = 26), permanent emigrants (7.0%, n = 1,295), refusals (11.4%, n = 2,123), no data but to be contacted later (1.6%, n = 287), and no data with no later contacts (12.5%, n = 2,318). However, only 5,168 (28%) had complete information on wheezing illness at all the sweeps during the life course up to age 42 years. Those having complete information on wheezing illness plus information on atopy and total IgE level from the biomedical data were only 3,646. This number excludes any cohort member who did not have information on wheezing illness in at least one sweep of the data collection throughout the life course.

Table 11-1 shows the prevalence of asthma or wheezy bronchitis at each sweep in the group with complete linked data and the corresponding values calculated using all available information. The estimates differ only slightly, suggesting minimal bias due to sample attrition. The estimates of incidence wheezing at different periods also remained relatively stable whether or not the analysis was restricted to cohort members with complete wheezing information across all surveys or to those who participated in the biomedical survey (Table 11-2). There was a large increase in the incidence from age 33 which may be due in part to the change in the definition of wheezing illness from asthma or wheezy bronchitis to asthma or wheezing/whistling in the chest.

The percentages of missing data in the covariates are shown in Tables 11-3 to 11-11 that also show the main body of the results. The highest percentage of missing data in the covariates was 26% for the age 16 psychological measures; however, when these variables are analysed together in a multivariable model, then these percentages are

expected to increase considerably, therefore, multiple imputation results were compared with the results of complete cases in order to asses if there was any bias due to missing data.

Table 11-1: Percentage prevalence of asthma or wheezing at each sweep in subjects with complete information on asthma in all the sweeps and using all available information at each sweep together with the cumulative incidence up to the given age. *

	Age 7	Age 11	Age 16	Age 23†	Age 33	Age 42
Report of asthma or wheezing ever (reported lifetime prevalence for fully linked data)						
Males	19.0 (463/2,433)	13.3 (324/2,433)	14.4 (350/2,433)	7.2 (175/2,433)	26.8 (651/2,433)	16.1 (392/2,433)
Females	16.7 (456/2,735)	10.2 (280/2735)	9.1 (249/2,735)	9.7 (266/2,735)	29.0 (793/2,735)	19.6 (535/2,735)
Total	17.8 (919/5,168)	11.7 (604/5,168)	11.6 (599/5,168)	8.5 (441/5,168)	27.9 (1,444/5,168)	17.9 (927/5,168)
Report of asthma or wheezing ever (Unlinked data: all available information)						
Males	20.5 (1,528/7,461)	14.1 (979/6,922)	13.7 (799/5,830)	8.1 (509/6,259)	28.9 (1,613 /5,578)	16.1 (901/5,603)
Females	16.1 (1,137/7064)	10.4 (684/6,581)	9.5 (528/5,562)	10.7 (672/6,265)	29.4 (1,696/5,769)	20.5 (1,184/5,773)
Total	18.4 (2,665/14,525)	12.3 (1663/13,503)	11.7 (1,327/11,392)	9.4 (1,181/12,524)	29.2 (3,309/11,347)	18.3 (2,085/11,376)
Cumulative incidence up to the given age for all the respondents‡						
Both M & F	18.4 (2,665/14,525)	22.0 (2,648/12,034)	24.7 (2,159/8,742)	28.6 (2,061/7,216)	42.9 (2,491/5,805)	45.8 (2,369/5,168)

* Data are presented as percentages (number of prevalent cases/total number with complete information on wheezing illness up to that age or all available cases for that sweep for the unlinked data).

† At age 23 the question referred only to asthma or wheezing since the 16th birthday.

‡ Cumulative incidence derived from successive follow ups, based on all prior information on wheezing illness.

Prevalence, incidence, and cumulative incidence

For NCDS, 6% (337/5,603) of men and 9% (544/5,772) of women reported having had asthma or wheezy bronchitis in the last 12 months at age 42 years. The prevalence of asthma or wheezy bronchitis among all subjects interviewed at each sweep (irrespective of whether they were part of the linked cohort) is reported in Table 11-1. The cumulative incidence of asthma or wheezy bronchitis, calculated on the basis of all prior information, was 18% by age 7, 22% by age 11, 25% by age 16, 29 % by age 23, 43% by age 33, and 46% by age 42 (Table 11-1).

The incidence at different periods for all the available data and for those with complete information over the life course is presented in Table 11-2. For the ages of 17 to 42 years, the proportion of incident asthma or wheezy bronchitis was about 28.5% (1,118/3,917) for those with complete information over the life course. This proportion remained the same whether the data was restricted to those with information on biomedical data or not. About 24% of the cohort members had a history of wheezing illness by age 16 and these were excluded from subsequent analysis.

Table 11-2: Comparing the incidence of wheezing illness at different age groups in different subsets of the NCDS data. †

	All available data		**Complete information on wheezing illness over life course**	
Age at onset of wheeze	**With no other restrictions**	**With information on total IgE & atopy**	**With no other restrictions**	**With information on total IgE & atopy**
Birth to age 7 yr	18.3 (2,665 / 14,525)	17.3 (1,135 /6,558)	17.8 (919/5,168)	17.4 (620/3,565)
Age 8-16 yr	7.8 (560 / 7,143)	7.9 (293/3,687)	7.8 (332/4,249)	8.0 (236/2,945)
Birth to age 16 yr	24.7 (2,159/ 8,742)	23.9 (1,068/4,462)	24.2 (1,251/5,168)	24.0 (856/3,565)
Age 17-33 yr	23.9 (1,073/ 4,396)	24.0 (666/ 2,776)	24.3 (950/3,917)	23.9(648/2709)
Age 17-42 yr	28.5 (1,118/3,917)	28.2 (765/2,709)	28.5 (1,118/3,917)	28.2 (765/2,709)
Birth to 42 yr	45.8 (2,369/5,168)	45.5 (1,621/3,565)	45.8 (2,369/5,168)	45.5 (1,621/3565)

† The incidence is based on asthma or wheezy bronchitis ever, reported at every sweep apart from age 23 where asthma or wheezy bronchitis since the age of 16 was reported. Data are presented as percentages (number of cohort members reporting a positive history of asthma or wheezy bronchitis during the period specified/ total number with complete information on wheezing illness for the period specified and with no history of wheezing illness reported at previous follow-ups.

11.1.1. Adult-onset wheezing

The results in this section are based on 3,917 cohort members with complete information on wheezing illness up to 42 years of age, excluding those who had the wheezing disease before age 17 years. For the analyses involving the variables collected during the biomedical survey, only 3,349 participants who had full information on asthma and wheezy bronchitis were used. For these subsets of the cohort, there were very few missing values (Table 11-3 to 11-7) in the covariates, and the complete-case and the estimates based on 10 multiply-imputed datasets were similar in most cases, so only the complete case results have been presented. The estimates based on all available information with no restriction to those who had full information on wheezing illness

were relatively similar to the ones of the fully linked data, therefore only the results based on fully linked dataset have been presented.

Table 11-3: The odds ratios (95% CI) for the effect of childhood psychological factors on adult onset (age 17-42) asthma or wheezy bronchitis in the 1958 birth cohort (NCDS).

	AW[1]	AW_F[2]	M[3]	Odds Ratio (95% CI)					
				Unadjusted			Adjusted†		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	1,116	2,793	0.2	1.04	(1.02 , 1.06)	<0.01	1.04	(1.02 , 1.06)	<0.01
Hyperactive	1,115	2,792	0.3	1.06	(1.00 , 1.13)	0.05	1.06	(1.00 , 1.13)	0.06
Emotional problems	1,115	2,793	0.2	1.04	(0.99 , 1.08)	0.12	1.03	(0.99 , 1.08)	0.17
Conduct problems	1,116	2,792	0.2	1.06	(1.01 , 1.11)	0.02	1.07	(1.02 , 1.13)	0.01
Child Behaviour at School (BSAG)									
Emotional problems	1,099	2,731	2.2	1.01	(0.99 , 1.03)	0.25	1.01	(0.99 , 1.03)	0.24
Conduct problems	1,099	2,731	2.2	1.02	(1.00 , 1.03)	0.02	1.03	(1.01 , 1.04)	<0.01
Miscellaneous Nervous Syndrome	1,099	2,730	2.3	1.09	(0.92 , 1.29)	0.34	1.09	(0.91 , 1.30)	0.36
At Age 11									
Child Behaviour at Home (Rutter A)									
Total Score	1,118	2,799	0.0	1.04	(1.02 , 1.07)	<0.01	1.05	(1.02 , 1.07)	<0.01
Hyperactive	1,118	2,798	0.0	1.06	(1.00 , 1.12)	0.05	1.06	(1.00 , 1.13)	0.04
Emotional problems	1,118	2,799	0.2	1.05	(1.00 , 1.09)	0.05	1.04	(1.00 , 1.09)	0.06
Conduct problems	1,118	2,797	0.1	1.10	(1.05 , 1.16)	<0.01	1.11	(1.06 , 1.17)	<0.01
Child Behaviour at School (BSAG)									
Emotional problems	1,052	2,649	5.5	1.01	(0.99 , 1.03)	0.42	1.01	(0.99 , 1.03)	0.50
Conduct problems	1,052	2,649	5.5	1.03	(1.01 , 1.05)	<0.01	1.04	(1.02 , 1.05)	<0.01
Miscellaneous Nervous Syndrome	1,052	2,649	5.5	0.98	(0.80 , 1.20)	0.86	1.00	(0.81 , 1.23)	0.98
At Age 16									
Child Behaviour at Home (Rutter A)									
Total Score	1,117	2,799	0.0	1.04	(1.02 , 1.06)	<0.01	1.04	(1.02 , 1.06)	<0.01
Hyperactive	1,117	2,798	0.1	1.15	(1.05 , 1.26)	<0.01	1.16	(1.06 , 1.28)	<0.01
Emotional problems	1,117	2,799	0.0	1.02	(0.97 , 1.07)	0.39	1.02	(0.97 , 1.07)	0.50
Conduct problems	1,117	2,798	0.1	1.18	(1.11 , 1.26)	<0.01	1.17	(1.10 , 1.25)	<0.01
Child Behaviour at School (Rutter B) total score			13.2						
Well adjusted	835	2,171							
With behavioural disorder	149	245		1.58	(1.27 , 1.97)	<0.01	1.47	(1.17 , 1.85)	<0.01
Subscales									
Neurotic	980	2,408	13.4	1.14	(1.07 , 1.22)	<0.01	1.12	(1.04 , 1.20)	<0.01
Antisocial	981	2,413	13.4	1.11	(1.05 , 1.17)	<0.01	1.11	(1.05 , 1.17)	<0.01
Childhood Adversity Score **	940	2,393	0.5	1.12	(1.08 , 1.16)	<0.01	1.11	(1.07 , 1.15)	<0.01

1 Adult onset asthma or wheezy bronchitis cases (ages 17 to 42 years)

2 Those with no reported cases of adult onset asthma or wheezy bronchitis

3 Percentage of missing data on covariates for those with complete information on wheezing illness.

† Adjusted for the effect of sex, maternal smoking, parity, pneumonia at age 7, social class of the father at 7, history of hay fever at 7 or 11 years, history of eczema at 7 or 11 years, and smoking at age 16 for 16 year old measures.

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

** Retrospective childhood adversity score (Path through life scale). Based on biomedical data at age 44-45.

Effect of childhood psychological factors

Table 11-3 shows the number of incident cases of asthma and wheezy bronchitis between age 17 and age 42 across several childhood psychological measures, the percentage of missing data in each covariate, and the odds ratios (and 95% CIs) for the effect of childhood psychological factors on adult-onset wheezing for both the adjusted and the unadjusted models. All the variables except the Rutter B scale at age 16 were analysed in continuous scale, therefore, the estimates represent an increase or decrease in the odds of being diagnosed with wheezing disease per unit increase in the behavioural scale score showing worse conditions of behavioural maladjustment.

Among the seven and eleven year old measures only the total Rutter score, conduct problems subscale of the Rutter scale, and the over-reaction/conduct problems at school (BSAG scale) were significantly and positively associated with adult-onset wheezing. Those who had higher scores on these behaviours (showing worse conditions of behavioural maladjustment) had a significantly higher risk of asthma or wheezy bronchitis as compared to those with lower scores. All the measures taken at age 16 years were significantly associated with adult-onset wheezing except emotional problems subscales of the Rutter mother's scale. Children who were highly hyperactive, those who showed antisocial behaviours and those who experienced higher level of childhood adversity by age 16 were at a greater risk of asthma or wheezy bronchitis in their early adult life.

Perinatal, and childhood biological, social and environmental factors

The estimates for the perinatal and childhood factors that were significantly associated with adult-onset asthma are presented in Table 11-4. Female cohort members, those whose mothers were smokers during pregnancy, those whose mothers had three or more children at the time of their birth, and those who had a history of pneumonia, hay fever, and eczema in childhood were significantly at higher risk of developing wheezing illness in mid life. Cohort members' smoking status at age 16 was also highly significantly associated with the adulthood asthma incidence. Children whose fathers were in the professional or managerial social class had a reduced risk of asthma or wheezy bronchitis later in mid adulthood. Many other variables were considered but were not significant predictors of adult onset asthma incidence and their results are not presented in the table.

They included mother's age at birth, measles infection by age 7, birthweight, being in care, breastfeeding, whooping cough, recurrent abdominal pain and migraine by age 7, and birth weight for gestational age. Housing tenure was excluded because of its close and significant association with father's social class.

Table 11-4: The odds ratios (95% CI) for the effect of perinatal and childhood biological, social, and environmental factors on adult onset asthma or wheezy bronchitis in the NCDS.

Variable (Reference category)	AW[1]	AW_F[2]	M[3] (%)	Unadjusted Odds Ratios (95% CI)
Sex (Male)	442	1,342	0.0	
Female	676	1,457		1.41 (1.22 , 1.62) <0.01
Maternal smoking during preg. (Non-smoker)	720	1,958	2.6	
Smoker	378	760		1.35 (1.16 , 1.57) <0.01
Parity (No prev aft 28wks)	404	1,073	2.6	
1 After 28wks	323	863		0.99 (0.84 , 1.18) 0.95
2 after28wks	168	418		1.07 (0.86 , 1.32) 0.55
3+ after 28wks	203	364		1.48 (1.21 , 1.82) <0.01
Pneumonia by age 7 (No)	1,074	2,731	0.1	
Yes	42	67		1.59 (1.08 , 2.36) 0.02
Hayfever by age 7 or 11 (No)	1,006	2,595	8.1	
Yes	112	204		1.42 (1.11 , 1.80) 0.01
Eczema by age 7 or 11 (No)	1,002	2,580	1.0	
Yes	105	192		1.41 (1.10 , 1.81) 0.01
Social class of father (I or II: Proff/Manager)	199	612	2.5	
III: skilled Non-manual	142	296		1.48 (1.14 , 1.91) <0.01
III:Skilled manual	490	1,224		1.23 (1.02 , 1.49) 0.03
IV or V-Partly/ Unskilled	252	606		1.28 (1.03 , 1.59) 0.03
No male hhh	35	61		1.76 (1.13 , 2.75) 0.01
Smoking at age 16 (Non-Smoker)	539	1,704	14.7	
Less than 3 packets	342	602		1.80 (1.52 , 2.12) <0.01
3+ packets	74	79		2.96 (2.13 , 4.13) <0.01

1 Adult onset asthma or wheezy bronchitis cases (ages 17 to 42 years)

2 Those with no reported cases of adult onset asthma or wheezy bronchitis

3 Percentage of missing data on covariates for those with complete information on wheezing illness excluding those who were diagnosed before age 17.

Early adulthood psychological factors

All the adulthood psychological factors considered in the bivariate model were highly associated with the adult-onset asthma with those who showed higher degree of psychological distress having a higher risk of the disease (Table 11-5).

Table 11-5: The odds ratios (95% CI) for the effect of adulthood psychological factors on adult onset asthma or wheezy bronchitis in the NCDS.

	AW[1]	AW_F[2]	M[3](	Odds Ratio (95% CI)
Psychological distress at 23 years (Malaise Inventory)			0.1	
Normal	1,006	2,677		
Depressed	111	120		2.46 (1.88 , 3.22) <0.01
Psychological distress at 42 years (Malaise Inventory)			0.5	
Normal	922	2,523		
Depressed	192	260		2.02 (1.65 , 2.47) <0.01
GHQ12 at 42 years*	1,114	2,783	0.5	1.04 (1.03 , 1.06) <0.01

1 Adult onset asthma or wheezy bronchitis cases (ages 17 to 42 years)

2 Those with no reported cases of adult onset asthma or wheezy bronchitis

3 Percentage of missing data on covariates for those with complete information on wheezing illness excluding those who were diagnosed before age 17.

* GHQ12 is recorded on a continuous scale ranging from 0-36: higher score indicate worse conditions.

Early adulthood environmental, social and lifestyle measures

Table 11-6 shows the unadjusted estimates for the effect of adulthood social and environmental factors on adult onset asthma or wheezy bronchitis in the NCDS. When considered separately, total IGE, atopy, smoking, being in manual social class, having drinking problems, and being overweight were all positively associated with the incidence of wheezing illness. Those with higher education achievement at age 23, those who had regular physical exercise, and those who regularly consumed fruits were at a lower risk of wheezing illness between age 17 and 42 years. Other variables that were considered in this category but were not significant included alcohol consumption at age 23 and consumption of salads or raw vegetables at age 33 and 42 years.

Adjustment for possible confounders

A number of childhood measures were found to be related to both the adult onset wheezing illness and the childhood psychological factors (Table 11-4); therefore, the observed associations between wheezing illness and the psychological factors could be positively confounded by these variables. All these variables were adjusted for in a multiple logistic regression for each childhood psychological measure and the crude and adjusted effect estimates were compared. The final adjusted model for all the psychological measures were simultaneously adjusted for the effects of sex, maternal smoking, parity, pneumonia, social class of the father at seven years, history of hay fever

at seven or 11 years, history of eczema at seven or 11 years, and smoking at age 16 for the 16 year old measures. There were no significant changes in the estimates after adjustment for these potential confounders (Table 11-3).

Table 11-6 : The odds ratios (95% CI) for the effect of adulthood social, lifestyle, and environmental factors on adult onset asthma or wheezy bronchitis in the NCDS.

Variable (Reference category)	AW[1]	AW_F[2]	M[3] (%)	Odds Ratio (95% CI)
Atopy (Negative)	517	1,559	17.4	
Weak/Moderate positive	72	163		1.33 (0.99 , 1.79) 0.06
High/very high positive	194	262		2.23 (1.81 , 2.76) <0.01
Total IgE (kU/L) (<10)	136	495	17.3	
10-30	222	690		1.17 (0.92 , 1.49) 0.20
31-99	245	524		1.70 (1.33 , 2.17) <0.01
>100	182	277		2.39 (1.83 , 3.12) <0.01
Smoking at age 42 (Never smoked)	361	1,505	0.0	
Used to smoke	324	654		2.07 (1.73 , 2.46) <0.01
Smokes occasionally	49	119		1.72 (1.21 , 2.44) <0.01
Smokes everyday < 1 packet	197	275		2.99 (2.41 , 3.71) <0.01
Smoked everyday 1+ packets	187	245		3.18 (2.55 , 3.97) <0.01
Forced vital capacity (log_{10})	921	2,338	2.7	0.42 (0.31 , 0.57) <0.01
Forced expiratory vol in 1sec (log_{10})	921	2,338	2.7	0.51 (0.40 , 0.65) <0.01
Consumption of fresh fruits (Never/occas/< 1 day a wk)	253	482	0.0	
1-6 days a wk	577	1,471		0.75 (0.62 , 0.89) <0.01
One or more a day	288	845		0.65 (0.53 , 0.80) <0.01
Educational level at age 23 (None)	149	254	6.1	
CSE 2-5/equiv nvq1	162	276		1.00 (0.76 , 1.32) 1.00
O level/equiv nvq2	392	981		0.68 (0.54 , 0.86) <0.01
A level /equiv nvq3 and Higher	352	1,111		0.54 (0.43 , 0.68) <0.01
Social class at age 33 (I or II: Proff/Manager)	370	1,020	6.7	
III: skilled Non-manual	239	673		0.98 (0.81 , 1.18) 0.83
III:Skilled manual	202	489		1.14 (0.93 , 1.39) 0.21
IV or V-Partly/ Unskilled	228	432		1.45 (1.19 , 1.78) <0.01
Drinking problem at 42-CAGE (No)	917	2,486	1.3	
Yes	186	276		1.83 (1.49 , 2.23) <0.01
Physical Exercise at age 42 (No)	300	661	0.0	
Yes	818	2,137		0.84 (0.72 , 0.99) 0.04
Sex specific waist circumference (Normal abdominal fat)	551	1,621	0.7	
Severe abdominal fat	392	762		1.51 (1.30 , 1.77) <0.01
BMI at age 42 (Normal)	479	1,374	2.1	
Underweight	17	28		1.74 (0.94 , 3.21) 0.08
Overweight	401	958		1.20 (1.03 , 1.40) 0.02
Obesity	202	375		1.55 (1.26 , 1.89) <0.01

1 Adult onset asthma or wheezy bronchitis cases (ages 17 to 42 years)

2 Those with no reported cases of adult onset asthma or wheezy bronchitis

3 Percentage of missing data on covariates for those with complete information on wheezing illness excluding those who were diagnosed before age 17.

Possible effect modifiers

Interaction effects were examined between the childhood psychological measures and a number of childhood perinatal and environmental variables which had significant associations with adult onset asthma. No interaction was significant at the 5% level showing no possible modification effect of these variables on the risk of attacks of asthma and wheezy bronchitis.

Possible roles of atopy

Since atopy is considered as one of the most significant risk factor for asthma, its effect on the relationship between psychological factors and asthma was examined separately. This was to rule out the possibility that the observed association between the childhood psychological factors and asthma may be as a result of atopy. Given that the IgE measures were taken after the diagnosis of asthma, we did not consider atopy as an intervening variable in a pathway from childhood psychological factors to asthma. Rather, we tested its modification effect by including an interaction term between atopy and each of the psychological measures. Results showed no significant interaction term between atopy and any of the early life psychological factors (Results not presented). This shows that the association between the psychological factors and asthma is independent of the levels of atopy.

A supplementary analysis was done by comparing the estimates between the atopic and the non-atopic subgroups having adjusted for all the identified potential childhood confounders. Within the atopic subgroup, having adjusted for sex and other childhood confounders, no significant associations were found between the psychological factors and asthma or wheezy bronchitis except for the modified Rutter home behaviour scale at age 7 and 16 (Table 11-7). However, the non-significance could also be a result of the low statistical power due to the small number of the atopic group. The estimates for the non-atopic subgroups followed the same pattern as that of both groups combined, though slightly stronger. Thus, the effect of childhood psychological factors on adult asthma or wheezy bronchitis appeared to be confined to the non-atopic group. Therefore, the effect of psychological factors on asthma is unlikely to be due to atopy.

Table 11-7: Comparing the effects of childhood psychological factors on adult-onset asthma between the atopic and non-atopic sub-groups. All models adjusted for all childhood confounders.

	Adjusted† Odds Ratios (95% CI)								
	Atopic group			Non-Atopic group			Both groups		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	1.06	(1.01 , 1.11)	0.02	1.05	(1.02 , 1.08)	<0.01	1.04	(1.02 , 1.06)	<0.01
Hyperactive	1.07	(0.93 , 1.23)	0.36	1.07	(0.98 , 1.17)	0.15	1.06	(1.00 , 1.13)	0.06
Emotional problems	1.14	(1.03 , 1.26)	0.01	1.03	(0.97 , 1.11)	0.33	1.03	(0.99 , 1.08)	0.17
Conduct Problem	1.02	(0.91 , 1.15)	0.71	1.10	(1.02 , 1.18)	0.01	1.07	(1.02 , 1.13)	0.01
Child Behaviour at School (BSAG)									
Underreaction	1.01	(0.96 , 1.05)	0.75	1.02	(1.00 , 1.05)	0.09	1.01	(0.99 , 1.03)	0.24
Overreaction	1.02	(0.98 , 1.05)	0.41	1.03	(1.01 , 1.06)	0.01	1.03	(1.01 , 1.04)	<0.01
Miscellaneous Nervous Syndrome	0.79	(0.48 , 1.31)	0.37	1.15	(0.90 , 1.46)	0.26	1.09	(0.91 , 1.30)	0.36
At Age 11									
Child Behaviour at Home (Rutter A)									
Total Score	1.03	(0.98 , 1.09)	0.20	1.07	(1.04 , 1.11)	<0.01	1.05	(1.02 , 1.07)	<0.01
Hyperactive	1.04	(0.90 , 1.20)	0.61	1.13	(1.03 , 1.23)	0.01	1.06	(1.00 , 1.13)	0.04
Emotional problems	1.04	(0.94 , 1.15)	0.49	1.08	(1.01 , 1.15)	0.02	1.04	(1.00 , 1.09)	0.06
Conduct Problem	1.09	(0.97 , 1.24)	0.16	1.16	(1.07 , 1.25)	<0.01	1.11	(1.06 , 1.17)	<0.01
Child Behaviour at School (BSAG)									
Underreaction	0.97	(0.93 , 1.02)	0.24	1.01	(0.98 , 1.04)	0.48	1.01	(0.99 , 1.03)	0.50
Overreaction	1.03	(0.99 , 1.08)	0.16	1.04	(1.01 , 1.06)	<0.01	1.04	(1.02 , 1.05)	<0.01
Miscellaneous Nervous Syndrome	0.85	(0.50 , 1.43)	0.54	1.16	(0.86 , 1.58)	0.34	1.00	(0.81 , 1.23)	0.98
At Age 16									
Child Behaviour at Home (Rutter A)									
Total Score	1.07	(1.01 , 1.13)	0.02	1.04	(1.01 , 1.07)	0.01	1.04	(1.02 , 1.06)	<0.01
Hyperactive	1.11	(0.88 , 1.41)	0.39	1.24	(1.09 , 1.41)	<0.01	1.16	(1.06 , 1.28)	<0.01
Emotional problems	1.11	(1.00 , 1.24)	0.06	1.01	(0.94 , 1.09)	0.73	1.02	(0.97 , 1.07)	0.50
Conduct Problem	1.09	(0.93 , 1.28)	0.30	1.19	(1.09 , 1.31)	<0.01	1.17	(1.10 , 1.25)	<0.01
Child Behaviour at School (Rutter B) total score									
Well adjusted									
With behavioural disorder	1.22	(0.68 , 2.18)	0.51	1.66	(1.20 , 2.31)	<0.01	1.47	(1.17 , 1.85)	<0.01
Subscales									
Neurotic	1.08	(0.92 , 1.27)	0.35	1.16	(1.04 , 1.29)	0.01	1.12	(1.04 , 1.20)	<0.01
Antisocial	1.12	(0.96 , 1.32)	0.15	1.10	(1.02 , 1.19)	0.01	1.11	(1.05 , 1.17)	<0.01
Childhood Adversity Score **	1.10	(1.01 , 1.20)	0.04	1.11	(1.06 , 1.17)	<0.01	1.11	(1.07 , 1.15)	<0.01

† All model adjusted for the effect of sex, maternal smoking, parity, pneumonia at age 7, social class of the father at 7 years, history of hay fever at seven or 11 years, history of eczema at seven or 11 years, and smoking at age 16 for the 16 year old

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

** Retrospective childhood adversity score (Path through life scale). Based on those who had biomedical data at age 44-45.

Potential mediation effects

To find out whether the distal determinant childhood psychological factors affect the wheezing disease partly through the proximate determinants (behavioural, lifestyle, biological, and social pathways), a series of structural equation models were fitted for each of the psychological measure. Two major pathways were tested: 1) that the effect of childhood psychological factors on adult-onset asthma is mediated by their effect on mid life obesity, and 2) that the childhood psychological factors would continue to mid-life psychological distress which in turn would increase the risk of asthma. All the models were tested after adjusting for all the potential confounders as well as the effect of mid life smoking, educational achievement, social class, and consumption of fruits.

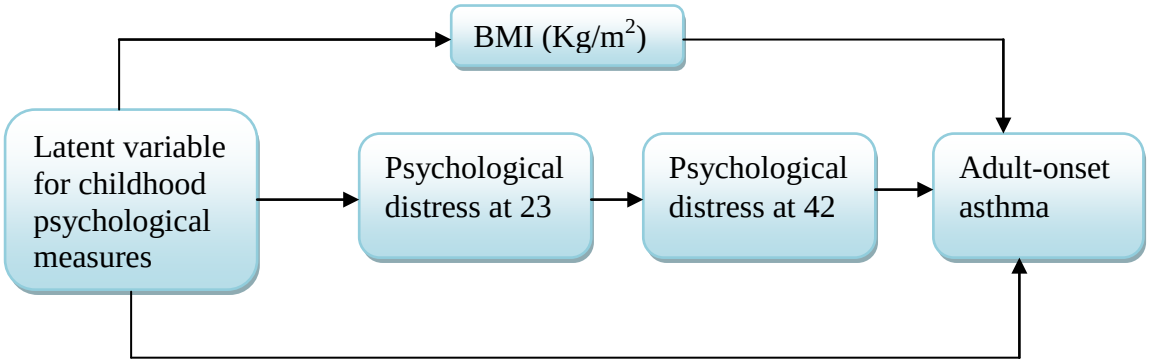


Figure 11-1: Possible pathways through which childhood psychological factors might affect the risk of asthma onset in mid life.

Table 11-8 presents the standardised coefficients, 95% CIs, and p-values for the direct and indirect effects of the childhood psychological factors on adult-onset asthma. The model fit indices- RMSEA (all < 0.038) and comparative fit index (CFI) showed a good fit for all the models.

After adjusting for the effect of childhood confounders including sex, maternal smoking, parity, pneumonia, social class of the father at seven years, history of hay fever at seven or 11 years, history of eczema at seven or 11 years, and smoking at age 16 for the 16 year old measures, there was still direct effect of most of the childhood externalising behavioural problems on adult-onset asthma. Hyperactive and conduct problems at home at both age 11 and 16 years and the antisocial behaviour at school by age 16 were

significantly associated with higher risk for adult onset asthma. A higher score on conduct, antisocial, and hyperactive problems, indicating poor behavioural adjustment at home, was associated with a higher risk for asthma or wheezy bronchitis in mid life. The significant indirect effects through mid life obesity and psychological distress implies that the association were partly mediated by these variables. Conduct problems at school assessed by the teacher at age 11 was also significantly directly associated with higher risk for adult-onset wheezing. Conduct problems at school by age 7 did not show a direct effect, however, its effects through BMI and adulthood psychological distress were strong enough such that the total indirect and the total effect were both significant. There were no significant changes in the estimates even after introducing other adulthood factors such as smoking status, educational achievement, social class and fruit consumption in the model.

Table 11-8: Direct and indirect effects (standardised coefficients, 95% CI, and p-values) for the effect of latent indicators for childhood psychological factors on adult-onset asthma for all the NCDS participants with full information on asthma/wheezy (*n* = 3917).

				Specific Indirect Effect				Total Indirect			Total Effect		
	Direct Effects			Path 1[1]		Path 2[2]							
	Est.	95% CI	Sig.	Est.	Sig.	Est.	Sig.	Est.	95% CI	Sig.	Est.	95% CI	Sig.
Age 7(Rutter A)													
Hyperactive	0.04	(-.02 , .10)	0.19	0.007	0.02	0.02	0.02	0.022	(.01 , .04)	<0.01	0.06	(.001 , .12)	0.04
Emotional problems	0.05	(-.001 , .11)	0.06	-0.005	0.08	0.01	0.24	0.002	(-.01 , .02)	0.74	0.06	(.001 , .11)	0.05
Conduct Problem	0.04	(-.02 , .09)	0.22	0.010	<0.01	0.02	<0.01	0.029	(.02 , .04)	<0.01	0.06	(.01 , .12)	0.02
Age 7 (BSAG)													
Emotional problems	0.02	(-.03 , .07)	0.40	0.004	0.08	0.02	<0.01	0.026	(.01 , .04)	<0.01	0.05	(-.001,.09)	0.06
Conduct problems	0.02	(-.03, .06)	0.54	0.010	<0.01	0.02	<0.01	0.029	(.02 , .04)	<0.01	0.04	(-.003 ,.09)	0.07
Age 11 (Rutter A)													
Hyperactive	0.03	(-.04 , 0.09)	0.42	0.011	0.00	0.03	<0.01	0.039	(.02 , .06)	<0.01	0.06	(.01 , .12)	0.03
Emotional problems	0.02	(-.03 , 0.08)	0.36	-0.003	0.19	0.02	<0.02	0.021	(.01 , .03)	<0.01	0.05	(-.01 , .09)	0.09
Conduct Problem	0.08	(.02 , .13)	0.01	0.012	<0.01	0.02	<0.01	0.032	(.02 , .05)	<0.01	0.11	(.05 , .16)	<0.01
Age 11 (BSAG)													
Emotional problems	0.00	(-.05 , .05)	0.94	0.004	0.07	0.03	<0.01	0.031	(.02 , .04)	<0.01	0.03	(-.02 , .08)	0.24
Conduct problems	0.05	(.01 , .09)	0.03	0.009	<0.01	0.02	<0.01	0.032	(.02 , .05)	<0.01	0.08	(.034 , .13)	<0.01
Age 16 (Rutter A)													
Hyperactive	0.08	(.003 , .15)	0.04	0.009	0.01	0.03	<0.01	0.041	(.02 , .06)	<0.01	0.12	(.05 , .19)	<0.01
Emotional problems	0.02	(-.05 , .08)	0.64	-0.003	0.23	0.04	<0.01	0.040	(.02 , .06)	<0.01	0.06	(-.01 , .11)	0.07
Conduct Problem	0.12	(.05 , .18)	<0.01	0.009	<0.01	0.04	<0.01	0.048	(.03 , .06)	<0.01	0.17	(.11 , .23)	<0.01
Age 16 (Rutter B)													
Neurotic	0.08	(.02 , .14)	0.01	0.006	0.03	0.04	<0.01	0.046	(.03 , .06)	<0.01	0.13	(.06 , .18)	<0.01
Antisocial	0.10	(.02 , .16)	0.01	0.010	<0.01	0.03	<0.01	0.043	(.03 , .06)	<0.01	0.14	(.07 , .21)	<0.01

1 Through mid-life obesity (BMI in Kg/m^2)

2 Through adulthood psychological distress at age 23 and age 42

* All the models have been adjusted for all the childhood confounding variables (sex, maternal smoking, pneumonia, social class of the father) and mid-life factors including smoking, educational achievement, and social class.

Emotional problems reported by both the parents and the teachers at age 7 and 11 had neither direct nor total effect on adult onset asthma or wheezy bronchitis. However, the age 11 emotional problem measures had an indirect effect through mid-life psychological distress. Conversely, the neurotic problem at school by age 16 had both direct and total effect on the risk for asthma.

11.1.2. Wheeze in the past 12 months at 42 years

The association between early life psychological factors as well as a range of perinatal, medical, social, environmental, and lifestyle variables and the twelve-month prevalence of asthma or wheezy bronchitis was examined using a series of logistic regression models. Structural equation models were used to test whether the hypothesised pathways between early life psychological factors and asthma fitted the data well. The results presented in this section are based on 11,375 cohort members who provided information on wheezing illness at age 42 years. Since there was a substantial amount of missing data in most of the covariates, the results based on both complete cases and on 10 multiply-imputed datasets are presented and compared.

Effect of childhood psychological factors on 12-months period prevalence of asthma

Table 11-9 summarises the effects of childhood psychological factors on the 12-month period prevalence of asthma or wheezy bronchitis at age 42 years in the 1958 birth cohort. Both the complete cases and multiply imputed data gave comparable results showing that the missing values in the covariates might have not introduced any substantial bias in the estimates. All the psychological factors assessed were significantly associated (at the 5% level) with the 12-month prevalence of asthma in logistic regression models except the emotional problems at school (the BSAG scale) at age seven and the miscellaneous nervous syndrome of the BSAG scale at age 11 years. Those with worse conditions of behavioural maladjustments were at a higher risk of having the wheezing illness at age 42 years as compared to those showing less behavioural deviance.

Table 11-9: The odds ratios (95% CIs) for the effect of childhood psychological factors on the 12-month period prevalence of asthma or wheezy bronchitis at age 42 years in the 1958 birth cohort (NCDS).

	AW[1]	AW_F[2]	M[3]	Odds ratio (95% CIs)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	776	9,176	12.5	1.04	(1.02 , 1.07)	<0.01	1.05	(1.03 , 1.07)	<0.01
Hyperactive	775	9,169	12.6	1.09	(1.03 , 1.16)	<0.01	1.10	(1.03 , 1.17)	<0.01
Emotional problems	776	9,175	12.5	1.07	(1.02 , 1.12)	<0.01	1.08	(1.03 , 1.13)	<0.01
Conduct Problem	776	9,173	12.5	1.06	(1.01 , 1.11)	0.02	1.07	(1.02 , 1.12)	0.01
Child Behaviour at School (BSAG)									
Emotional problems	785	9,335	11.0	1.01	(0.99 , 1.02)	0.49	1.01	(0.99 , 1.02)	0.54
Conduct problems	785	9,335	11.0	1.02	(1.01 , 1.03)	<0.01	1.02	(1.01 , 1.03)	<0.01
Miscellaneous Nervous Syndrome	785	9,334	11.0	1.22	(1.04 , 1.44)	0.01	1.23	(1.04 , 1.46)	0.02
At Age 11									
Child Behaviour at Home (Rutter A)									
Total Score	735	8,930	15.0	1.05	(1.03 , 1.07)	<0.01	1.06	(1.04 , 1.08)	<0.01
Hyperactive	735	8,929	15.0	1.13	(1.07 , 1.20)	<0.01	1.14	(1.08 , 1.21)	<0.01
Emotional problems	735	8,929	15.0	1.07	(1.02 , 1.12)	0.01	1.07	(1.02 , 1.12)	<0.01
Conduct Problem	735	8,927	15.1	1.10	(1.04 , 1.16)	<0.01	1.11	(1.05 , 1.16)	<0.01
Child Behaviour at School (BSAG)									
Emotional problems	751	9,031	14.0	1.02	(1.01 , 1.04)	0.01	1.02	(1.01 , 1.04)	0.01
Conduct problems	751	9,031	14.0	1.03	(1.02 , 1.04)	<0.01	1.03	(1.01 , 1.04)	<0.01
Miscellaneous Nervous Syndrome	751	9,031	14.0	0.99	(0.81 , 1.22)	0.96	0.97	(0.79 , 1.20)	0.80
At Age 16									
Child Behaviour at Home (Rutter A)									
Total Score	649	7,762	26.1	1.05	(1.03 , 1.08)	<0.01	1.05	(1.03 , 1.07)	<0.01
Hyperactive	647	7,756	26.1	1.19	(1.09 , 1.29)	<0.01	1.17	(1.08 , 1.27)	<0.01
Emotional problems	649	7,760	26.1	1.08	(1.03 , 1.14)	<0.01	1.09	(1.03 , 1.14)	<0.01
Conduct Problem	648	7,759	26.1	1.16	(1.09 , 1.23)	<0.01	1.17	(1.09 , 1.25)	<0.01
Child Behaviour at School (Rutter B)-total score									
Well adjusted	535	6,952	22.1						
With behavioural disorder	146	1,229		1.54	(1.27 , 1.87)	<0.01	1.56	(1.30 , 1.85)	<0.01
Subscales for Rutter B									
Neurotic	678	8,154	22.4	1.15	(1.08 , 1.22)	<0.01	1.14	(1.08 , 1.21)	<0.01
Antisocial	677	8,160	22.3	1.07	(1.03 , 1.12)	<0.01	1.08	(1.04 , 1.12)	<0.01
Childhood adversity Score **	691	8,320	0.8	1.10	(1.07 , 1.13)	<0.01	1.10	(1.07 , 1.13)	<0.01

1 Asthma or wheezy bronchitis cases in the past 12 months at age 42.

2 Those with no reported cases of asthma or wheezy bronchitis in the past 12 months.

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

** Retrospective childhood adversity score (Path through life scale) for those who had biomedical data at age 44/45.

Perinatal, and childhood biological, social and environmental factors

Of the large number of perinatal and childhood factors considered (listed in Section 10.4.1), only a few presented in Table 11-10 were found to be significantly associated with 12-month period prevalence of asthma at age 42 years. Female cohort members were more likely to have wheezing illness by age 42 as compared to their male counterparts (OR=1.63, 95% CI= 1.42-1.87). The most prominent perinatal factor was the maternal smoking during pregnancy; those whose mothers were smokers during pregnancy were at a higher risk of asthma compared to those whose mothers were not (OR=1.27, 95% CI=1.09-1.49). Among the childhood infections, those who reported cases of eczema, hay fever, whooping cough, and pneumonia by age 7 or 11 were at a significantly higher risk of having wheezing illness later in life compared to those who did not.

A number of other childhood factors were considered but none emerged as significant predictors of wheezing illness at age 42 years in the bivariate model. These included parental education- whether mother (p = 0.09) or father (p = 0.13) left school after the minimum school age, mother's age at delivery (p = 0.24), social class of the mother's husband by age 7 (p= 0.47), measles infection by age 7(p= 0.45), child cognitive measures (reading and arithmetic scores), breast feeding (p= 0.87), child being in care (p= 0.78), and birth weight for gestational age (p = 0.19). Cohort member's smoking status at age 16 was also notably not a significant predictor of asthma or wheezy bronchitis at age 42 even though being significant for the adult onset (17-42 years) asthma. Also the number of children in the household and tenure of accommodation were not significant.

Early adulthood psychological factors

All the adulthood psychological factors considered were found to be significantly associated with the 12-months prevalence of wheezing illness at age 42 (Table 11-11). The odds of reporting asthma or wheezy bronchitis was twice for those who showed signs of psychological distress at age 26 as measured by Malaise inventory compared to those who did not show any sign of psychological distress (OR=2.09, 95% CI = 1.67-2.62). The odds increased to 2.43 for those who showed signs of psychological distress at

age 42. Higher scores of GHQ12 at age 42, indicating worse conditions of mental problem over the past few weeks, was also highly associated with the wheezing illness.

Table 11-10: The odds ratios (95% CI) for the effect of perinatal and other childhood factors on the 12-month period prevalence of asthma or wheezy bronchitis at age 42 years in the 1958 birth cohort.

				Odds Ratio (95% CI)					
				Complete Cases			MI[4]		
	AW[1]	AW_F[2]	M[3] (%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Sex									
Male	337	5,266	0.0	Ref					
Female	544	5,228		1.63	(1.41 , 1.87)	<0.01	1.63	(1.41 , 1.87)	<0.01
Maternal smoking during pregnancy			5.2						
Non-Smoker	521	6,754		Ref					
Smoker	314	3,198		1.27	(1.10 , 1.47)	<0.01	1.28	(1.09 , 1.49)	<0.01
Parity			5.2						
No prev aft 28wks	327	3,713		Ref					
1 After 28wks	247	3,113		0.90	(0.76 , 1.07)	0.23	0.89	(0.75 , 1.06)	0.19
2 after28wks	109	1,563		0.79	(0.63 , 0.99)	0.04	0.79	(0.63 , 0.99)	0.04
3+ after 28wks	152	1,561	13.0	1.11	(0.90 , 1.35)	0.33	1.09	(0.89 , 1.33)	0.39
Pneumonia by age 7									
No	708	8,731		Ref					
Yes	62	399		1.92	(1.45 , 2.53)	<0.01	1.98	(1.51 , 2.60)	<0.01
Whooping cough by age 7			15.3						
No	618	7,542		Ref					
Yes	137	1,334		1.25	(1.03 , 1.52)	0.02	1.30	(1.07 , 1.57)	0.01
Hayfever by age 7 or 11			5.1						
No	664	9,087		Ref					
Yes	167	874		2.61	(2.18 , 3.14)	<0.01	2.66	(2.21 , 3.19)	<0.01
Eczema by age 7 or 11			15.4						
No	609	8,090		Ref					
Yes	125	803		2.07	(1.68 , 2.54)	<0.01	1.97	(1.62 , 2.39)	<0.01
Birthweight			5.5						
<2.5	63	559		1.39	(1.03 , 1.89)	0.03	1.35	(0.99 , 1.83)	0.06
up to 3	166	2,050		Ref					
up to 3.5	333	3,601		1.14	(0.94 , 1.39)	0.18	1.13	(0.92 , 1.38)	0.24
up to 4	213	2,772		0.95	(0.77 , 1.17)	0.63	0.94	(0.76 , 1.16)	0.55
>4	58	930		0.77	(0.57 , 1.05)	0.10	0.75	(0.55 , 1.02)	0.07
Smoking at age 16 (#of packets)			24.5						
Non-Smoker	407	5,189		Ref					
Less than 3	207	2,330		1.13	(0.95 , 1.35)	0.16	1.09	(0.93 , 1.28)	0.29
3+	41	414		1.26	(0.90 , 1.77)	0.17	1.27	(0.90 , 1.81)	0.17

1 Asthma or wheezy bronchitis cases in the past 12 months at age 42; Ref = Reference category

2 Those with no reported cases of asthma or wheezy bronchitis in the past 12 months.

3 Percent of missing data; 4 Analysis based on combined results of 10 multiply-imputed datasets

Table 11-11 : The odds ratios (95% CI) for the effect adulthood psychological factors on the 12-month period prevalence of asthma or wheezy bronchitis at age 42 years in the 1958 birth cohort (NCDS).

	AW[1]	AW_F[2]	M[3]	OR(95% CI) Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological distress at 23 years (Malaise)			15.5						
Normal	657	8,285							
Depressed	89	582		1.93	(1.52 , 2.44)	<0.01	2.09	(1.67 , 2.62)	<0.01
Psychological distress at 42 years (Malaise)			0.9						
Normal	651	9,127							
Depressed	221	1,278		2.42	(2.06 , 2.85)	<0.01	2.43	(2.06 , 2.86)	<0.01
GHQ12 at 42 years	872	10,407	0.8	1.05	(1.04 , 1.07)	<0.01	1.05	(1.04 , 1.07)	<0.01

1 Asthma or wheezy bronchitis cases in the past 12 months at age 42.

2 Those with no reported cases of asthma or wheezy bronchitis in the past 12 months.

3 Percent of missing data

4 Analysis based on combined results of 10 multiple-imputed datasets

Effects of adulthood biological, environmental and social factors

Table 11-12 shows the unadjusted effects (odds ratios and 95% CI) of adulthood biological, social and environmental factors on the 12-month period prevalence of asthma or wheezy bronchitis at age 42 years in the NCDS. Only variables that were significantly associated with the 12-months prevalence of asthma at age 42 years are presented in the table. Other variables that were tested but remained non-significant at 5% significance level included alcohol consumption at ages 23 ($p = 0.46$) and consumption of salads or raw vegetables at age 42 ($p = 0.34$).

The cohort members who were classified as highly atopic were at a higher risk of the wheezing illness (OR=3.61, 95% CI= 3.0-4.36) compared to those classified as non-atopic. Those who had total IgE >30kU/L, the daily smokers at age 42, those in unskilled manual social class at age 33, those with drinking problems at age 42, the overweight and obese at age 42, and those with severe abdominal fat were all positively associated with the 12-months prevalence of asthma at age 42 years. A decrease in both the lung function measures (FVC and FEV_1) was also significantly associated with the 12-month period prevalence of wheezing illness. Daily consumption of fresh fruits at age 42, achievement of higher education by age 23, and daily physical exercise by age 42 had a protective effect on the 12-months prevalence asthma or wheezy bronchitis.

Table 11-12 : The Effects of adulthood environmental and social factors on 12-month prevalence of asthma or wheezy bronchitis at age 42 years in the NCDS.

Variable (Reference category)	AW[1]	AW_F[2]	M[3]	Odds Ratios (95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Atopy (Negative)	267	5,048	17.9						
Weak/Moderate positive	61	619		1.86	(1.39 , 2.49)	<0.01	1.86	(1.39 , 2.49)	<0.01
High/very high positive	234	1,224		3.61	(3.00 , 4.35)	<0.01	3.61	(3.00 , 4.36)	<0.01
Total IgE, kU/L (<10)	61	1,475	17.8						
10-30	114	2,243		1.23	(0.89 , 1.69)	0.20	1.23	(0.89 , 1.69)	0.20
31-99	173	1,902		2.20	(1.63 , 2.97)	<0.01	2.20	(1.63 , 2.97)	<0.01
>100	216	1,282		4.07	(3.04 , 5.47)	<0.01	4.07	(3.04 , 5.47)	<0.01
Smoking at age 42 (Never)	343	4,728	0.0						
Used to smoke	225	2,643		1.17	(0.99 , 1.40)	0.07	1.17	(0.99 , 1.40)	0.07
Smokes occasionally	35	456		1.06	(0.74 , 1.52)	0.76	1.06	(0.74 , 1.52)	0.76
Smokes everyday < 1 packet	129	1,339		1.33	(1.08 , 1.64)	0.01	1.33	(1.07 , 1.64)	0.01
Smoked everyday 1+ packets	149	1,326		1.55	(1.27 , 1.90)	<0.01	1.55	(1.27 , 1.90)	<0.01
Forced vital capacity (log_{10})	665	8,140	3.0	0.25	(0.18 , 0.33)	<0.01	0.25	(0.18 , 0.33)	<0.01
Forced expiratory vol in 1s (log_{10})	665	8,140	3.0	0.32	(0.27 , 0.39)	<0.01	0.32	(0.27 , 0.39)	<0.01
Fresh fruits (Never/Occas/<1 day)	214	2,028	0.0						
1-6 days a wk	412	5,372		0.73	(0.61 , 0.86)	<0.01	0.73	(0.61 , 0.86)	<0.01
One or more a day	254	3,092		0.78	(0.64 , 0.94)	0.01	0.78	(0.64 , 0.94)	0.01
Educational level at age 23 (None)	129	1,027	19.3						
CSE 2-5/equiv nvq1	96	1,118		0.68	(0.52 , 0.90)	0.01	0.74	(0.57 , 0.97)	0.03
O level/equiv nvq2	243	3,123		0.62	(0.49 , 0.78)	<0.01	0.67	(0.53 , 0.84)	<0.01
A level /equiv nvq3 and Higher	238	3,201		0.59	(0.47 , 0.74)	<0.01	0.63	(0.51 , 0.78)	<0.01
Social class at 33 (I or II: Proff)	235	3,135	19.5						
III: Skilled non-manual	170	2,060		1.10	(0.90 , 1.35)	0.36	1.12	(0.92 , 1.37)	0.26
III: Skilled manual	129	1,692		1.02	(0.81 , 1.27)	0.88	1.05	(0.82 , 1.34)	0.71
IV or V-Partly/ unskilled	166	1,570		1.41	(1.15 , 1.74)	<0.01	1.40	(1.14 , 1.73)	<0.01
Drinking problem at 42 (No)	727	9,026	1.4						
Yes	140	1,321		1.32	(1.09 , 1.59)	0.01	1.31	(1.08 , 1.58)	0.01
Physical exercise at age 42 (No)	263	2,682	0.0						
Yes	618	7,809		0.81	(0.69 , 0.94)	0.01	0.81	(0.69 , 0.94)	0.01
Sex specific WC (Normal abd. fat)	396	5,468	0.8						
Severe abdominal fat	290	2,850		1.41	(1.20 , 1.65)	<0.01	1.41	(1.20 , 1.65)	<0.01
BMI at age 42 (Normal)	347	4,859	2.6						
Underweight	15	111		1.89	(1.09 , 3.28)	0.02	1.79	(1.03 , 3.09)	0.04
Overweight	319	3,677		1.21	(1.04 , 1.42)	0.02	1.21	(1.03 , 1.42)	0.02
Obesity	176	1,581		1.56	(1.29 , 1.89)	<0.01	1.58	(1.30 , 1.91)	<0.01

1 Asthma or wheezy bronchitis cases in the past 12 months at age 42.

2 Those with no reported cases of asthma or wheezy bronchitis in the past 12 months.

3 Percent of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Possible confounding effects of other childhood measures

A number of childhood measures were found to be related to both the 12-month period prevalence of asthma at age 42 and the childhood psychological factors. Therefore, the observed associations between wheezing illness and the psychological factors could be positively confounded by these variables. All these variables were adjusted for in a multiple logistic regression for each childhood psychological measure and the crude and adjusted effect estimates were compared. A final model was the one adjusted for the effects of cohort member's sex, maternal smoking, history of pneumonia by age seven, history of hay fever at seven or 11 years, and history of eczema at seven or 11 years. Parity, birthweight, and childhood whooping cough, though significantly associated with wheezing illness in the bivariate model, became non-significant in the multivariable model and were excluded from the adjusted model.

Table 11-13 presents the odds ratios (95% CI) for the effects of childhood psychological factors on 12-month period prevalence of the wheezing illness at age 42 in the NCDS after adjusting for the possible confounders. The results based on complete cases and the ones based on multiply-imputed data are comparable in most cases. Generally, the effects remained unchanged as compared to the unadjusted models. However, emotional problems at both age 7 and 11 became non-significant after including both hay fever and eczema in the model but were still significant if only one of the variables was in the model. At age 16 emotional problems became non-significant after the inclusion of either hay fever or eczema at age 7 or 11 in the model. Therefore, the childhood emotional problems could possibly be positively confounded by the childhood atopic illnesses However, childhood atopy and adult asthma might also share a common aetiology involving emotional factors. Children who showed extreme outwardly expressed behaviours had a significant higher risk for recent asthma and wheeze in the previous 12 months later in life compared to children who did not express such extreme behaviours after adjusting for the other childhood measures. On the other hand, children who had internalising problems or who showed withdrawn inhibited behaviours as assessed by their parents at ages 7, 11 and 16 years did not show a significantly higher risk of asthma at age 42 years.

Table 11-13 : The adjusted effects of childhood psychological factors on the 12-months period prevalence of asthma and wheezy bronchitis at age 42 in the NCDS.

	Adjusted OR (95% CI)[1]					
	Complete Cases			MI[2]		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	1.04	(1.02 , 1.07)	<0.01	1.04	(1.02 , 1.07)	<0.01
Hyperactive	1.11	(1.04 , 1.18)	<0.01	1.09	(1.03 , 1.16)	0.01
Emotional problems	1.05	(0.99 , 1.10)	0.09	1.05	(1.00 , 1.11)	0.05
Conduct Problems	1.08	(1.03 , 1.14)	<0.01	1.08	(1.03 , 1.14)	<0.01
Child Behaviour at School (BSAG)						
Emotional problems	1.00	(0.99 , 1.02)	0.62	1.01	(0.99 , 1.02)	0.46
Conduct problems	1.03	(1.01 , 1.05)	<0.01	1.03	(1.01 , 1.04)	<0.01
Miscellaneous Nervous Syndrome	1.24	(1.03 , 1.49)	0.03	1.27	(1.06 , 1.51)	0.01
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	1.05	(1.03 , 1.08)	<0.01	1.06	(1.03 , 1.08)	<0.01
Hyperactive	1.15	(1.08 , 1.23)	<0.01	1.14	(1.08 , 1.21)	<0.01
Emotional problems	1.05	(1.00 , 1.11)	0.06	1.05	(1.00 , 1.10)	0.05
Conduct Problems	1.11	(1.05 , 1.17)	<0.01	1.13	(1.07 , 1.19)	<0.01
Child Behaviour at School (BSAG)						
Emotional problems	1.02	(1.00 , 1.04)	0.04	1.03	(1.01 , 1.05)	<0.01
Conduct problems	1.03	(1.02 , 1.05)	<0.01	1.04	(1.02 , 1.05)	<0.01
Miscellaneous Nervous Syndrome	1.11	(0.88 , 1.40)	0.39	1.02	(0.83 , 1.26)	0.82
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	1.04	(1.02 , 1.07)	<0.01	1.05	(1.03 , 1.07)	<0.01
Hyperactive	1.22	(1.10 , 1.34)	<0.01	1.19	(1.10 , 1.29)	<0.01
Emotional problems	1.03	(0.97 , 1.10)	0.31	1.05	(1.00 , 1.11)	0.05
Conduct Problems	1.15	(1.07 , 1.24)	<0.01	1.16	(1.08 , 1.25)	<0.01
Child Behaviour at School (Rutter B) total score						
Well adjusted						
Behavioural disorder	1.44	(1.14 , 1.83)	<0.01	1.62	(1.35 , 1.95)	<0.01
Subscales						
Neurotic	1.11	(1.03 , 1.19)	0.01	1.12	(1.05 , 1.18)	<0.01
Antisocial	1.08	(1.03 , 1.14)	<0.01	1.10	(1.05 , 1.14)	<0.01
Childhood Adversity Score **	1.08	(1.05 , 1.12)	<0.01	1.09	(1.06 , 1.13)	<0.01

1 Adjusted for the effect of sex, maternal smoking, history of pneumonia by age 7, hay fever by age 7 or 11 and eczema at age 7 or 11.

2 Analysis based on combined results of 10 multiple-imputed datasets

* For all psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

** Retrospective childhood adversity score (Path through life scale). Based on those who had biomedical data at age 44/45.

Assessing the possible effect of atopy

Similar to the analysis of adult onset asthma risks, the possible modification effect of adulthood atopy was examined by including an interaction term between atopy and each of the psychological factors in the model. For this analysis only 7,453 subjects who provided information on IgE in the biomedical data were included. Table 11-14 presents the results of the interaction effects. Only results for significant interactions are shown.

Table 11-14: Interaction terms between childhood psychological factors and atopy on their effect on 12-months period prevalence asthma or wheezy bronchitis at age 42 years.

	OR	(95% CI)	Sig
At Age 7			
Child Behaviour at Home (Rutter A)			
Atopy *	4.44	(3.02 , 6.54)	<0.01
Total Score	1.08	(1.04 , 1.12)	<0.01
Atopy x Total score	0.95	(0.90 , 0.99)	0.03
Atopy	3.72	(2.89 , 4.79)	<0.01
Hyperactive	1.20	(1.08 , 1.33)	<0.01
Atopy x Hyperactive	0.84	(0.72 , 0.97)	0.02
Atopy	4.18	(3.04 , 5.75)	<0.01
Conduct problems	1.14	(1.04 , 1.23)	<0.01
Atopy x Conduct problems	0.86	(0.76 , 0.97)	0.02
At Age 11			
Atopy	3.97	(3.07 , 5.15)	<0.01
Hyperactive	1.25	(1.14 , 1.39)	<0.01
Atopy x Hyperactive	0.85	(0.73 , 0.99)	0.04
Child Behaviour at School (BSAG)			
Atopy	3.72	(2.92 , 4.75)	<0.01
Emotional problems	1.04	(1.01 , 1.08)	<0.01
Atopy x Emotional problems	0.95	(0.91 , 0.99)	<0.01
Atopy	3.28	(2.70 , 3.98)	<0.01
Miscellaneous nervous syndrome	1.16	(0.82 , 1.65)	0.40
Atopy x Miscellaneous nervous syndrome	0.47	(0.25 , 0.91)	0.03
At Age 16			
Atopy	3.54	(2.75 , 4.55)	<0.01
Conduct problems	1.26	(1.15 , 1.39)	<0.01
Atopy x Conduct problems	0.84	(0.72 , 0.97)	0.02
Child Behaviour at School (Rutter B)			
Atopy	3.47	(2.71 , 4.43)	<0.01
Neurotic	1.28	(1.16 , 1.41)	<0.01
Atopy x Neurotic	0.84	(0.72 , 0.99)	0.03

* Atopy is categorised in to atopic and non-atopic (Reference category)

Unlike in the analysis for the adult onset asthma where there were no significant interaction terms, a number of significant interaction terms were present for the 12-months period prevalence asthma. This could be as a result of the proximity of the 42 year old data on asthma to the 45 years when the information on IgE was collected. Thus, the relationship between psychological factors listed in Table 11-14 depends on the level of atopy. Since all the odds ratios of all these variables increased upon the addition of the interaction terms, the effect of atopy has an intensifying effect on the temporal association between these psychological factors and 12-months period prevalence of asthma at age 42 years.

Additionally, a sub-group analysis was performed on atopic and non-atopic subjects. Table 11-14 shows the results of the two groups and the combined results for both atopic and non-atopic based on multiple imputed data. Within the atopic subgroup, having adjusted for sex and all other childhood confounders, no significant associations were found between the psychological factors and asthma or wheezy bronchitis except for the conduct problems at age 11 and hyperactive behavioural problems at age 16 years. The effects for the non-atopic subgroup were slightly stronger but followed the same pattern as that of both groups combined except for the emotional problems which were significant in the non-atopic subgroup but not significant in the combined data. Thus, the modifying effects of atopy seemed to have reduced upon simultaneous adjustment by other confounding factors. Since the effects of childhood psychological factors on 12-months period prevalence of asthma or wheezy bronchitis were confined to the non-atopic group, these effects are unlikely to be due to atopy. However, this approach of subgroup analysis should be treated with caution since there were fewer subjects within the atopic subgroup which could hinder any significant association to be realised due to less statistical power.

Potential mediation effects

To test the hypothesis that childhood psychological factors affect the wheezing disease partly through other pathways along the life course, structural equation models were fitted for each of the psychological measure. A similar model to the one for adult onset asthma (Figure 11-1) was tested with the 12-months period prevalence asthma or wheezing. The results for the mediation analysis followed the same pattern as that for adult-onset asthma (results not presented).

Table 11-15: Comparing the effects of childhood psychological factors on 12-months period prevalence asthma or wheezy bronchitis at age 42 between the atopic and non-atopic sub-groups. All models adjusted for all childhood confounders.[‡]

	Adjusted[†] Odds Ratios (95% CI)								
	Atopic group			Non-Atopic group			Both groups		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig	OR	(95% CI)	Sig
At Age 7*									
Child Behaviour at Home (Rutter A)									
Total Score	1.01	(0.98 , 1.05)	0.45	1.08	(1.04 , 1.12)	<0.01	1.04	(1.02 , 1.07)	<0.01
Hyperactive	0.99	(0.88 , 1.11)	0.82	1.21	(1.09 , 1.33)	<0.01	1.09	(1.03 , 1.16)	0.01
Emotional problems	1.05	(0.97 , 1.14)	0.25	1.10	(1.01 , 1.20)	0.03	1.05	(1.00 , 1.11)	0.05
Conduct Problem	1.01	(0.92 , 1.11)	0.83	1.17	(1.08 , 1.27)	<0.01	1.08	(1.03 , 1.14)	<0.01
Child Behaviour at School (BSAG)									
Emotional problems	1.00	(0.96 , 1.03)	0.77	1.03	(1.00 , 1.06)	0.10	1.01	(0.99 , 1.02)	0.46
Conduct problems	1.01	(0.98 , 1.04)	0.58	1.03	(1.00 , 1.05)	0.04	1.03	(1.01 , 1.04)	<0.01
Miscellaneous Nervous Syndror	1.22	(0.86 , 1.72)	0.26	1.39	(1.06 , 1.83)	0.02	1.27	(1.06 , 1.51)	0.01
At Age 11									
Child Behaviour at Home (Rutter A)									
Total Score	1.03	(1.00 , 1.07)	0.08	1.09	(1.06 , 1.13)	<0.01	1.06	(1.03 , 1.08)	<0.01
Hyperactive	1.07	(0.95 , 1.20)	0.26	1.28	(1.16 , 1.41)	<0.01	1.14	(1.08 , 1.21)	<0.01
Emotional problems	1.02	(0.94 , 1.11)	0.61	1.07	(0.99 , 1.16)	0.07	1.05	(1.00 , 1.10)	0.05
Conduct Problem	1.10	(1.01 , 1.21)	0.04	1.21	(1.10 , 1.33)	<0.01	1.13	(1.07 , 1.19)	<0.01
Child Behaviour at School (BSAG)									
Emotional problems	1.00	(0.96 , 1.03)	0.76	1.05	(1.02 , 1.08)	<0.01	1.03	(1.01 , 1.05)	<0.01
Conduct problems	1.01	(0.98 , 1.04)	0.53	1.05	(1.02 , 1.07)	<0.01	1.04	(1.02 , 1.05)	<0.01
Miscellaneous Nervous Syndror	0.56	(0.31 , 1.00)	0.05	1.22	(0.85 , 1.75)	0.27	1.02	(0.83 , 1.26)	0.82
At Age 16									
Child Behaviour at Home (Rutter A)									
Total Score	1.03	(0.99 , 1.07)	0.11	1.08	(1.04 , 1.12)	<0.01	1.05	(1.03 , 1.07)	<0.01
Hyperactive	1.21	(1.03 , 1.42)	0.02	1.28	(1.11 , 1.46)	<0.01	1.19	(1.10 , 1.29)	<0.01
Emotional problems	1.00	(0.91 , 1.11)	0.95	1.11	(1.02 , 1.21)	0.01	1.05	(1.00 , 1.11)	0.05
Conduct Problem	1.07	(0.97 , 1.19)	0.19	1.27	(1.14 , 1.40)	<0.01	1.16	(1.08 , 1.25)	<0.01
Child Behaviour at School (Rutter B) total score									
Well adjusted									
With behavioural disorder	1.26	(0.87 , 1.83)	0.22	2.16	(1.58 , 2.96)	<0.01	1.62	(1.35 , 1.95)	<0.01
Subscales									
Neurotic	1.01	(0.90 , 1.15)	0.82	1.22	(1.10 , 1.34)	<0.01	1.12	(1.05 , 1.18)	<0.01
Antisocial	1.04	(0.96 , 1.13)	0.31	1.13	(1.05 , 1.21)	<0.01	1.10	(1.05 , 1.14)	<0.01
Childhood Adversity Score **	1.03	(0.98 , 1.09)	0.28	1.13	(1.08 , 1.19)	<0.01	1.09	(1.06 , 1.13)	<0.01

† All model adjusted for the effect of sex, maternal smoking, parity, pneumonia at age 7, social class of the father at 7 years, history of hay fever at seven or 11 years, history of eczema at seven or 11 years, and smoking at age 16 for the 16 year old measures.

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

** Retrospective childhood adversity score (Path through life scale). Based on those who had biomedical data at age 44-45.

‡ Combined results of 10 multipy-imputed datasets

After adjusting for all the childhood confounders and adulthood smoking status, educational achievement, social class at age 33, and fruit consumption, there was still a

direct effect of the hyperactive and conduct problems as viewed by the mother at both age 11 and 16 years. Teacher assessed conduct problems in school at both age 7 and 11 were also directly significantly associated with the 12-months prevalence asthma at age 42. Cohort members with higher scores in conduct problems at home and at school, and hyperactive behaviours, indicating poor behavioural adjustment, were at a higher risk for asthma or wheezy bronchitis at age 42. Emotional problems did not have a direct effect but their effect was mediated via mid life psychological distress and obesity.

11.2. The BCS70 Results

Subjects

Of the original 18,732 cohort members with at least some data since birth, 11,261 (60%) provided information at the fifth sweep of data collection when the cohort members were 30 years old. Of these, 11,226 provided information on specific health problems including asthma and wheezy bronchitis at age 30 years. About 70% of the cohort (*n*= 13,110) had full information on asthma and wheezy bronchitis provided by parents at the 5-year follow-up. However, only 3,541 (19%) had complete information on wheezing illness at all the sweeps during the life course up to age 30 years. Table 11-16 summarises the study participants based the available information on asthma or wheezy bronchitis in all the sweeps of data collection.

Table 11-16: Summary of the BCS70 based on the information provided on asthma or wheezy bronchitis at each sweep.

Missing data indicator for asthma/wheezy bronchitis	Freq.	%
Complete data on asthma/wheezy bronchitis at all the sweeps	3,541	18.9
No data on asthma/wheezy bronchitis at only one sweep	4,479	23.9
No data on asthma/wheezy bronchitis in any two sweeps	3,915	20.9
No data on asthma/wheezy bronchitis in any three sweeps	2,611	13.9
No data on asthma/wheezy bronchitis in any four sweeps	1,698	9.1
No information on asthma/wheezy bronchitis in all the surveys	2,488	13.3
Total	18,732	100.0

Prevalence and cumulative incidence

The reported prevalence of asthma or wheezy bronchitis "ever" at each sweep, and in the past 12 months at age 30 is shown in Table 11-17 for the subjects who had full information at all the sweeps (fully linked data) and those who had information in at least one sweep of data collection (partially linked).

Table 11-17: Percentage prevalence of asthma or wheezy bronchitis at each sweep in subjects with data at each sweep (fully linked data) and using all available information in the BCS70.

	Age 5	**Age 10**	**Age 16**	**Age 26†**	**Age 30**
	Report of asthma or wheezing ever for fully linked data				
Males	8.1(122/1,515)	15.6(237 /1,515)	13.5(204/1,515)	13.1(198/1,515)	15.5(234/1,515)
Females	5.5(111/2,026)	11.3(229 /2,026)	8.0(162/2,026)	15.9(323/2,026)	17.2(355/2,026)
Total	6.6(233/3,541)	13.2(466/3,541)	10.3(366/3,541)	14.7(521/3,541)	16.6(589/3,541)
	Report of asthma or wheezing ever using all available information				
Males	8.3(564/6,790)	17.5(1,073 /6,142)	13.6(594/4,382)	14.4(590/ 4,102)	17.1(933 /5,443)
Females	5.6(355/6,320)	12.3(727/5,905)	8.9(402/4,533)	17.6(862/4,901)	19.0(1,098/5,768)
Total	7.0(919/13,110)	14.9(1,800/12,047)	11.2(996/8,915)	16.1(1,452/9,003)	18.1(2,031/11,211)
	Cumulative incidence up to the given age for all the respondents				
Linked‡	7.0(919/13,110)	17.5(1,749/10,006)	19.3(1,191/6,156)	24.3(1,495/6,156)	29.5(1,046/3,541)
All info*	7.0(919/13,110)	14.8(2,236/15,151)	17.5(2,664/15,205)	23.2(3,541/15,296)	26.0(4,223/16,244)
	12-months period prevalence at age 30				
Males					7.3(395/5,443)
Females					9.3(535/5,767)
Total					8.3(930/11,210)

Data are presented as percentage (number of prevalent cases/total number with complete information on wheezing up to that age or all available cases for that sweep for the unlinked data

† At age 26 the question referred only to asthma since age 16

‡ Cumulative incidence derived from successive follow-ups, based on those with full information on wheezing illness up to that particular age

* Cumulative incidence derived from successive follow-ups, based on all available information on wheezing illness

For both the fully linked data and that based on all available information, males had a higher annual period prevalence up to age 16; thereafter, prevalence ratio reversed with a substantially higher prevalence in females at age 26 and 30 years. The annual period prevalence of asthma or wheezing remained relatively stable whether or not the analysis was restricted to cohort members with complete wheezing information across all surveys or to those with partial information suggesting minimal bias due to sample attrition. The

12-month period prevalence of asthma or wheezy bronchitis at age 30 years among all subjects interviewed at that sweep was 8.3% (7.3% in males and 9.3% in females).

The cumulative incidence, calculated on the basis of all prior information, was slightly higher for the fully linked data as compared to partially linked data. The proportion of the cohort who had experienced asthma or wheezy bronchitis by 30 years of age was 29.5% for the fully linked data and 26.0% based on all available information. This was slightly lower than that of the 1958 cohort where 29% and 43% had experienced asthma or wheezy bronchitis by age 23 and 33 years, respectively.

11.2.1. Adult-onset wheezing

The logistic regression analyses results presented in this section are based on the incident wheezing in early adult life outcome, defined as those who reported asthma or wheezy bronchitis after age 16 years and no history of asthma or wheezing illness before age 16 years. Two categories of outcome were considered: those with full information on asthma and wheezy bronchitis at all the sweeps from age 5 to age 30 excluding those with history before age 16 (n = 2,886); and those who had information at either age 26 or age 30 years or both but no history of asthma or wheezing illness before age 16 (n= 10,532). The results did not differ in terms of the significance and only those for all available information have been presented. Tables 11-18 to 11-21, which also show the main body of univariable results, present the amount of missing data for each covariate considered in the analysis. There were substantial amount of missing data especially for the age 16 measures where up to 41% did not provide information on some items of the behavioural scales. As a result, both the complete case analysis and that based on 10 multiply-imputed datasets were performed and the results compared.

Effect of childhood psychological factors

Table 11-18 presents the odds ratios (95% CI) for the effect of childhood psychological factors on adult onset (age 17-30) asthma or wheezy bronchitis. For each variable, the number of those who reported and those who did not report asthma or wheezy bronchitis after age 16 are presented. Unlike in the NCDS where majority of the childhood psychological factors significantly predicted adult onset asthma or wheezy bronchitis, only a few turned out to be significant in the BCS70.

Table 11-18: The odds ratios (95% CI) for the effect of childhood psychological factors on adult onset (age 17-30) asthma or wheezy bronchitis in the 1970 birth cohort.

	AW[1]	AW_F[2]	M[3]	Odds Ratios (95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological factors at age 5*									
Child Behaviour at Home (Rutter A)									
Total Score	1,211	7,156	20.6	1.01	(0.99 , 1.02)	0.42	1.01	(0.99 , 1.02)	0.28
Hyperactive	1,209	7,148	20.7	1.01	(0.97 , 1.05)	0.68	1.01	(0.97 , 1.05)	0.73
Emotional problems	1,210	7,146	20.7	1.01	(0.97 , 1.04)	0.63	1.01	(0.98 , 1.04)	0.59
Conduct Problem	1,209	7,151	20.6	1.00	(0.97 , 1.03)	0.97	1.01	(0.98 , 1.03)	0.64
Psychological factors at age 10									
Child Behaviour at Home (Rutter A)									
Total Score	1,302	7,524	16.2	1.00	(0.99 , 1.00)	0.50	1.00	(0.99 , 1.00)	0.59
Hyperactive	1,299	7,515	16.3	1.00	(1.00 , 1.00)	0.95	1.00	(1.00 , 1.00)	0.80
Emotional problems	1,300	7,515	16.3	1.00	(1.00 , 1.00)	0.86	1.00	(1.00 , 1.00)	0.86
Conduct Problem	1,300	7,513	16.3	1.00	(0.99 , 1.00)	0.05	1.00	(0.99 , 1.00)	0.07
At Home (Conners' Mother self completion)									
Impulsive	1,298	7,510	16.4	1.00	(1.00 , 1.00)	0.86	1.00	(1.00 , 1.00)	0.88
Hyperactive/Inattention	1,297	7,514	16.3	1.00	(1.00 , 1.00)	1.00	1.00	(1.00 , 1.00)	0.89
Clumsy	1,297	7,497	16.5	1.00	(1.00 , 1.00)	0.72	1.00	(1.00 , 1.00)	0.91
Poor Motor Coordination	1,295	7,496	16.5	0.99	(0.99 , 1.00)	0.11	1.00	(0.99 , 1.00)	0.19
At School (Child Development Behaviour)									
Antisocial Behaviour	1,222	7,046	21.5	1.01	(1.00 , 1.02)	<0.01	1.01	(1.00 , 1.02)	<0.01
Disorganised activity	1,222	7,046	21.5	1.00	(1.00 , 1.01)	0.24	1.00	(1.00 , 1.01)	0.33
Neurotism/Anxiety	1,222	7,046	21.5	1.01	(1.00 , 1.02)	0.01	1.01	(1.00 , 1.02)	0.03
Clumsiness	1,222	7,046	21.5	1.01	(1.00 , 1.02)	0.01	1.01	(1.00 , 1.02)	0.03
Poor hand-Eye Coordination	1,222	7,045	21.5	1.00	(0.99 , 1.00)	0.28	1.00	(0.99 , 1.00)	0.30
Hyper/Kinesis	1,222	7,045	21.5	1.01	(1.00 , 1.02)	0.08	1.01	(1.00 , 1.02)	0.09
Introversion/Extroversion	1,222	7,043	21.5	1.00	(1.00 , 1.01)	0.52	1.00	(0.99 , 1.01)	0.89
Behavioural Trauma	1,187	6,790	21.5	1.02	(1.00 , 1.04)	0.09	1.02	(0.99 , 1.04)	0.17
Dressing	1,217	6,998	24.3	1.00	(0.99 , 1.00)	0.15	1.00	(0.99 , 1.00)	0.47
At School (Self Completion)									
Locus of Control[5]	1,225	7,023	22.0	0.99	(0.97 , 1.00)	0.09	0.99	(0.97 , 1.00)	0.08
Self Esteem[6]	1,225	7,023	21.7	0.98	(0.97 , 0.99)	<0.01	0.98	(0.97 , 1.00)	0.01
Psychological factors at age 16									
Child Behaviour at Home (Rutter A)									
Total Score	873	5,382	40.6	1.01	(1.00 , 1.03)	0.13	1.01	(0.99 , 1.02)	0.30
Hyperactive	858	5,294	41.6	1.06	(0.99 , 1.13)	0.07	1.07	(1.01 , 1.13)	0.02
Emotional problems	866	5,324	41.2	1.01	(0.97 , 1.05)	0.56	1.01	(0.97 , 1.05)	0.77
Conduct Problem	867	5,324	41.2	1.00	(0.97 , 1.04)	0.83	1.00	(0.97 , 1.03)	0.96

1 Those who reported having asthma or wheezy bronchitis after age 16 based on all available information. All those who provided information in at least one sweep of data collection are included; cohort members reporting a positive history of asthma or wheezy bronchitis up to age 16 have been excluded from analysis.

2 Cohort members who did not report any positive history of asthma or wheezy bronchitis.

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

5 Higher scores indicate greater internalization; 6 Higher score indicate higher self-esteem.

* For the rest of the psychological measures, higher score indicate worse conditions of behavioural maladjustment.

All the Rutter mother's behavioural subscales and the Conner's mother self completion questionnaire were not associated with adult onset wheezing illness except the hyperactive behaviour at age 16 years. However, some of the behavioural problems identified by the teachers at age 10 were significantly associated with the wheezing illness. Individuals who scored high on neuroticism, antisocial behaviour, and clumsiness were more likely than the average to experience asthma or wheezy bronchitis in mid life. In contrast, individuals with higher self esteem at age 10 were less likely to develop asthma or wheezy bronchitis in mid life.

Early adulthood psychological factors

Psychological distress at age 26 and age 30 and higher scores on the GHQ12 at age 30 were significantly and positively associated with the risk of adult-onset asthma or wheezy bronchitis (Table 11-19).

Table 11-19: The odds ratios (95% CI) for the effect of mid life psychological factors on adult onset asthma or wheezy bronchitis in the BCS70.

	AW[1]	AW_F[2]	M[3]	Odds Ratios (95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological distress at 26 yrs (Malaise Inventory)			29.1						
Normal	914	5,586							
Depressed	228	767		1.82	(1.54 , 2.14)	<0.01	1.79	(1.53 , 2.11)	<0.01
Psychological distress at 30 yrs (Malaise Inventory)			11.8						
Normal	1,145	6,993							
Depressed	252	898		1.71	(1.47 , 2.00)	<0.01	1.69	(1.44 , 1.98)	<0.01
GHQ12 at 30 years	1,397	7,893	11.8	1.03	(1.02 , 1.04)	<0.01	1.03	(1.02 , 1.05)	<0.01

1 Those who reported having asthma or wheezy bronchitis after age 16 based on all available information. All those who provided information in at least one sweep of data collection are included; cohort members reporting a positive history of asthma or wheezy bronchitis up to age 16 have been excluded from analysis.

2 Cohort members who did not report any positive history of asthma or wheezy bronchitis.

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Perinatal, and childhood biological, social and environmental factors

A number of perinatal and childhood biological and environmental factors were tested for their association with adult-onset asthma so that their effect could be adjusted for. Table 11-20 presents the estimates for these variables.

Table 11-20: The odds ratios (95% CI) for the effect of perinatal and childhood biological, social and environmental factors on adult onset asthma or wheezy bronchitis in the BCS70.

Variable (Reference category)	AW[1]	AW_F[2]	M[3]	Odds Ratios (95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Sex (Male)	614	4,386	0.0						
Female	945	4,587		1.47	(1.32 , 1.64)	<0.01	1.47	(1.32 , 1.64)	<0.01
Family history of atopy (No)	676	4,431	22.0						
Yes	513	2,593		1.30	(1.14 , 1.47)	<0.01	1.24	(1.11 , 1.39)	<0.01
Eczema up to age 10 (No)	1,177	7,185	8.1						
Yes	243	1,071		1.39	(1.19 , 1.61)	<0.01	1.33	(1.16 , 1.54)	<0.01
Hayfever up to age 10 (No)	1,192	7,656	8.2						
Yes	224	593		2.43	(2.06 , 2.86)	<0.01	2.10	(1.80 , 2.45)	<0.01
Pneumonia up to age 10 (No)	1,388	8,134	8.2						
Yes	28	116		1.41	(0.93 , 2.15)	0.10	1.28	(0.78 , 2.09)	0.32
Whooping cough to 10 (No)	1,129	6,667	20.1						
Yes	102	518		1.16	(0.93 , 1.45)	0.18	1.13	(0.89 , 1.43)	0.30
Mother's age at delivery (<21)	301	1,614	9.0						
22-25	463	2,611		0.95	(0.81 , 1.11)	0.53	0.97	(0.83 , 1.13)	0.68
26-30	399	2,333		0.92	(0.78 , 1.08)	0.30	0.93	(0.79 , 1.10)	0.41
31+	260	1,608		0.87	(0.72 , 1.04)	0.12	0.88	(0.73 , 1.06)	0.17
Maternal smoking at preg.(No)	845	5,092	8.5						
Smoker	587	3,117		1.13	(1.01 , 1.27)	0.03	1.14	(1.01 , 1.29)	0.03
Parity (No prev. aft 28 wks)	576	3,002	8.6						
1 After 28wks	446	2,820		0.82	(0.72 , 0.94)	0.01	0.83	(0.73 , 0.94)	0.01
2 after28wks	233	1,339		0.91	(0.77 , 1.07)	0.25	0.91	(0.77 , 1.07)	0.25
3+ after 28wks	174	1,038		0.87	(0.73 , 1.05)	0.15	0.87	(0.72 , 1.05)	0.14
Social class of father (I or II)	424	2,451	7.3						
III non-manual	146	812		1.04	(0.85 , 1.27)	0.71	1.06	(0.87 , 1.28)	0.57
III Manual	618	3,788		0.94	(0.83 , 1.08)	0.39	0.94	(0.83 , 1.08)	0.38
IV or V	249	1,278		1.13	(0.95 , 1.34)	0.17	1.12	(0.94 , 1.34)	0.21
Birthweight (up to 3 Kg)	308	1,458	8.5						
<2.5	79	462		0.81	(0.62 , 1.06)	0.12	0.83	(0.64 , 1.09)	0.18
up to 3.5	540	3,287		0.78	(0.67 , 0.91)	<0.01	0.78	(0.66 , 0.91)	<0.01
up to 4	387	2,298		0.80	(0.68 , 0.94)	0.01	0.79	(0.67 , 0.93)	<0.01
>4	117	698		0.79	(0.63 , 1.00)	0.05	0.78	(0.62 , 0.97)	0.03
Breastfed (No)	744	4,398	20.8						
Under 1 month	190	1,164		0.96	(0.81 , 1.15)	0.68	0.97	(0.82 , 1.15)	0.72
Over 1 month	263	1,579		0.98	(0.85 , 1.15)	0.84	0.98	(0.83 , 1.17)	0.86
Mother's Education (None)	591	3,696	23.5						
Vocational, O-level	415	2,303		1.13	(0.98 , 1.29	0.09	1.09	(0.97 , 1.23)	0.16
A Level +	158	893		1.11	(0.91 , 1.34)	0.30	1.10	(0.91 , 1.33)	0.32
Father's Education (None)	480	2,980	24.4						
Vocational, O-level	295	1,878		0.98	(0.83 , 1.14)	0.75	1.00	(0.83 1.20)	0.99
A Level +	298	1,679		1.10	(0.94 , 1.29)	0.22	1.06	(0.92 , 1.22)	0.43
No Male hhh	63	292		1.34	(1.00 , 1.79)	0.05	1.23	(0.87 , 1.75)	0.23

1 Those who reported having asthma or wheezy bronchitis after age 16 based on all available information.

2 Cohort members who did not report any positive history of asthma or wheezy bronchitis.

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Females were at a higher risk for the wheezing illness as compared to males (OR=1.47, CI= 1.32-1.64). The risk of developing asthma in adulthood was about 30% higher in those who had a family history of atopy defined by the presence of hayfever, eczema, or asthma in either parent or any sibling as compared to those with no history. The risk was also higher for those with childhood hayfever and eczema. Those whose mothers were smokers during pregnancy were also at a higher risk of developing asthma or wheezing later in life. High birthweight had a protective effect on adult incidence asthma or wheezing. Many other variable were tested but did not show significant association with wheezing illness. These included childhood pneumonia and whooping cough, breastfeeding, social class of the mother's husband by age 7, parent's education status, the child's cognitive ability (British ability scale at age 10), housing tenure, being in care, and recurrent abdominal pain, and migraine in childhood.

Early adulthood environmental, social and lifestyle measures

Table 11-21 presents the odds ratios (95% CI) for the effect of adulthood social, lifestyle, and environmental factors on adult onset asthma or wheezy bronchitis. Only smoking status and BMI at age 30 were significant predictors on asthma or wheezy bronchitis with the current smokers and those who were obese at higher risk.

Possible modification effect

No interaction effect was observed between a number of childhood perinatal and environmental variables and any of the childhood psychological variables showing no possible modification effect of these variables on the attacks of asthma and wheezy bronchitis.

Confounders adjusted models

After adjusting for sex, family history of atopy, history of hayfever up to age 10, history of eczema up to age 10, mother's age at birth, maternal smoking during pregnancy, and birth weight, there were no significant changes on the effects of childhood psychological factors on adult onset wheezing. The child development behaviour scale items that were significant in the univariate case remained significant (Table 11-22). A higher score in neuroticism, antisocial behaviour, and clumsiness in school at age 10 were still significantly associated with higher risk for asthma or wheezy bronchitis in mid life.

Therefore the observed associations between these variables and wheezing illness are unlikely to be positively confounded by other childhood factors. Self esteem also remained significant with those with higher self esteem by age 10 having lower risk for wheezing illness later in life. Other items of the child development behaviour scale that turned significant after adjusting for the potential confounders included disorganised activity and poor hand-eye coordination.

Table 11-21: The odds ratios (95% CI) for the effect of adulthood social, lifestyle, and environmental factors on adult onset asthma or wheezy bronchitis in the BCS70 (Ref= reference category).

				Odds Ratios (95% CI)					
				Complete Cases			MI[4]		
	AW[1]	AW_F[2]	M[3] (%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Alcohol consumption at age 23			30.5						
None	303	1,582		Ref					
Light	173	1,069		0.84	(0.69 , 1.03)	0.10	0.89	(0.73 , 1.08)	0.23
Medium	437	2,339		0.98	(0.83 , 1.14)	0.76	0.95	(0.81 , 1.10)	0.47
Heavy	202	1,211		0.87	(0.72 , 1.06)	0.16	0.85	(0.70 , 1.02)	0.08
Educational level at age 26			33.4						
No qualification	63	328		Ref					
CSE 2-5/equiv nvq1	188	1,025		0.95	(0.70 , 1.30)	0.77	1.00	(0.73 , 1.36)	1.00
O level/equiv nvq2	420	2,447		0.89	(0.67 , 1.19)	0.45	0.98	(0.77 , 1.26)	0.88
A level and Higher	386	2,162		0.93	(0.70 , 1.24)	0.62	1.00	(0.75 , 1.32)	0.97
Social class at age 30			12.8						
I or II: Proff/Manager	484	2,865		Ref					
III: Skilled Non-manual	420	2,066		1.20	(1.04 , 1.39)	0.01	1.18	(1.02 , 1.38)	0.03
III: Skilled manual	240	1,565		0.91	(0.77 , 1.07)	0.26	0.92	(0.78 , 1.08)	0.30
IV or V: Partly/ Unskilled	234	1,315		1.05	(0.89 , 1.25)	0.55	1.06	(0.88 , 1.27)	0.53
Smoking at age 30			0.0						
Never smoked	685	4,603		Ref					
Occasional/former smokers	412	2,123		1.30	(1.14 , 1.49)	<0.01	1.30	(1.14 , 1.49)	<0.01
Daily smokers	462	2,247		1.38	(1.22 , 1.57)	<0.01	1.38	(1.22 , 1.57)	<0.01
Physical Exercise at age 30			11.1						
No	306	1,661		Ref					
Yes	1,104	6,290		0.95	(0.83 , 1.09)	0.49	0.95	(0.82 , 1.11)	0.52
BMI at age 30			13.5						
Underweight	32	195		1.02	(0.69 , 1.49)	0.93	0.96	(0.65 , 1.40)	0.82
Normal	717	4,445		Ref					
Overweight	436	2,299		1.18	(1.03 , 1.34)	0.01	1.16	(1.03 , 1.32)	0.02
Obesity	175	808		1.34	(1.12 , 1.61)	<0.01	1.34	(1.11 , 1.61)	<0.01

1 Those who reported having asthma or wheezy bronchitis after age 16 based on all available information. All those who provided information in at least one sweep of data collection are included; cohort members reporting a positive history of asthma or wheezy bronchitis up to age 16 have been excluded from analysis.

2 Cohort members who did not report any positive history of asthma or wheezy bronchitis.

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Table 11-22: The adjusted odds ratios (95% CI) for the effect of childhood psychological factors on adult onset asthma or wheezy bronchitis in the BCS70.

	Adjusted OR (95% CI)[1]					
	Complete Cases			MI[2]		
	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological factors at age 5*						
Child Behaviour at Home (Rutter A)						
Total Score	1.00	(0.98 , 1.02)	0.88	1.00	(0.99 , 1.02)	0.72
Hyperactive	0.98	(0.94 , 1.04)	0.55	0.99	(0.94 , 1.04)	0.63
Emotional problems	1.00	(0.96 , 1.05)	0.89	1.01	(0.97 , 1.05)	0.54
Conduct Problem	1.00	(0.97 , 1.04)	0.90	1.00	(0.97 , 1.04)	0.80
Psychological factors at age 10						
Child Behaviour at Home (Rutter A)						
Total Score	1.00	(0.99 , 1.01)	0.94	1.00	(0.99 , 1.01)	0.75
Hyperactive	1.00	(1.00 , 1.01)	0.34	1.00	(1.00 , 1.01)	0.24
Emotional problems	1.00	(0.99 , 1.00)	0.20	1.00	(0.99 , 1.00)	0.34
Conduct Problem	1.00	(0.99 , 1.00)	0.61	1.00	(0.99 , 1.01)	0.80
At School (Conners' Mother self completion)						
Impulsive	1.00	(1.00 , 1.01)	0.90	1.00	(1.00 , 1.01)	0.68
Hyperactive/Inattention	1.00	(1.00 , 1.01)	0.31	1.00	(1.00 , 1.01)	0.27
Clumsy	1.00	(0.99 , 1.00)	0.63	1.00	(0.99 , 1.00)	0.74
Poor Motor Coordination	1.00	(0.99 , 1.01)	0.60	1.00	(0.99 , 1.01)	0.94
At School (Child Development Behaviour)						
Antisocial Behaviour	1.02	(1.01 , 1.03)	<0.01	1.02	(1.01 , 1.03)	<0.01
Disorganised activity	1.02	(1.01 , 1.03)	<0.01	1.02	(1.01 , 1.03)	<0.01
Neurotism/Anciety	1.01	(1.00 , 1.03)	0.01	1.02	(1.00 , 1.03)	0.01
Clumsiness	1.01	(1.00 , 1.03)	0.05	1.01	(1.00 , 1.03)	0.02
Poor hand-Eye Coordination	1.00	(0.99 , 1.01)	0.46	0.99	(0.98 , 1.00)	0.02
Hyper/Kinesis	1.01	(1.00 , 1.03)	0.03	1.01	(1.00 , 1.03)	0.01
Introversion/Extroversion	1.00	(0.99 , 1.01)	0.51	0.99	(0.99 , 1.00)	0.15
Behavioural Trauma	1.02	(0.98 , 1.05)	0.33	1.02	(0.99 , 1.05)	0.26
Dressing	1.00	(0.99 , 1.00)	0.36	0.99	(0.99 , 1.00)	0.10
At School (Self Completion)						
Locus of Control[3]	0.99	(0.97 , 1.01)	0.40	0.99	(0.97 , 1.01)	0.19
Self Esteem[4]	0.98	(0.96 , 1.00)	0.02	0.98	(0.96 , 0.99)	0.01
Psychological factors at age 16						
Child Behaviour at Home (Rutter A)						
Total Score	1.02	(1.00 , 1.05)	0.07	1.02	(1.00 , 1.04)	0.10
Hyperactive	1.11	(1.02 , 1.21)	0.01	1.08	(1.00 , 1.17)	0.06
Emotional problems	1.05	(0.99 , 1.11)	0.09	1.04	(0.98 , 1.11)	0.19
Conduct Problem	1.01	(0.96 , 1.06)	0.68	1.02	(0.98 , 1.05)	0.41

Adjusted for sex, family histoty of atopy, history of childhood eczema up to age 10, history of hayfever up to age 10, mother's age at birth, maternal smoking during pregnancy , and birthweight.

2 Analysis based on combined results of 10 multiple-imputed datasets

3 Higher scores indicate greater internalization; 4 Higher score indicate higher self-esteem.

* For the rest of the psychological measures, higher score indicate worse conditions of hehavioural maladjustment.

11.2.2. Wheeze in the past 12 months at 30 years

Effect of childhood psychological factors

Only the antisocial behaviour, disorganised activity, neuroticism and clumsiness subscales of child development behaviour, and self esteem at age 10 significantly predicted the 12-months period prevalence of asthma or wheezy bronchitis at age 30 years (Table 11-23) in the univariable model.

Effect of perinatal, and childhood biological, social and environmental factors

The association between the perinatal and childhood factors and asthma or wheezing in the past 12 months followed the same pattern as the one for adult- onset asthma (table not shown). Sex, family history of atopy, history of childhood eczema up to age 10, history of hayfever up to age 10, mother's age at birth, maternal smoking during pregnancy, and birthweight were all significantly associated with the 12-months period prevalence of asthma or wheezy bronchitis at age of 30 years. All other variable presented in Table 11-20 did not show any significant association with 12-months prevalence of asthma at age 30 years. Other non-significant variables included mother’s age at birth, measles infection by age 7, being in care, birthweight for gestational age, breastfeeding, whooping cough, and recurrent abdominal pain and migraine. All the significant variables were adjusted for in the mutually adjusted model for childhood psychological factors.

Adjusting for possible confounders

After adjustment for sex, family history of atopy, history of childhood eczema up to age 10, history of hayfever up to age 10, mother's age at birth, maternal smoking during pregnancy, and birthweight; the effects slightly attenuated but remained significant (table not shown). This shows that observed associations between asthma symptoms in the past 12 months and childhood psychological factors were unlikely to be positively confounded by these factors. Those with higher scores on antisocial behaviour, disorganised activity, neuroticism and clumsiness, implying more behavioural difficulties, had a higher risk for asthma in the past 12 months, while those with higher self esteem by age 10 had a reduced risk.

Table 11-23: The odds ratios (95% CI) for the effect of childhood psychological factors on adult onset (age 17-30) asthma or wheezy bronchitis in the BCS70.

	AW[1]	AW_F[2]	M[3]	Odds Ratios (95% CI)					
				Complete Cases			MI[4]		
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological factors at age 5*									
Child Behaviour at Home (Rutter A)									
Total Score	758	8,361	18.7	1.01	(0.99 , 1.03)	0.31	1.01	(0.99 , 1.03)	0.21
Hyperactive	755	8,353	18.8	1.00	(0.95 , 1.04)	0.86	1.00	(0.95 , 1.04)	0.91
Emotional problems	757	8,349	18.8	1.03	(0.99 , 1.08)	0.10	1.04	(1.00 , 1.08)	0.05
Conduct Problem	756	8,352	18.8	1.00	(0.97 , 1.04)	0.79	1.00	(0.97 , 1.03)	0.84
Psychological factors at age 10									
Child Behaviour at Home (Rutter A)									
Total Score	809	8,837	14.0	1.00	(1.00 , 1.01)	0.32	1.00	(1.00 , 1.01)	0.43
Hyperactive	808	8,824	14.1	1.00	(1.00 , 1.01)	0.22	1.00	(1.00 , 1.01)	0.26
Emotional problems	808	8,828	14.0	1.00	(1.00 , 1.00)	0.88	1.00	(1.00 , 1.00)	0.92
Conduct Problem	807	8,824	14.1	1.00	(0.99 , 1.01)	0.81	1.00	(0.99 , 1.01)	0.77
At Home (Conners' Mother self completion)									
Impulsive	807	8,820	14.1	1.00	(1.00 , 1.01)	0.32	1.00	(1.00 , 1.01)	0.42
Hyperactive/Inattention	807	8,822	14.1	1.00	(1.00 , 1.01)	0.26	1.00	(1.00 , 1.01)	0.22
Clumsy	805	8,803	14.3	1.00	(1.00 , 1.01)	0.93	1.00	(1.00 , 1.01)	0.74
Poor Motor Coordination	805	8,803	14.3	1.00	(0.99 , 1.01)	0.67	1.00	(0.99 , 1.01)	0.75
At School (Child Development Behaviour)									
Antisocial Behaviour	728	8,241	20.0	1.02	(1.01 , 1.03)	<0.01	1.02	(1.01 , 1.03)	<0.01
Disorganised activity	728	8,241	20.0	1.01	(1.01 , 1.02)	<0.01	1.01	(1.00 , 1.02)	0.01
Neurotism/Anciety	728	8,241	20.0	1.02	(1.01 , 1.03)	<0.01	1.02	(1.01 , 1.03)	<0.01
Clumsiness	728	8,241	20.0	1.02	(1.00 , 1.03)	0.01	1.01	(1.00 , 1.03)	0.03
Poor hand-Eye Coordination	728	8,240	20.0	0.99	(0.98 , 1.00)	0.07	0.99	(0.98 , 1.00)	0.08
Hyper/Kinesis	728	8,240	20.0	1.01	(1.00 , 1.02)	0.04	1.01	(1.00 , 1.02)	0.07
Introversion/Extroversion	728	8,239	20.0	0.99	(0.99 , 1.00)	0.06	0.99	(0.99 , 1.00)	0.16
Behavioural Trauma	728	8,239	20.0	1.02	(0.99 , 1.04)	0.30	1.01	(0.98 , 1.04)	0.39
Dressing	706	7,962	22.7	1.00	(0.99 , 1.00)	0.14	0.99	(0.99 , 1.00)	0.12
At School (Self Completion)									
Locus of Control[5]	729	8,189	20.4	0.99	(0.97 , 1.01)	0.25	0.99	(0.97 , 1.01)	0.27
Self Esteem[6]	736	8,217	20.1	0.98	(0.96 , 0.99)	0.01	0.98	(0.96 , 0.99)	<0.01
Psychological factors at age 16									
Child Behaviour at Home (Rutter A)									
Total Score	558	6,381	38.1	1.02	(1.00 , 1.04)	0.06	1.02	(1.00 , 1.04)	0.04
Hyperactive	550	6,278	39.0	1.08	(1.00 , 1.16)	0.07	1.08	(1.00 , 1.16)	0.06
Emotional problems	553	6,314	38.7	1.06	(1.01 , 1.11)	0.03	1.06	(1.00 , 1.12)	0.05
Conduct Problem	551	6,319	38.7	1.01	(0.96 , 1.05)	0.81	1.02	(0.98 , 1.05)	0.36

1 Those who reported having asthma/wheezy bonchitis in the past 12 months at age 30 years;

2 No reported cases of asthma/wheezy bronchitiss in the past 12 months at age 30 years;

3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

5 Higher scores indicate greater internalization; 6 Higher score indicate higher self-esteem

* For other psychological measures, higher score indicate worse conditions of behavioural maladjustment.

Early adulthood psychological factors

All the adulthood psychological measures considered in the bivariate model were highly associated with the adult-onset asthma (Table 11-24), with those who showed higher degree of psychological distress having a higher risk of the disease.

Table 11-24: The odds ratios (95% CI) for the effect of adulthood psychological factors on 12-months prevalence of asthma or wheezy bronchitis at age 30 in the BCS70.

				Odds Ratios(95% CI)					
				Complete Cases			MI[4]		
	AW[1]	AW_F[2]	M[3]						
			(%)	OR	(95% CI)	Sig	OR	(95% CI)	Sig
Psychological distress at 26 (Malaise Invent.)			32.3						
Normal	494	6,109							
Depressed	124	863		1.78	(1.44 , 2.19)	<0.01	1.72	(1.38 , 2.14)	0.01
Psychological distress at 30 (Malaise Invent.)			0.9						
Normal	736	8,966							
Depressed	189	1,220		1.89	(1.59 , 2.24)	<0.01	1.88	(1.59 , 2.23)	<0.01
GHQ12 at 30 years	925	10,189	0.9	1.04	(1.03 , 1.06)	<0.01	1.04	(1.03 , 1.06)	<0.01

1 Those who reported having asthma/wheezy bronchitis in the past 12 months at age 30 years;
2 No reported cases of asthma/wheezy bronchitis in the past 12 months at age 30 years;
3 Percentage of missing data; 4 Analysis based on combined results of 10 multiple-imputed datasets

Early adulthood environmental, social and lifestyle measures

All the adulthood social, lifestyle, and environmental variables shown in Table 11-21 for the adult onset asthma were also tested for the 12-months prevalence of asthma at age 30 years. Only obesity at age 30 significantly predicted asthma or wheezy bronchitis in the past 12 months at age 30 years (table not presented).

Chapter 12

Adult-onset Asthma: Discussion and Conclusions

Despite considerable knowledge with regard to the pathologic basis of asthma, the ongoing increases in asthma prevalence cannot yet be fully explained by the well established host and environmental factors. The coexistence of asthma and psychological problems especially depression has now become the focus of considerable research interest. Previous studies have explored the possible roles that adulthood psychological factors may play in explaining asthma onset. However, less is known on the possible contribution from the childhood psychological factors. In this section, we examined whether there is a temporal relationship between psychological factors measured between age 5 and age 16 and the development of asthma in mid life, and to establish whether such associations can be explained by pre-existing physical, social, and environmental confounding and mediating factors.

Findings and similar research

Using two nationally representative prospective data that have followed subjects from childhood to middle age, this study found that those with history of asthma or wheezy bronchitis after the age of 16 years, and those who reported asthma or wheezy bronchitis in the last 12 months at age 42 years in the NCDS, had significantly higher scores on most of the behavioural and emotional scales, implying that behavioural maladjustment or emotional problems were significantly associated with an increased risk of asthma or wheeze attacks. The findings from the BCS70, however, gave a slightly different picture, with only a few behavioural problems at school significantly increasing the risk of adult onset asthma. In this cohort, those with higher scores on antisocial behaviour, disorganised activity, neuroticism and clumsiness, implying more behavioural difficulties at school, had a higher risk for both adult onset asthma and the 12-months prevalence of asthma at age 30 years; those with higher self esteem by age 10 had a reduced risk.

On the modified Rutter home behaviour scale in the NCDS, which reflects the parental view of the child's behaviour, cohort members who reported asthma or wheezy bronchitis between age 17 and 42 years had significantly higher mean scores than those with no reported cases at all the three childhood sweeps (at ages 7, 11 and 16 years), indicating

an adverse result. This difference persisted after adjusting for sex, social class of the father, maternal smoking during pregnancy, parity of the mother, and history of childhood pneumonia, eczema and hayfever. Among the specific sub-scales of the Rutter behavioural scale, conduct problems were consistently associated with adult-onset (ages 17-42) asthma or wheezy bronchitis at all the childhood sweeps. Hyperactive problems were only associated with adult onset asthma at age 11 and 16 years, while emotional problem was not associated with adult-onset asthma at any of the childhood sweeps.

Social adjustment at school as measured by the BSAG scale and Rutter teacher behaviour scale also showed similar patterns of association. A high score in externalising behaviours, here referred to as overreaction or conduct problems, indicating poor adjustment in school, was significantly associated with adult-onset asthma at both age 7 and age 11 years even after adjusting for potential childhood confounders, while the internalising problems, here referred to as the undereaction or emotional problems, did not show any association, except for the Rutter teacher scale at age 16 years.

Based on a theoretical model of how psychological disorder can affect physical health (Cohen and Rodriguez, 1995) and the cumulative model of the life course approach (Kuh and Ben-Shlomo, 2004), we proposed that childhood psychological problems influence adult onset asthma through its effect on obesity and through its cumulative effects over the life course to mid life psychological distress. Such hypothesis was guided by two principles: 1) obesity is one of the host factors thought to cause the development of asthma and has been found to be a significant risk factor for asthma in many studies (Schachter *et al.*, 2001; Guerra *et al.*, 2002; Weiss and Shore, 2004; Chinn *et al.*, 2006); and 2) a growing number of studies have also established that psychological factors including depression, emotional problems, conduct problems, and hyperactivity in childhood and adolescence are prospectively associated with development and persistence of obesity in young adulthood (Goodman and Whitaker, 2002; Lumeng *et al.*, 2003; Mamun *et al.*, 2009; Duarte *et al.*, 2010).

Having adjusted for the childhood confounders including sex, maternal smoking, parity, pneumonia, social class of the father at seven years, history of hay fever at seven or 11 years, history of eczema at seven or 11 years; and adulthood factors including smoking status, educational achievement, social class and fruit consumption, there was still a direct effect of conduct and hyperactive problems on adult-onset asthma at both age 11

and age 16. Findings of this nature suggest that childhood behavioural problems especially conduct problems in adolescence are independent predictors of young adults onset asthma and wheezy bronchitis. These findings also provide some evidence for the impact of childhood behavioural problems on the later development of asthma through mid life obesity and psychological distress.

Although there was no direct effect of emotional problems in predicting adult onset asthma or wheezy bronchitis having adjusted for other well known risk factors, they contributed to an elevated risk of wheezing illness indirectly through their cumulative effect through young adulthood psychological distress. Apart from the age 7 emotional problems, there were significant effects of emotional problems at later ages through the mid-life psychological distress pathway. However, no mediation effect was observed through obesity.

The cumulative effect through adulthood psychological factors in which childhood psychological problems continue into adulthood psychological distress and their effect over the life course increase the risk of asthma or wheeze can be explained by a plausible direct biological link involving the involvement of interaction pathways between the nervous and the immune system in the airways. It has been suggested that stress may modulate the immune system to increase the magnitude of the airway inflammatory response to allergens and irritants (Wright *et al.*, 1998; Nagata *et al.*, 1999; Lehrer *et al.*, 2002; Wright, 2005; Wright *et al.*, 2005; Vig *et al.*, 2006; Veres *et al.*, 2009), and this could be one of the pathway through which childhood psychological factors might affect asthma or wheezy bronchitis in mid life.

The second pathway through which the conduct problems were associated with the asthma or wheeze later in life was through adulthood obesity. The proposed mechanisms by which childhood behavioural problems may influence weight include a neurobiological link (Wurtman, 1993), physiological changes (Ludwig, 2002) and unhealthy environment especially in females (Anderson *et al.*, 2006). Through the neurobiological link, it is theorized that low brain serotonin levels in depressed individuals may cause them to have perturbations in mood which result in an excessive intake of carbohydrate-rich foods and resistance to engaging in physical activity (Wurtman, 1993). Depressed children have more difficulty taking good care of

themselves because of symptoms and consequences of depression, such as difficulty adhering to fitness regiments, overeating, and having negative thoughts.

The findings of this study confirm a few prior studies of an association between childhood psychological problems, majorly, childhood adversities, and adult onset asthma (Scott *et al.,* 2008), and extend them through the use of prospectively collected data and by testing both the direct and indirect effects or whether the effects accumulate with time or follows other behavioural pathways. The findings in this study also support a number of studies that have found a link between adulthood psychological factors, including stressor exposure such as negative life event and daily stress; psychological distress (internalizing, anxious, or depressive symptom, stress-related personality, family dysfunction, immature coping skills, etc.); poor social support such as social isolation, impoverished and social relationships, and asthma (Chida *et al.*, 2008).

The findings are also in line with other studies that have found that adolescents who exhibit externalising (but not internalising) behaviour experience multiple social and health impairments that adversely affect them throughout adult life (Colman *et al.,* 2009). Other studies have also established that children exposed to adverse psychosocial experiences have enduring emotional, immune, and metabolic abnormalities that contribute to explaining their elevated risk for age-related disease (Danese *et al.*, 2009).

Strengths and limitations

The major strength of this study draws from its use of two general population based cohorts of individuals followed from birth to adult life, thus benefiting from their large sample size and national coverage. In addition, both the datasets provide truly prospective studies of asthma incidence throughout childhood into early adult life. This eliminates the recall bias in most studies where parents are interviewed at one point in time and asked to recall past episodes of wheezing in their children. This study also benefits from the availability of a wide range of factors that might confound or mediate the relationship between psychological factors and the onset of asthma or wheezy bronchitis. In addition, the results drawn from the analysis of the two cohorts provides firmer evidence since such association are unlikely to be by chance.

This study, however, presents a number of limitations. The first is the reliance on self reported asthma or wheezy bronchitis which may be different from the clinical diagnostic of asthma in an individual. As a result, the prevalence of current asthma symptoms is not equivalent to the prevalence of clinical asthma. A clinical diagnosis of asthma is made on the basis of combined information from history, physical examination, and physiological tests, often over a period of time. Since there is no single test or clinical feature which defines the presence or absence of asthma, it would be impractical to have such an outcome particularly from epidemiological studies of large populations. However, previous studies have reported that asthma based on self report of physician's diagnosis have high agreement with clinical diagnosis (Torén *et al.*, 1993; Jenkins *et al.*, 1996). It is also reassuring that at the age of 42 years in the NCDS and age 30 in the BCS70, the cohort members were asked about the age at onset of their asthma or wheezy bronchitis; the pattern of age at onset reported retrospectively in this way corresponded closely to the pattern derived from the linked data.

Secondly, since this is a multi-disciplinary socio-medical study, there are a number of other well known risk factors such environmental exposures, occupational sensitizers, and viral infections specific to asthma that have not been extensively documented. Among the environmental exposures, only parental smoking (mother in pregnancy, mother and father postnatally) and air pollution exposures were documented. Factors such as the parents' smoking habits were not assessed at either age 7 or 11, nor is there information on parental atopic disorders in the NCDS.

Thirdly, the identification of asthma and wheezing differed at different ages of interview as to phrasing of the questions and to the method of grading frequency. This is unlikely to have influenced the results to any great extent because both diagnosed asthma and wheezing illness were assessed at each interview, as was their occurrence over the past 12 months, which is the conventional period for describing current asthma. Fourthly, measurements of total and specific IgE were made only at age 44 to 45 years. These measures were taken after the disease had been reported at age 42 or earlier and therefore may not adequately reflect the allergic status earlier in life.

There is also the problem of sample attrition especially the loss to follow up of those from disadvantaged groups. The incomplete response rates at each sweep, though individually acceptable, tend to accumulate when the data are linked to reduce the overall

response even further. Although substantial for the asthma analysis, based on the small number of the subjects with full information at all the sweeps, this seems to have had only a marginal effect on estimates of disease incidence (Table 11-1). Also those with and without full information on asthma and wheezing differed only slightly with respect to early indicators of atopy, that is, hayfever and eczema at ages 7 and 11 years. Further, comparisons on several other variables of the fully linked data and all available information did not differ substantially, showing that sample attrition may not be a serious problem in this study. Further bias could be a result of missing data in terms of item non-response in the covariates. Nevertheless, the use of full information maximum likelihood and multiple imputation to deal with missing data in the covariates solved the problem of such bias. Though there were slight differences in the estimates for the complete and multiple imputed data results, overall, for most of the variables, the conclusion remained the same.

In spite of the above limitations, this study makes an important contribution in our knowledge of the important roles that childhood emotional and behavioural problems play in adult onset asthma and the pathways through which they may influence the disease.

Conclusions

In conclusion, this study provides evidence that early life psychological factors may impact on the later development of asthma or wheezy bronchitis in mid life either directly (especially conduct problems), cumulatively through their effect on the mid life psychological distress, or through other mid life pathways such as negative health behaviours. The results demonstrate a positive association between emotional and behavioural problems during childhood and attacks of asthma or wheezy bronchitis in mid life even after adjusting for history of atopy in childhood and other potential confounders. The association is however, partly mediated through adulthood psychological distress which may result to weakened immune system, and through risky health behaviours, particularly obesity.

This study therefore shows that behavioural difficulty is clearly an important risk factor for adult wheeze along with other host and environmental factors, and any intervention programs aimed at decreasing asthma morbidity in adulthood should involve a

multipronged approach including conventional physical and pharmacological therapies as well as targeting the prevention, recognition, and treatment efforts of emotional and behavioural difficulties in childhood and adolescence.

Future data availability and possibly clinical diagnosis of asthma to objectively evaluate the clinical outcome will undoubtedly prove helpful in understanding further these relationships. Additional prospective research is also needed to extend the finding to other atopic diseases other than asthma and to control for all the putative behavioural and environmental covariates which were not extensively measured in this study.

SECTION V

FINAL CONCLUSIONS AND IMPLICATIONS

Chapter 13

Final Conclusions and Implications

13.1. Summary of the Study

This thesis presented results from studies of the role of early life psychological factors in the development of three conditions- cancer, diabetes, and asthma- using data from two British birth cohort studies following large numbers of individuals over long periods of time. This chapter summarises the findings across the disease subtypes highlighting commonalities and divergences.

The focus of the study was to explore potential links between early life personality and behaviour and the development of subsequent cancer, diabetes, and asthma in mid life. To be sure that the diseases are occurring some time after personality and behaviour are measured, all those subjects who had the disease at the same time or before the early life psychological measures were excluded from the analyses.

To test the hypothesis that there is a temporal relationship between psychological factors (personality, behaviour, and motivation) measured during the life course and the development of chronic diseases (cancer, diabetes, and asthma) in middle age, discrete-time survival models, estimated using logistic regression were fitted. Initial models were only adjusted for the age at diagnosis. Further adjustments were made in order to test whether such associations can be explained by pre-existing physical, social, and environmental confounding factors.

Another objective of the study was to use an existing theoretical model of the link between psychological factors and disease (Cohen and Rodriguez, 1995) to test whether associations are mediated by biological, behavioural, social, and/or cognitive pathways. Specific models for each disease group, based on this theoretical framework, were proposed and tested using structural equation models. To test whether physical, social, and environmental factors have a moderating (i.e. intensifying or diminishing) effect on the temporal association between psychological factors and chronic disease, interaction terms between possible moderating variables and the psychological factors were tested.

Table 13-1: An overview of the main results for the association between childhood psychological factors and the three disease groups in the NCDS.

	Was there a significant association ($p<0.05$) between the childhood psychological factors and the disease before and after adjustment for potential confounders?											
	Cancer				**Diabetes**				**Asthma**			
	All sites		**Cervical**		**Self Reported**		**$HbA_{1c}\geq 6$**		**Adult onset**		**12-months preval.**	
	Un.	**Adj.**	**Un.**	**Adj.**	**Un.**	**Adj.**	**Un.**	**Adj.**	**Un.**	**Adj.**	**Un.**	**Adj.**
At Age 7*												
Child Behaviour at Home (Rutter A)												
Total Score	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes
Hyperactive	No	No	No	No	No	No	No	No	No	No	Yes	Yes
Emotional problems	No	No	No	No	No	No	No	No	No	No	Yes	No
Conduct Problem	No	No	No	No	No	No	Yes	No	Yes	Yes	Yes	Yes
Child Behaviour at School (BSAG)												
Emotional problems	No	No	No	No	Yes	Yes	Yes	Yes	No	No	No	No
Conduct problems	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Miscellaneous Nervous Syndrome	No	No	No	No	No	No	Yes	Yes	No	No	Yes	Yes
At Age 11												
Child Behaviour at Home (Rutter A)												
Total Score	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes
Hyperactive	No	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes
Emotional problems	No	No	No	No	No	No	No	No	No	No	Yes	No
Conduct Problem	No	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Child Behaviour at School (BSAG)												
Emotional problems	No	No	No	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Conduct problems	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Miscellaneous Nervous Syndrome	No	No	No	No	Yes	Yes	No	No	No	No	No	No
At Age 16												
Child Behaviour at Home (Rutter A)												
Total Score	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Yes
Hyperactive	Yes	No	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes
Emotional problems	Yes	Yes	Yes	Yes	No	No	No	No	No	No	Yes	No
Conduct Problem	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	Yes	Yes
Child Behaviour at School (Rutter B) total score												
Well adjusted												
With behavioural disorder	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Subscales for Rutter B												
Neurotic	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Antisocial	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes

Un.= Age-adjusted effects; Adj.= Age and confounder adjusted effects

Summary of the main results

Table 13-1 summarises the results of the association between childhood psychological factors and the three disease groups before and after adjusting for the potential confounders. Findings varied across the disease groups but there were also some commonalities in findings. Thus, whether the results support the hypotheses of this study is dependent on the disease outcome and the type of psychological measure.

There were significant relationships between some but not all the psychological factors and overall cancer. None of the age seven and age 11 psychological factors was significantly associated with overall cancer risk except the total Rutter mother's score and teacher assessed conduct problems at school (BSAG) by age 11 years. All the 16 year old psychological factors were significantly associated with cancer risk in the unadjusted model. However, the hyperactive behaviour as reported by the mother and the antisocial behaviour reported by the teacher lost their significance upon the introduction of smoking at age 16 years in the model. Unlike the results for all cancer sites analysed together, the link between conduct problems and cervical cancer was evident as early as seven years. The observed association between conduct problems and cervical cancer was independent of the social class of the father, birthweight, smoking status of the mother during pregnancy, and cognitive ability of the child. However, the association between conduct problems at age 16 years and cervical cancer lost its significance when cigarette smoking at age 16 years was introduced in the model.

By analysing other cancer sites excluding cervical cancer, no association was observed between any of the psychological factors and cancer. One possible explanation is that the association between childhood psychological factors and cancer may be specific to certain cancer sites, especially those that are related to viruses like those involved in cervical cancer. This is in line with previous research that have suggested that if psychological factors can affect cancer development through a biological pathway, through an impaired immune system which predisposes to malignant growth, then such association can especially be observed in the types of cancer mainly associated with a DNA tumour virus, retrovirus insertion near a cellular oncogene, and other viruses such as Epstein-Barr virus (Reiche *et al.*, 2004). Another explanation could be that the non-significance association could be a result of the low statistical power since cervical

cancer comprised almost a third of cancer cases and excluding them in the analysis would substantially reduce the number of cancer cases to be analysed.

When the mediation model (Figures 1-1, 4-1 and 5-3) was tested, no direct association was observed between childhood psychological factors and cancer. However, there were significant indirect association through mid life psychological distress and health behaviours, particularly cigarette smoking. Thus, the effect of childhood psychological factors on the risk of cancer was completely mediated by the two specific indirect effects.

As such we found little evidence for the hypothesis that childhood psychological problems are directly associated with cancer risk, but instead an indirect link through unhealthy behaviours and the accumulation of psychological distress risk to mid life. Thus, based on the existing theoretical model of the link between psychological factors and disease (Figure 1-1), the associations between childhood psychological factors, majorly conduct problems, and cancer are mainly mediated by behavioural pathways such as poor health practices, and biological pathways through the accumulation of psychological distress to mid-life.

The findings for diabetes gave a different picture with the significant associations before and after adjustment for confounders confined to the teacher reported (but not mother assessed) behavioural problems at age 7 and 11 years. In addition, the neurotic and antisocial behaviours reported by the teacher at age 16 were also significantly associated with the prevalence with $HbA_{1c} \geq 6$. Such associations persisted even after introducing mid life psychological factors- education attainment, social class, and obesity along the pathway as possible mediators in the SEM model. Such findings reveal that severe behavioural maladjustment in school may predict the risk of Type 2 diabetes and glucose metabolism in mid life independent of the effect of established risk factors such as obesity. Thus the hypothesis that there is a temporal relationship between psychological factors and diabetes risk in mid life seems to be supported only by the teacher assessed conduct and emotional problems by age 7 and 11 years (through BSAG). Such association was also found to be independent of pre-existing physical, social, and environmental confounding factors such as sex, family history of diabetes, social class of the father, and maternal smoking. Further, the existing theoretical model of the link between psychological factors and disease (Figure 1-1) was only supported by the teacher assessed conduct and emotional problems. For these variables, the pathways

identified were through mid life psychological distress, which would be a predominantly a biological pathway, and through obesity and social class in mid life. However, such findings need to be confirmed in other large prospective studies since we failed to find such association with the parents' reported behavioural problems.

The results for asthma followed a different pattern from those of cancer and diabetes. The hypothesis of a temporal relationship between early life psychological factors and both adult onset asthma and 12-months period prevalence of asthma was supported by most of the psychological measures. In fact, all the conduct problem measures at all ages were significantly associated with asthma. These associations persisted even after adjustment for the effect of sex, maternal smoking, parity, pneumonia at age 7, social class of the father at 7 years, history of hay fever at seven or 11 years, history of eczema at seven or 11 years, and smoking at age 16 for the 16 year old measures. Significant direct effect for the conduct problems at ages 11 and 16 were also observed in the mediation model. These findings suggest that conduct problems may predict asthma onset independently of other known risk factors such as obesity, smoking or atopy. Thus, the effect of childhood psychological factors in the development of chronic disease was found to be strongest on asthma.

The adjusted population-attributable fraction for each of the childhood psychological factor that had a significant direct effect on both Type 2 diabetes and asthma were quite modest ranging from 3% to 24% (Table B17). For example, for ages 17 to 42 years in the NCDS, proportion of incident asthma or wheezy bronchitis that could be attributed to the mother reported conduct problems at age 11 was estimated to be 5% (95% CI, 3%-8%) increasing to 11% (95% CI, 7% -15%) for the conduct problems at age 16 years. These figures provide a strong argument for the possible role of some of the childhood psychological factors in the development of Type 2 diabetes and asthma.

Developmental trajectories of emotional and behavioural problems

Results in all the three disease groups have shown that there is some continuity of childhood psychological factors to adulthood psychological distress, which in turn increases the risk of chronic disease. Childhood and adolescence are critical periods for early identification of psychiatric symptoms and prevention of many mental disorders, including disruptive behaviours, mood, and anxiety disorders. Substantial evidence is

accumulating from longitudinal birth cohort studies and nationally representative surveys to suggest that there are developmental trajectories of psychiatric problems, many of which onset at young ages.

Many longitudinal studies have established that childhood psychological health is an important independent distal factor in adulthood psychological health irrespective of the sex (Pine *et al.*, 1998; Kim-Cohen *et al.*, 2003; Roza *et al.*, 2003; Clark *et al.*, 2007; Karevold *et al.*, 2009). These studies have shown that childhood psychological ill health persists for midlife psychological health. They have also shown that affective and anxiety disorders in early adulthood are associated with internalizing and externalizing disorders in childhood. All these studies concur that the identification of trajectories of childhood psychological factors, especially measures of externalising behaviour, is important in predicting later psychological health and other life outcomes.

Comparison with studies of other conditions

Although there is little previous research on the roles of childhood psychological factors on cancer, diabetes, and asthma, the findings of this study are in line with previous published studies on the relation between early-life psychological factors and other physical illnesses in mid life. Pang and his colleagues (2010) recently carried out a study using the NCDS to determine whether childhood behaviour is associated with the likelihood of chronic widespread pain (CWP) in adulthood, and if any such relationship is mediated through adult psychological distress. Their findings showed that teacher-assessed maladjusted behaviour was associated with increased long-term CWP and that such association was not explained by social class, nor mediated through childhood symptom reporting or adult psychological distress. Another recent study (Temcheff *et al.*, 2010) also found out that childhood aggression was directly and positively associated with medical service usage, as well as medical visits due to lifestyle-related illnesses and injuries, with indirect paths through educational attainment also present. Colman and colleagues (2009) using the 1946 British birth cohort data concluded that adolescents who exhibit externalising behaviour experience multiple social and health impairments that adversely affect them, their families, and society throughout adult life.

Studies have also suggested that childhood problem behaviours may predict injury risk over the life course from childhood to midlife, with externalizing behaviours increasing

and internalizing behaviours decreasing this risk (Jokela *et al.*, 2009b). In another study using the NCDS, Jokela and his colleagues (2009a) found out that childhood problem behaviours are associated with increased long-term mortality risk beyond childhood and adolescence. Thus the effect of childhood psychological factors on physical health is now an area of active research and investigation continue for many other conditions.

Simultaneous analyses of several outcomes

Since psychological factors may be broad spectrum risk factors that increase risks of diverse chronic conditions in later life, prospective studies of childhood psychological factors may be most productive if multiple disease outcomes are assessed in the same study. This study assessed the effect in three different disease groups and found a consistent pathway through which psychological factors might affect physical health.

The value of the research to public health and patient care

The chronic diseases considered in this study, namely, cancer, diabetes, and asthma, are known to be of high impact to both patients and health services. The findings from this study suggest that the childhood psychological factors contribute to adult physical disease either independently, cumulatively or through other behavioural and environmental pathways. Such finding has important implications for the prevention of chronic disease and could provide a means of addressing inequalities in health.

Policy implications

This study underscores the important role of childhood behavioural problems in influencing long-term health. As evidenced by the results of this study and the findings from previous studies, adulthood psychological problems might develop in childhood and persist in adulthood and have a lifelong impact on chronic disease. They may also onset in adulthood for which symptom may have manifested early. Emotional and behavioural disorders in childhood not only affect the individual's physical well being later in life but also incur high psychosocial and economic costs for the young people who experience them, for their families, and for the society in which they live, study, and will work (O'connell *et al.*, 2009). Consequently, effective interventions during early life stages have the potential to support the positive neurobiological, cognitive, and psychosocial development that is needed for successful transition from youth to

adulthood (Warner and Bott, 2010). The type of intervention that might be needed may also be guided by other mediation pathways such as smoking and obesity that have been identified in this study. Thus policy might also be aimed at specific pathways rather than directly at childhood behavioural problems.

Other forms of intervention might be aimed at the factors that might increase the risk of childhood behavioural problems. These include among others the mental and physical health of the parents, family functioning, reward strategies and punishment regimes, family relationships, social life, and stigma. Depressed mothers are more critical, disapproving, and aversive in their interactions with other family members than non-depressed mothers and their children are more likely to develop behavioural problems (Meltzer *et al.*, 2000). The quality of parenting that a child receives including harsh parental discipline (Thompson *et al.*, 2003), parental time spent with the child and parental supervision of the child (Meltzer *et al.*, 2000), have all been found to be influential in the development of childhood behavioural problems. Children with high levels of callous-unemotional traits (i.e. lack of empathy, remorselessness and shallow affects) have also been found to show numerous behavioural, emotional, cognitive, and personality problems (Enebrink *et al.*, 2005; Frick, 2009). Thus, the modification of parental attitudes and improvement in the quality of parenting, which might play a part in the development of behavioural problems in children, is vital.

13.2. Methodological Considerations

Adopting a life course approach presents major challenges based on its complex design and other analytical challenges which are discussed in this section.

Can we claim causality?

One major objective of this study was to test whether the association between childhood psychological factors and mid-life chronic disease is mediated by other biological and behavioural pathways. This was accomplished by testing an existing theoretical model using SEMs. Much of the controversy surrounding SEM is related to the degree of certainty with which causal statements can be drawn from these procedures. Just by its definition, a mediator variable refers to a variable that occurs in a “causal” pathway from an independent to a dependent variable and “causes” variation in the dependent variable,

and itself is "caused" to vary by the independent variable (Baron and Kenny, 1986). Clearly, both the temporal precedence and the knowledge of causal associations are necessary to implement this definition. Even though the temporal precedence of the childhood psychological measures and the disease is met in this study, the assumption of causality needs further discussion. Although the ideal posits causal association between the constructs, we cannot infer causality from observation of association in a sample, particularly when using non-experimental data (Kraemer *et al.*, 2001). We can usually only say that what we observe is consistent with what we would expect to see if a causal path leading from the predictor to the outcome were in force.

There is a long history of philosophical and scientific debate about what "cause" means and how to demonstrate that "*X* causes *Y*" (Hill, 1965; Rubin, 1974; Bollen, 1989; Bullock *et al.*, 1994; Pearl, 2000; Rothman and Greenland, 2005). All these researchers agree that there is no single set of necessary and sufficient causal criteria that can be used to distinguish causal from non-causal relations in epidemiologic studies. Nevertheless, lists of causal criteria that provide a roadmap to causality have become popular. Probably, the most commonly used criteria was the one proposed by Hill (1965). Hill suggested that the following aspects of an association be considered in attempting to distinguish causal from non-causal associations: (1) strength of the association, (2) consistency- whether there are repeated observation of an association in different populations under different circumstances, (3) specificity- requires that a cause leads to a single effect, not multiple effects, (4) temporality- the necessity for a cause to precede an effect in time, (5) biological gradient- the presence of a dose-response curve, (6) plausibility- the biological plausibility of the hypothesis, (7) coherence- that the cause-and effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease, (8) experimental evidence, and (9) analogy. Hill himself was ambivalent about the utility of these criteria and at one point in his paper he stressed that "…what I do not believe- and this has been suggested- is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect". Therefore, it is not possible to confirm whether all these assumptions have been met in the SEMs using an observational study.

Although SEMs cannot ensure that necessary causal conditions have been met, it is argued that SEM methods may offer the potential for tentative causal inferences to be drawn when used with carefully specified and controlled designs (Bullock *et al.*, 1994).

Three conditions for causality have been widely accepted with regards to SEMs. These are: 1) temporal order 2) isolation- that is, control for all other causes, and 3) association (Bollen, 1989). Each of these conditions is difficult to meet, but we discuss below how closely they were met in this study.

Association

As already presented under the results, there were mixed results of bivariate association between each psychological factor and the disease. In fitting the mediating models, we used all the psychological measures irrespective of their bivariate association with the disease since this is not a necessary condition for mediation as already discussed in Section 4-7. The same condition applies to the SEMs. It has been shown that bivariate association is neither a necessary nor sufficient condition for a causal relation (Bollen, 1989). Rather, association, net of other influences is necessary to establish causality Therefore, despite some of the bivariate association not being significant, the condition for causality based on the association criteria was not violated in this case.

Temporal order

Since the childhood psychological measures were assessed before the disease, there is a clear temporal precedence of the main explanatory variables and the chronic disease. However, it was not clear whether the temporal priority was met among the intervening variables. We could not be sure whether some of the mediator variables in adulthood were measured before the disease. If they were not, then they could be a consequence rather than predictors of the disease. Even though this was somehow addressed in the analysis by treating them as time-varying covariates, this could not be fully resolved since it was difficult to know which one occurred first between the data collection sweeps.

Isolation: omitted variables

One of the most difficult conditions to meet is that of isolation; it is perhaps impossible to be certain that a cause and an effect are isolated from all other influences in observational studies, no matter how many variable we control for. By using SEMs to assess whether the models fit the data well, we used the global model fit indices, to test the overall model fit. But it is worth noting that good fit by no means guarantees the

inclusion of all relevant variables in a model. We recognize that the variables available in this study are only a small sample of the set of factors that could theoretically mediate the effects of early life psychological factors and chronic disease. Nevertheless, they are variables that have been used in many other behavioural medicine studies, and it would be of considerable interest if any of them was shown to confound, potentiate, or mediate the positive effects of childhood psychological factors on chronic health.

A second reason to downplay the omitted variables is that structural equation models routinely include residual terms that denote the composite effects of the unmeasured influences on a given variable (Tomarken and Waller, 2005). The variances of such residual terms are typically freely estimated parameters in structural models. Alternative models may be available that could fit the data equally well or better.

Therefore, despite the use of causal analysis in order to establish the pathways from childhood psychological measures to mid-life chronic disease, we do not claim to have established the fundamental true cause of how childhood psychological factors may affect adult health. Rather, we have taken the most widely believed pathways on how psychological factors relate to health, and assessed the empirical evidence for each using the two datasets.

In spite of the challenges presented by the methodological approaches applied in this study, we have to keep in mind that no statistical methodology can in itself determine causality. We must regards all the models as approximations to reality since the statistical tests can only disconfirm models, they can never prove a model or the causal relations within it (Bollen, 1989).

Challenges about choosing the correct theoretical model

Though the life course approach is not new to public health or unique to epidemiology, it still presents a number of challenges particularly the choice of the theoretical framework. Biological knowledge about epidemiologic hypotheses is often scant, making the hypotheses of causal association between exposure and disease sometimes vague. In this study, a theoretical model linking psychological disorders to physical illness was tested. But this is rather a general model, not specific to the three conditions considered in this study. In coming up with the specific hypotheses for each disease group, we relied on

literature to formulate the pathways linking psychological disorders to a particular disease. Thus, there is no guarantee that all the possible pathways were explored and we might have missed out other competing theories to be tested.

13.3. Strengths and Limitations of the Study

The strengths and limitations for each of the disease groups have been discussed separately in the previous chapters. Universal benefits among the three disease groups included: 1) the use of two general population based cohorts of individuals followed from birth to adult life, representing a rare source of prospectively collected childhood data that can be linked with adult disease outcome; 2) the use of two cohorts allowed the comparison of the results; 3) the ability to test the temporal relationship between the childhood psychological factors and the disease since the childhood psychological factors were recorded before the disease onset; 4) limiting the problem of recall biases since the information was prospectively recorded; 5) large sample size, thus having more power to detect any effect; and 6) availability of a wide range of factors that might confound or mediate the relationship between psychological factors and the disease.

Despite the advantages derived from prospectively collected data, the design also has the disadvantage of a long wait for studies of life course effects on adult outcomes, and other potential disadvantages that may increase with the study's longevity. These include the fact that the sample selection may not be appropriate for some later purposes, the data collected in childhood may not be precisely what is later required, and the scale of loss of sample members may be too great and/or too distorted through loss for later requirements.

A number of other limitations have been recognized in this study. Loss to follow up especially of those from disadvantaged groups is a common limitation of birth cohort studies. However, this may not be a major problem in this study based on the comparisons on several variables of the achieved sample with the target sample. Another problem was that of missing data in the covariates in terms of item non-response. The possible biases arising from such a problem was eliminated by use of full information maximum likelihood, and multiple imputation procedure. Both the methods rely on an assumption that the data are missing at random.

Further, the two cohorts considered are still relatively young and would not be expected to have fully developed conditions like cancer and diabetes which manifest themselves in earnest through middle-adulthood and into late-adulthood. As a result, the number of the individual cancers were still too few to permit an in depth examination of the site-specific relationships of psychological factors with cancer thus restricting us to analysing only one cancer site as well as all the sites together. The number of diabetes cases were also quite few especially the BCS70 and thus could not permit any meaningful analysis for that cohort.

Another limitation is the possible lack of accuracy in reporting the disease, occasioned by the extended interval between the first manifestations and correct diagnosis of such rare diseases such as cancer. Such diagnosis excludes the pre-diagnostic period between first manifestations and confirmed diagnosis of the disease.

13.4. Conclusions and Future Research

The conclusions slightly varied across the disease groups but there were commonalities on the possible biological pathway involving the continuities of childhood psychological problems to adulthood psychological distress which eventually lead to increased risk of the disease. The study found no significant direct effect of childhood psychological factors on cancer development upon adjustment for mid-life risk factors, but there were indirect effects through adulthood psychological distress and risky health behaviours, particularly cigarette smoking. Maladjusted behaviour at school was found to be both directly and indirectly associated with Type 2 diabetes and glucose metabolism in mid life. Conduct problems were found to be significantly associated with adult onset asthma both directly and indirectly.

The results of this study are novel and represent a significant advance in the understanding of the association between childhood behavioural problems and other psychological attributes to the physical health in adulthood. The study extends the current body of knowledge regarding the long term negative physical health resulting from behavioural problems such as aggression observed in childhood, by examining both direct and indirect paths. Previous studies have found the link between psychological factors and physical health but have used majorly the adulthood psychological measures.

Avenues for future research

Despite our finding of a possible biological pathway between childhood psychological factors and mid life chronic disease, interpreting a causal association between the observational evidence and a reduction in chronic disease risk is problematic, as the potential for bias and confounding are extremely difficult to exclude. Even though we adjusted for a majority of the well established risk factors, there is no guarantee that we did not miss any important confounding or mediating factors. Further research may therefore be conducted by adopting a Mendelian randomization approach or conducting a randomised control trial in order to provide causal evidence.

Future data availability when the cohorts have grown older and more incident cases of the diseases are detected will prove helpful in further understanding of these relationships. The data for the last sweep of data collection carried out in 2008/2009 was not ready by the time of this analysis and it would be interesting to find out if we can replicate the findings with that data. A possible linkage with the national cancer registries will confirm the cancer cases and enable us to deal with clinically diagnosed outcome. The new datasets will also provide more cases of diagnosed chronic diseases. Future biomedical surveys will also provide more objective outcome measures for diabetes and asthma and will be useful in confirming the results of this study. Therefore, some of the unresolved issues in this study may be resolved in the later sweeps as the cohort ages.

Future analysis for cancer can be done for individual cancer sites such as breast cancer. Since most of the previous studies examining the roles of psychological factors on cancer have analysed breast cancer, analysis of the roles of childhood psychological factors on breast cancer should be carried out using future data from these cohorts in order to compare the results with the results of other previous studies. Even as the cohort ages, the number of cases for other individual sites would still be only modest for specific analyses of other cancer sites.

In this study, the childhood psychological factors were considered at individual ages in order to determine at which age they had their effect most. An aggregate measure of the childhood psychological problems can be created by combining the severe childhood behavioural problems into one cumulative effect variable for further analysis.

Further analysis can also be carried out using the most current data for the Type 2 diabetes in the BCS70 since with the current data there were very few cases. Also further analyses can be done using Type 1 diabetes to confirm whether the childhood psychological factors have an effect in glucose metabolism.

Future research can also incorporate other chronic conditions. Psychological factors has long been associated with an increased risk of CVD and investigating other factors likely to increase the risk for CVD such as high blood pressure can be explored given that the objective measures of high blood pressure were obtained during the biomedical survey. Other conditions that can be considered include back pain. Pang and his colleagues (2010) recently investigated using the NCDS whether childhood behaviour is associated with the likelihood of chronic widespread pain (CWP) in adulthood, and if any such relationship is mediated through adult psychological distress. Such study can be extended to incorporate other biological and behavioural pathways.

13.5. Contribution to Knowledge

This research has contributed to new knowledge in this field in many ways. Psychological factors in adulthood have long been associated with poorer physical health, but less is known on whether they exert their effect from childhood. This study bridges that gap by investigating whether psychological factors, particularly behavioural and emotional problems measured in childhood have an impact on three chronic diseases, namely, cancer, diabetes, and asthma, which are known to be of high impact to both patients and health services. In addition, the pathways from childhood psychological factors to the three chronic diseases in mid-life have been investigated. The study therefore adds to our knowledge base of the important role that psychological problems, particularly behavioural and emotional problems, measured in childhood play in the development of chronic disease in mid life.

The study benefits from the use of longitudinal datasets of sufficient duration so that the psychological factors measured in childhood and the chronic disease in mid life are temporally distinct. In this way, the information about circumstances and experience early in life is used to predict the outcomes later in life domains. The use of such longitudinal data remains one of the most powerful ways to test life course models. Many studies that have investigated the roles of psychological factors in the development of

chronic disease have used cross-sectional research designs or quasi-prospective designs in which the disease status is measured either at the same time or preceding the psychological measures. This study, having taken into account the temporal sequence of the two measures, adds to the literature on the risks of developing chronic disease as a result of psychological problems in childhood.

The datasets used in this study also provided a unique opportunity to use an existing theoretical model of the link between psychological factors and physical illness (Cohen and Rodriguez, 1995) to test whether associations are mediated by biological and behavioural pathways. Not many studies have tested empirically such psychologically and biologically plausible models linking psychological disorders and physical disease. Thus, empirically testing an original theoretically proposed model is also a major contribution of this study. The theoretical framework was very vital as a tool for organising the existing literature and a source of hypothesis about the pathways linking the early life psychological factors and chronic disease in mid life.

In addition, the use of the two datasets enables comparisons between cohorts born at different times, or between different age groups at the same point in time. Similarly, a significant association of the risk factors and the chronic disease in both the cohorts give more evidence that the association is unlikely to be a chance finding.

The use of advanced statistical methodologies appropriate for the analysis of this type of longitudinal data was also a major contribution of this study, and was the key to the extra insights gained from it. The analysis took into account the temporal hierarchies among the childhood exposures and the mid-life risk factors through the use of structural equation modelling. This study therefore adds to the number of a few epidemiological publications that have explicitly stated the temporal ordering of exposure variables and their inter-relationships, both directly and through intermediary variables, with the outcome measure. The use of measurement (latent variable) model for the childhood psychological measures also enabled better measurements of these concepts by potentially reducing biases inherent in single item measures. The use of standard analytical methods such as regression modelling would not take into account the temporal sequence implied by the different pathways.

Another contribution of this study involved the use of complex path models with latent variables, multiple mediators, and indirect pathways. By modelling all the pathways simultaneously, we can look at the wider effect of childhood psychological factors on chronic disease through indirect as well as direct effects. In another context, Singh-Manoux *et al.* (2002) demonstrated how temporally distant effects may be understated if indirect effects are ignored. Considering all the pathways together also allowed us to consider the relative impact of each pathway, and to determine whether any of the pathways are spurious, that is, solely due to chance associations with the factors in other pathways.

Given that missing data is a pervasive problem in many longitudinal studies including the ones used in this study, we used estimation techniques which protect against non-response bias under the missing at random assumption. Moreover, repeated measurement of the childhood factors and the chronic diseases offers opportunities for checking the data consistencies across the sweeps and for statistical controls in the modelling process.

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Appendix A: Description of the Variables and the Scales

Table A 1: Bristol Social Adjustment Guide (BSAG): The full scale used in the NCDS for boys at age 7 (from the NCDS 1965 manual); girls had a similar table. Similar scale was used at age 11.

N4 N1

Local Authority Code No.			Child's Code No.					

Confidential

BG—1

See page 4 for syndrome code numbers.

BRISTOL SOCIAL-ADJUSTMENT GUIDES—No. 1

THE CHILD IN SCHOOL—(BOY)

(For the Observation of Day-School Children, 5-15 years).

Prepared by D. H. Stott, Ph.D. and Miss E. G. Sykes

The object of this Guide is to give a picture of the child's behaviour and to help in the detection of emotional instability.

Name of child.....

Birth date..... Date of this record.....

Teacher making record.....

School.....

METHOD OF USE

Underline in ink the phrases which describe the child's behaviour or attitudes over the past term or so. If any feature is very marked, underline twice. More than one item may be underlined in each paragraph, but do not underline any unless definitely true of the child. Add any remarks necessary beside the underlining, or at the end of the Guide. Where an item seems inappropriate because of age, etc., it can be ignored. If nothing is applicable mark 'n.n.' (nothing noticeable). Do not bother to *rule* underlinings.

ATTITUDES TOWARDS THE TEACHER

Greeting teacher:	Over-eager to greet/greets normally/sometimes eager sometimes definitely avoids/ waits to be noticed before greeting/absolutely never greets/n.n.
Response to greeting:	Usually friendly/can be surly or suspicious/mumbles shyly, awkwardly/does not answer/answers politely/n.n.
Helping teacher with jobs:	Always willing/very anxious to do jobs/offers except when in a bad mood/ never offers but pleased if asked/has no wish to volunteer/n.n.
Answering questions:	Always ready to answer/sometimes eager sometimes doesn't bother/eager except when in one of his moods/gets nervous, blushes, cries when questioned/not shy but unconcerned/n.n.
Asking teacher's help:	Always finding excuses for engaging teacher/seeks help only when necessary; seldom needs help/too shy to ask/not shy but never comes for help willingly/ too apathetic to bother/at times very forward, at times unsociable/depends on how he feels.
General manner with teacher:	Natural, smiles readily/over-friendly/shy but would like to be friendly/makes no friendly or eager response/sometimes friendly, sometimes in a bad mood/ quite cut off from people, you can't get near him as a person/not open or friendly; sometimes 'seems to be watching you to see if you know'/n.n.
Talking with teacher:	Normally talkative/forward (opens conversation)/over-talkative (tires with constant chatter)/inclined to be moody/says very little; can't get a word out of him/ avoids talking (distant, deep)/avoids teacher but talks to other children.
	Talks to t. about own doings, family or possessions—normally for age/excessively/ never makes any first approach/chats only when alone with teacher/n.n.
Contacts with teacher:	Very anxious to bring/sometimes brings/never brings flowers, gifts, although classmates often do.
	Brings objects he has found, drawings, models, etc. to show teacher—very often/ sometimes/never, although classmates often do.
	Sidles up to or hangs round teacher/minimises contacts but not backward with other children/like a suspicious animal/n.n.
Liking for attention:	Appreciates praise/tries to monopolise t./put out if he can't get attention/ wants adult interest but can't put himself forward/suspicious (on the defensive)/ unconcerned about approval or disapproval.

Page 1

Liking for sympathy:	Craves for sympathy (comes unnecessarily with minor scratches, bumps, etc., complains of being hurt by others)/doesn't make unnecessary fuss/keeps clear of adults even when hurt or wronged/likes sympathy but reluctant to ask/takes advantage of sympathy or interest/n.n.
Classroom behaviour:	Well-behaved/too timid to be naughty/occasionally naughty/has no life in him/ constantly needs petty correction/very naughty, difficult to discipline/plausible, sly; will abuse trust, hard to catch/n.n.
Truthfulness:	Always or nearly always truthful/lies from timidity/sometimes a fluent liar/ habitual slick liar; has no compunction about lying/tells fantastic tales.
Honesty:	Copies from others/normally honest with school work.
	'Borrows' books from desks without permission/has stolen money, sweets (candy), valued objects—frequently/once or twice/never.
Attitude to correction:	Normal for age/bursts into tears/resentful muttering or expression at times/ aggressive defiance (screams, threats, violence)/plays the hero.
Effect of correction:	Behaves better/too immature to heed/too restless to remember for long/can't resist playing to the crowd/bears a grudge, always regards punishment as unfair/ becomes antagonistic/treats lenience as weakness/n.n.

ATTITUDE TO SCHOOL WORK

Attentiveness:	Apathetic ('just sits')/won't bother to learn/dreamy and distracted ('lives in another world')/cannot attend or concentrate for long (cannot sit still when read to or during broadcasts, plays with things under desk, etc.)/n.n.
Persistence (classwork):	Works steadily/too restless ever to work alone/works only when watched or compelled/can work alone but has no energy/varies very noticeably from day to day.
Classwork standard:	Reading (English): Good/average/poor for age/cannot read. Arithmetic (Math): Good/average/poor for age/completely incompetent.
Persistence (manual tasks):	Sticks to job/gives up easily/impatient, loses temper with job/depends on his mood/varies greatly/lacks physical energy/works only when watched or compelled/distant and uninterested.
Standard (manual):	Work good or average/very erratic (seems at times to do badly on purpose)/ rough-and-ready, slapdash.

GAMES AND PLAY

Team games:	Plays steadily and keenly; with great energy/eager to play but loses interest/ inclined to fool around/dreamy, uninterested/always sluggish, lethargic/ sometimes alert, sometimes lethargic/n.n.
	Fits in well with team/bad loser (makes a fuss when game goes against him)/ bad sportsman (plays for himself only, cheats, fouls)/submissive, takes less wanted position, a 'ball fetcher'.
	Over-brave (takes unnecessary risks)/timid, poor-spirited; can't let himself go/ normally courageous.
Informal play:	Shrinks from active play/plays childish games for his age/healthily noisy and boisterous/starts off others in scrapping and rough play/disturbs others' games; teases, likes to frighten others/n.n.
Individual games:	Likes sedentary games (board games, cards, etc.)/is too restless/good loser/bad loser. Honest/cunning, dishonest/n.n.
Free activity:	Can always amuse himself; works patiently at models, etc./does not know what to do with himself, can never stick at anything long/sometimes lacks interest/n.n.

Favourite activity .....

ATTITUDES TO OTHER CHILDREN

Companionship: Good mixer/associates with one other child only and mostly ignores the rest/distant, shuns others/sometimes wanders off alone/can never keep a friend long (tries to pal up with newcomers)/over-anxious to be in with the gang (tries to buy favour with others, easily led)/likes to be the centre of attention/mostly on bad terms with others.

Ways with other children: Gets on well with others; generally kind, helpful/sometimes nasty to those outside own set/squabbles, makes insulting remarks/selfish, scheming, a spoil sport/hurts by pushing about, hitting/spiteful to weaker children/tells on others, underhand (tries to get others into trouble)/n.n.

Plays only or mainly with older/younger children/those of own age.

Physical prowess: Never fights/fights gamely/gets bullied/strikes brave attitudes but backs out/flies into a temper if provoked/fights viciously (bites, kicks, scratches, uses dangerous objects as weapons)/n.n.

Liking the limelight: Brags to other children. Shows off (makes silly faces, mimics, clowns). Misbehaves when teacher is out of room/n.n.

Attitude of other children: Liked/disliked, shunned/on the fringe, somewhat of an outsider/associates mostly with unsettled types/gets cheated, fooled.

PERSONAL WAYS

Attendance: Good/frequently absent for day or half-day/has had long absences/has truanted—once or twice, often, suspected of truancy/parent condones absences, malingering, etc./stays away to help parent.

Punctuality: Good or fairly good/often late/has cut lessons.

Belongings: Looks after books, etc./careless, untidy; often loses or forgets books, pen/destructive, defaces with scribbling.

Ability at class jobs: Sensible/irresponsible, scatterbrain/untrustworthy/varies with mood/just stupid/n.n.

Care for appearance: Adopts extreme youth fashions/not much concerned with looks/slovenly, very dirty/gets very dirty during day/smart and tidy for age/n.n.

Speech: Stutters, stammers, can't get the words out/thick, mumbling, inaudible/jumbled/incoherent rambling chatter/babyish (mispronounces simple words)/n.n.

Eyes: Dull, listless/unresponsive (doesn't seem to see you)/can't look you in the face/has a wild hostile look; looks from under brows/blinking/bright/n.n.

Posture: Slumps, lolls about/walks alertly/shuffles listlessly/n.n.

Expression: Miserable, depressed ('under the weather'), seldom smiles/vacant/serious/placid, complacent/perky/n.n.

Fidgets, etc.: Unwilled twitches, jerks; makes aimless movements with hands/bites nails badly. Jumpy/sucks thumb or finger (over ten years)/continually giggling/n.n.

Nuisance: Damage to public property, etc. (of school, fences, unoccupied houses)/damage to personal property (cars, delivery vehicles, occupied houses or gardens, teacher's or workmen's belongings, etc.)/foolish pranks when with a gang/spoils or hides other children's things/follower in mischief/bad language; vulgar stories, rhymes, drawings/obscene behaviour/n.n.

Sexual development: Early; very keen on opposite sex/normal/abnormal tendency/delayed.

Appearance: Attractive/not so attractive as most/looks undernourished/has some abnormal feature/n.n.

General health: Poor breathing, wheezy, asthmatic, easily winded/frequent colds, tonsillitis, coughs; running nose: mouth breather/running, infected ears/skin troubles, sores/ complains of tummy aches, feeling ill or sick; is sometimes sick/headaches; bad turns, goes very pale; fits/nose-bleeding/sore, red eyes/very cold hands/ good health.

Physical defects: Bad eyesight; squint; bulging eyes; poor hearing; gawky (bad co-ordination); contorted features (face screwed up on one side, eyes half closed, etc.); holds limb or body in unnatural posture.

Size: Tall for age/ordinary/small/unusually small. Very fat/very thin/n.n.

Anything special about this child which is not covered in the form.:

Unforthcomingness - N432
Withdrawal - N434
Depression - N436
Anxiety - N438
Hostility towards Adults - N440
"Writing off" of Adults and Adults Standards - N442
Anxiety for Acceptance by Children - N444
Hostility Towards Children - N446

Summary, recommendations; comments:

Restlessness - N448
"Inconsequential" Behaviour - N450
Miscellaneous Symptoms - N452
Miscellaneous "Nervous" Symptoms - N454
Total for all syndromes - N455
Attendance - N458
Appearance - N462
Miscellaneous - N466
Health Factors - 1 - N470
Health Factors - 2 - N472
Health Factors - 3 - N481
Size - N427

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Table A 2: BSAG: A description of the aggregated scale with behaviours that define each core syndrome.

Serial Letter	**Syndrome**	**Description** *(List of items)*[*]
U	Unforthcomingness	Characterised by shyness and lack of confidence, self-assertion and curiosity both with people and with fresh things or new situations; finds all such a great strain. *(Chats only when alone with teacher; burst into tears when corrected; …)*
W	Withdrawal	The child sets up defence against human contact and against being loved. *(Absolutely never greets; does not answer; …)*
D	Depression	Pointing to motivational deficits and failure to seek out or respond to environmental stimuli, showing ups and downs of energy, irritability, and continuous depression and neuro-physical exhaustion. *(Sometime eager, sometimes doesn't bother;…; impatient, loses temper with job; …; can work alone but has no energy; …)*
X	Anxiety	Anxiety or uncertainty about adult interest and affection: Making sure of acceptance and notice; seeking attention and over-demanding of affection; great anxiety for acceptance. (*Very anxious to do jobs; …; talks excessively to teacher about own doings, family or possessions; …; craves for sympathy ;…)*
HA	Hostility towards adults	A mild rejecting attitude which may be incipient hostility or merely depression; hostile rejecting moods alternating with anxiety for acceptance; active hostility showing itself in anti-social behaviour; a more thoroughgoing , uncontrolled habitual hostility. *(…; offers except when in bad mood; …; bad language, vulgar stories; …; bears a grudge, always regards punishment as unfair; …)*
K	Writing-off of adults and adult standards	An attitude of unconcern for adults' approval and 'writing off' adults; in its severe form amount to a loss of human feeling and moral impairment. Lack of desire to please, unconcern about being in good books of adults; …; serious loss of feelings and moral impairment.*(Wont bother to learn;…; has no wish to volunteer; …)*
XC	Anxiety for acceptance by children	Anxiety for approval of and acceptance by other children, sometimes to the extent of being led into mischief.
HC	Hostility towards children	From jealous rivalry to enmity and lack of human feelings. (*Disturbs others' games, teases, likes frightening*; …)
R	Restlessness	An inability to persevere, concentrate or reflect and a liking for easy moment-to-moment satisfaction. *(Gets very dirty during day; too restless to remember for long; …)*
I	Inconsequential behaviour	Impulsive acting out without regard for consequences
M	Miscellaneous symptoms	Miscellaneous symptoms of emotional tension, strain, or disturbance. Immaturity, high fears and truancy and unpunctuality. *(Plays childish games for his age; …; gets bullied ;..)*
M	Miscellaneous 'Nervous' symptoms	The gravity may depend on the child's age and may be the aftermath of earlier disturbance. *(Stutter, jumbled speech, blinking eyes, unwilled twitches …)*
BSGA Score	Total behavioural deviance	The total amount of behavioural deviance (or maladjustment) as measured by the Guide

[*] For complete list of items under each symptom, consult the Manual to the Bristol Social Adjustment Guides, University of London Press (Stott, 1963, 1971).

Table A 3: Varimax-rotated factor loadings of the syndromes of the BSAG scale for the 7 year old in the NCDS. The first 2 factors explained 50.3% of the variance.

Syndromes	Factor 1	Factor 2
Unforthcomingness	-0.111	**0.796**
Withdrawal	0.026	**0.761**
Depression	0.257	**0.738**
Anxiety for acceptance by adults	**0.533**	-0.186
Hostility towards adults	**0.661**	0.232
Writing off adults	**0.440**	**0.584**
Anxiety for acceptance by children	**0.745**	-0.064
Hostility towards children	**0.733**	0.098
Restlessness	**0.625**	0.152
Inconsequential behaviour	**0.786**	0.224
Miscellaneous symptoms	0.226	**0.676**
Miscellaneous nervous symptoms	0.313	0.233

Table A 4: Rutter Child Behaviour Scale- Individual Rutter behaviour questions and ages at which they were asked in BCS70 and NCDS. In its original form, the respondents were asked to place a cross against each statement in one of the boxes: "does not apply"-scored 0; "applies somewhat"-scored 1; and "certainly applies"-scored 2.

	BCS70			**NCDS**			
	Age of CM when data collected						
Specific Wording of Question	**5 M[2]**	**10 M**	**16 M**	**7 M**	**11 M**	**16 M**	**16 T[3]**
1a. Very restless. Often running about or jumping up and down. Hardly ever still.°	✓	✓	✓				
1b. Very restless. Has difficulty staying seated for long.						✓	✓
2a. Is squirmy or fidgety.	✓	✓	✓	✓	✓		
2b. Squirmy, fidgety child°						✓	✓
3a. Often destroys own or others' belongings.°	✓	✓	✓				
3b. Often destroys own or others' property.						✓	
3c. Often destroys or damages own or others' property.							✓
3d. Destroys own or others' belongings (e.g. tears or breaks).				✓	✓		
4a. Frequently fights with other children.°	✓	✓					
4b. Fights with other children				✓	✓		
4c. Frequently fights with others.			✓				
4d. Frequently fights or is extremely quarrelsome with other children.						✓	✓
5a. Not much liked by other children.°	✓	✓				✓	✓
5b. Not much liked by others.			✓				
6a. Often worried, worries about many things°	✓	✓	✓			✓	

6b. Often worries, worries about many things							✓
6c. Worries about many things				✓	✓		
7a. Tends to do things on his/her own – rather solitary. [o]	✓	✓	✓			✓	✓
7b. Prefers to do things on his/her own rather than with others				✓	✓		
8a. Irritable. Is quick to fly off the handle. [o]	✓	✓	✓			✓	
8b. Is irritable, quick to fly off the handle.				✓	✓		
8c. Irritable, touchy, is quick to fly off the handle.							✓
9a. Often appears miserable, unhappy, tearful or distressed. [o]	✓	✓	✓			✓	✓
9b. Is miserable or tearful				✓	✓		
10a. Sometimes takes things belonging to others.[*]	✓	✓	✓				
10b. Has stolen things on one or more occasions in the last 12 months [o]							✓
11a. Has twitches, mannerisms or tics of the face or body. [o]	✓	✓	✓			✓	✓
11b. Has twitches or mannerisms of the face, eyes or body.				✓	✓		
12a. Frequently sucks thumb or finger. [o]	✓	✓	✓			✓	✓
12b. Sucks thumb or finger during the day.				✓	✓		
13a. Frequently bites nails or fingers. [o]	✓	✓	✓			✓	✓
13b. Bites nails				✓	✓		
14a. Is often disobedient. [o]	✓	✓	✓			✓	✓
14b. Is disobedient at home				✓	✓		
15a. Cannot settle to anything for more than a few moments. [o]	✓	✓	✓			✓	✓
15b. Has difficulty in settling to anything for more than a few moments				✓	✓		
16a. Tends to be fearful or afraid of new things or new situations. [o]	✓	✓	✓			✓	✓
16b. Is upset by new situation, by things happening for first time				✓	✓		
17a. Is over fussy or over particular.	✓	✓	✓				
17b. Fussy or over-particular child. [o]						✓	✓
18. Often tells lies.	✓	✓	✓			✓	✓
19a. Bullies other children. [o]	✓	✓				✓	✓
19b. Bullies others.			✓				
19c. Is bullied by other children.				✓	✓		
20. Truants from school.							✓
21. Tends to be absent from school for trivial reasons.							✓
22. Unresponsive, inert or apathetic							✓
23. Often complains of aches or pains							✓
24. Has had tears on arrival at school or has refused to come into the building in the past 12 months							✓
25. Has a stutter or stammer							✓
26. Resentful or aggressive when corrected							✓

[2] Completed by the parents (mostly mothers) of the cohort member (Child scale A)
[3] Completed by the teachers of the cohort member (Child Scale B)
[o] Wording as used in the original questionnaire
[*] This behaviour was not included in the original Child Scale A

Rutter Child Scale A: Health problems and habits

Besides the list of behavioural statements above, the child scale A questionnaire also asked about various kinds of behaviours that many children show at some time. These included minor health problems and habits.

Health problems

The health problems were categorised as never in the last year, less often than once per month, at least once per month, and at least once per week. The list included:

A. Complains of headaches
B. Has stomach ache or vomiting
C. Complains of biliousness
D. Wets his/her bed or pants
E. Soils him/herself or loses control of bowels
F. Has temper tantrums (that is, complete loss of temper with shouting, angry movements, etc).
G. Had tears on arrival at school or refused to go into the building.
H. Truants from school.

Habits

I. Does he/she stammer or stutter? (No, Yes-mildly, Yes-severely)
II. Has he/she any difficulty with speech other than stammering or stuttering? (No, Yes-mild, Yes-severe). If 'Yes' is the difficulty lisping, cannon say word properly, or other.
III. Does he/she ever steel things
IV. Does he/she have any eating difficulty?
V. Does he/she have any sleeping difficulty?

Table A 5: Malaise Inventory: Asked to the 1958 cohort members at ages 23, 33, and 41-42 and to the 1970 cohort members at ages 16, 26, and 29/30 years. Parents of the 1970 cohort were also asked to complete the questionnaire when their children were aged 5, 10 and 16 years. The respondents were asked to ring the correct answer.

1.	Do you often have back-ache?	Yes	No
2.	Do you feel tired most of the time?	Yes	No
3.	Do you often feel miserable or depressed?	Yes	No
4.	Do you often have bad headaches?	Yes	No
5.	Do you often get worried about things?	Yes	No
6.	Do you usually have great difficulty in falling or staying asleep?	Yes	No
7.	Do you usually wake unnecessarily early in the morning?	Yes	No
8.	Do you wear yourself out worrying about your health?	Yes	No
9.	Do you often get into a violent rage?	Yes	No
10.	Do people often annoy and irritate you?	Yes	No
11.	Have you at times had a twitching of the face, head or shoulders?	Yes	No
12.	Do you often suddenly become scared for no good reason?	Yes	No
13.	Are you scared to be alone when there are no friends near you?	Yes	No
14.	Are you easily upset or irritated?	Yes	No
15.	Are you frightened of going out alone or of meeting people?	Yes	No
16.	Are you constantly keyed up and jittery?	Yes	No
17.	Do you suffer from indigestion?	Yes	No
18.	Do you suffer from an upset stomach?	Yes	No
19.	Is your appetite poor?	Yes	No
20.	Does every little thing get on your nerves and wear you out?	Yes	No
21.	Does your heart often race like mad?	Yes	No
22.	Do you often have bad pain in eyes?	Yes	No
23.	Are you troubled with rheumatism or fibrosis?	Yes	No
24.	Have you ever had a nervous breakdown?	Yes	No

Table A 6: GHQ12: Completed by the NCDS cohort members at 42 years and BCS70 at 16 years.

GHQ	**Description**
GHQ1	Can concentrate on what you are doing?
GHQ2	Lost much sleep over worry?
GHQ3	Felt you were playing a useful part in things?
GHQ4	Felt capable of making decisions?
GHQ5	Felt constantly under strain?
GHQ6	Felt could not overcome difficulties?
GHQ7	Been able to enjoy normal activities?
GHQ8	Been able to face up to your problems?
GHQ9	Been feeling unhappy and depressed?
GHQ10	Been losing confidence in yourself?
GHQ11	Been thinking yourself as worthless?
GHQ12	Been feeling reasonable happy?

Table A 7 : Child Development Scale: Completed at 10 years by the teachers of the BCS70 cohort members.

Item No.	Description of Scale Items
1.	Child is daydreaming
2.	Afraid of new things/situations
3.	Cannot concentrate on particular task
4.	Wetting pants during class
5.	Complains about things
6.	Trips falls bumps
7.	Works deftly with hands
8.	Displays outbursts of temper
9.	Teases other children
10.	Clumsy at games
11.	Cries for little cause
12.	Becomes bored during class
13.	Shows perseverance
14.	Difficulty kicking ball
15.	Dresses/undresses competently
16.	Interferes with others
17.	Confused or hesitant
18.	Difficulty picking up small objects
19.	Behaves 'nervously'
20.	Fussy or over-particular
21.	Changes mood quickly
22.	Excitable impulsive
23.	Worried and anxious
24.	Shows restless or over-active behaviour
25.	Squirmy and fidgety
26.	Easily distracted
27.	Manipulates small objects with hands
28.	Drops things being carried
29.	Pays attention in class
30.	Relations with others unhappy/tearful
31.	Obsession about unimportant tasks
32.	Forgetful on complex task
33.	Rather solitary
34.	Quarrels with other kids
35.	Can use manipulative equipment
36.	Shows lethargic/listless behaviour
37.	Destroys belongings
38.	Hums or makes odd vocals
39.	Rhythmic tapping in class
40.	Inadequate control of pencil/paint brush
41.	Soils pants during class
42.	Accident prone
43.	Bullies other children
44.	Sullen or sulky
45.	Has twitches, mannerisms/tics
46.	Truants from school
47.	Fearful in movements
48.	Completes tasks
49.	Is easily frustrated
50.	Holds instruments appropriately
51.	Fails to finish tasks
52.	Extrovert-introvert
53.	Anxious-unworried

Table A 8 : LAWSEQ Self-esteem Questionnaire: Administered to the BCS70 cohort at 10 and 16 years.

1. Do you think that your parents usually like to hear about your ideas?
2. Do you often feel lonely at school?
3. Do other children often break friends or fall out with you?
4. Do you like team games?[§]
5. Do you think that other children often say nasty things about you?
6. When you have to say things in front of teachers, do you usually feel shy?
7. Do you like writing stories or doing other creative writing?
8. Do you often feel sad because you have nobody to play with at school?
9. Are you good at mathematics?
10. Are there lots of things about yourself you would like to change?
11. When you have to say things in front of other children, do you usually feel foolish?
12. Do you find it difficult to do things like woodwork or knitting?
13. When you want to tell a teacher something, do you usually feel foolish?
Do you often have to find new friends because your old friends are playing with somebody else?
15. Do you usually feel foolish when you talk to your parents?
16. Do other people often think that you tell lies?

[§] Questions 4, 7, 9, and 12 are distractor questions. Each "No" response counts as two points, don't know as a point, except for the first question where "Yes" equals two points. High scores indicate positive self-esteem. The Chronbach's $\alpha = .68$ for the full 10-year sample.

Table A 9: CARALOC Locus of Control questionnaire: Administered to the BCS70 cohort at 10 and 16 years.

1. Do you feel that most of the time it's not worth trying hard because things never turn out right anyway?
2. Do you feel that wishing can make good things happen?
3. Are people good to you no matter how you act towards them?
4. Do you like taking part in plays or concerts? ‡
5. Do you usually feel that it's almost useless to try in school because most children are cleverer than you?
6. Is a high mark just a matter of 'luck' for you?
7. Are you good at spelling?
8. Are tests just a lot of guess work for you?
9. Are you often blamed for things which just aren't your fault?
10. Are you the kind of person who believes that planning ahead makes things turn out better?
11. Do you find it easy to get up in the morning?
12. When bad things happen to you, is it usually someone else's fault?
13. When someone is very angry with you, is it impossible to make him your friend again?
14. When nice things happen to you is it only good luck?
15. Do you feel sad when it's time to leave school each day?
16. When you get into an argument is it usually the other person's fault?
17. Are you surprised when your teacher says you've done well?
18. Do you usually get low marks, even when you study hard?
19. Do you like to read books?
20. Do you think studying for tests is a waste of time?

‡Questions 4, 7, 11, and 19 are distractor questions. Each "No" response counts as one point, except for question ten where "Yes" equals one point. High scores indicate greater internal locus of control. α = .66 for the full 10-year sample.

Table A 10: Items of the Conner's mother scale in the 10 year old in the BCS70 together with their Varimax-rotated factor loadings.

	Impulsive	**Hyperactive**	**Clumsy**	**Motor co-ord.**
Noticeably clumsy	0.0935	0.2038	**0.8253**	0.1303
Trips or falls easily	0.1404	0.15	**0.805**	0.1557
Inattentive, easily distracted	0.1558	**0.7647**	0.2099	-0.0087
Hums or makes odd noises	0.2466	**0.4367**	0.0595	0.3173
Difficulty picking up small objects	0.0917	0.0248	0.3043	**0.7685**
Drops things being carried	0.1246	0.1075	**0.6513**	0.4286
Obsessional	**0.5082**	0.1055	0.088	0.3358
Requests must be met immediately	**0.6454**	0.2896	0.0276	0.1378
Restless or over-active behaviour	0.4161	**0.5489**	-0.0038	0.2232
Impulsive, excitable	0.4726	**0.4904**	0.0321	0.1301
Interferes with other children	**0.4053**	0.3786	0.1111	0.2628
Sullen or sulky	0.6579	0.0696	0.2458	-0.0636
Fails to finish things	0.125	**0.7818**	0.2107	-0.0017
Given to rhythmic tapping/kicking	0.2731	**0.4066**	0.0304	0.3941
Cries for little cause	**0.6179**	0.0379	0.2311	0.0782
Changes mood quickly/drastically	**0.7681**	0.2067	0.1305	0.0415
Outbursts of temper unpredictable	**0.7213**	0.1946	0.0811	0.093
Difficulty using scissors	0.0192	0.1125	0.2071	**0.7464**
Difficulty concentrating on task	0.1217	**0.7258**	0.1712	0.174

Appendix B: Supplementary Analyses

Standardized Estimates for Childhood Psychological Measures

When independent variables are measured at different scales like the childhood psychological measures in this study, the β coefficients can be standardized to compare the strength of the relationship between the dependent variable and the many independent variables. By standardizing the coefficients, the independent variables can be compared directly to determine which has the largest magnitude on the dependent variable.

This section presents the standardized estimates for the risk of childhood psychological measures on cancer, diabetes and asthma. Regression coefficients for both the full standardization and the X-standardization have been presented. With full standardization, both the X and the Y variables are standardized to have a mean of 0 and a standard deviation of 1, while in the X-standardization only the X variables are standardized.

The X-standardized coefficients are in the column labelled StdX. Each regression coefficient represents the effect of a standard deviation change in a predictor, controlling for the other variables. For example, in Table B1 we see that in the unadjusted model, a one standard deviation increase in conduct problem score at age 11 produces, on average, leads to a 0.062 increase in the log odds of being diagnosed with cancer. Hence, by standardizing the Xs only, you can see the relative importance of the Xs, while still keeping the dependent variable in its original metric.

The fully standardized coefficients are in the column labelled StdXY. Interpretation of these standardized coefficients is quite straightforward. A one standard deviation increase in the independent variable (X) produces a StdXY value standard deviation change in the log odds of Y. For example, in Table B1 we see that in the unadjusted model, a one standard deviation increase in conduct problem score at age 11, on average is associated with an increase of 0.052 standard deviations in the log odds of being diagnosed with cancer.

Standardized estimates for cancer analysis

Table B 1: Standardized coefficients for the effects of childhood psychological measures on the risk of all cancers between ages 17 and 42 years old in the NCDS for both the unadjusted and the confounder adjusted model.

	Age-adjusted			Age & confounder adjusted†		
	StdX	StdXY	Sig	StdX	StdXY	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	0.041	0.033	0.555	0.033	0.027	0.631
Hyperactive	0.090	0.073	0.149	0.075	0.059	0.232
Emotional problems	0.107	0.087	0.096	0.103	0.081	0.119
Conduct Problem	-0.079	-0.064	0.282	-0.083	-0.066	0.269
Child Behaviour at School (BSAG)						
Emotional problems	-0.109	-0.088	0.166	-0.145	-0.113	0.078
Conduct problems	0.102	0.082	0.047	0.076	0.059	0.141
Miscellaneous Nervous Syndrome	-0.003	-0.002	0.939	-0.003	-0.003	0.946
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	0.085	0.071	0.171	0.062	0.051	0.335
Hyperactive	0.073	0.062	0.260	0.064	0.053	0.329
Emotional problems	0.025	0.021	0.676	0.007	0.006	0.892
Conduct Problem	0.062	0.052	0.333	0.026	0.022	0.682
Child Behaviour at School (BSAG)						
Emotional problems	0.009	0.008	0.828	-0.030	-0.024	0.678
Conduct problems	0.168	0.138	0.002	0.164	0.130	0.003
Miscellaneous Nervous Syndrome	0.029	0.024	0.578	0.041	0.033	0.457
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.205	0.159	0.001	0.110	0.080	0.096
Hyperactive	0.131	0.103	0.040	0.069	0.050	0.330
Emotional problems	0.146	0.114	0.037	0.145	0.105	0.048
Conduct Problem	0.166	0.129	0.007	0.049	0.035	0.427
Child Behaviour at School (Rutter B) total Score						
Well adjusted						
With behavioural disorder	0.151	0.124	0.012	0.057	0.044	0.356
Subscales for Rutter B						
Neurotic	0.172	0.141	0.005	0.133	0.104	0.030
Antisocial	0.117	0.096	0.017	0.029	0.023	0.556

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

† Adjusted for the effect of maternal smoking, social class of the father, birth weight and smoking by age 16 years for the age 16 psychological measures.

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

Table B 2: Standardized coefficients for the effects of childhood psychological measures on the risk of cervical cancer between ages 17 and 42 years old in the NCDS for both the unadjusted and the confounder adjusted model.

	Age-adjusted			Age & confounder adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	0.207	0.191	0.043	0.128	0.105	0.262
Hyperactive	0.115	0.107	0.276	0.071	0.058	0.524
Emotional problems	0.164	0.152	0.131	0.092	0.076	0.391
Conduct Problem	0.168	0.155	0.108	0.114	0.094	0.290
Child Behaviour at School (BSAG)						
Emotional problems	0.085	0.079	0.395	-0.027	-0.022	0.907
Conduct problems	0.226	0.207	0.006	0.196	0.161	0.001
Miscellaneous Nervous Syndrome	-0.008	-0.008	0.839	-0.026	-0.021	0.981
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	0.259	0.237	0.007	0.271	0.218	0.011
Hyperactive	0.164	0.153	0.121	0.186	0.152	0.085
Emotional problems	0.071	0.066	0.464	0.066	0.054	0.536
Conduct Problem	0.308	0.278	0.002	0.296	0.237	0.007
Child Behaviour at School (BSAG)						
Emotional problems	0.122	0.113	0.112	0.045	0.038	0.525
Conduct problems	0.334	0.298	<0.001	0.329	0.272	<0.001
Miscellaneous Nervous Syndrome	0.130	0.121	0.095	0.166	0.139	0.053
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.390	0.334	<0.001	0.259	0.178	0.012
Hyperactive	0.261	0.230	0.002	0.143	0.099	0.206
Emotional problems	0.277	0.244	0.006	0.332	0.226	0.007
Conduct Problem	0.297	0.260	0.002	0.069	0.048	0.449
Child Behaviour at School (Rutter B) total Score						
Well adjusted						
With behavioural disorder	0.429	0.367	<0.001	0.193	0.140	0.038
Subscales for Rutter B						
Neurotic	0.257	0.231	0.012	0.066	0.048	0.534
Antisocial	0.349	0.306	<0.001	0.192	0.140	0.008

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

† Adjusted for the effect of maternal smoking, social class of the father, birth weight and smoking by age 16 years for the age 16 psychological measures.

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

Table B 3: Standardized coefficients for the effects of childhood psychological measures on the risk of all cancers between ages 17 and 30 years old in the BCS70 for both the unadjusted and the confounder adjusted model.

	Age-adjusted			Age & confounder adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
Psychological factors at age 5*						
Child Behaviour at Home (Rutter A)						
Total Score	0.081	0.070	0.386	0.039	0.033	0.660
Hyperactive	0.104	0.090	0.291	0.088	0.074	0.377
Emotional problems	0.062	0.054	0.458	0.040	0.034	0.628
Conduct Problem	-0.013	-0.011	0.942	-0.079	-0.066	0.460
Psychological factors at age 10						
Child Behaviour at Home (Rutter A)						
Total Score	0.131	0.114	0.085	0.102	0.087	0.206
Hyperactive	0.196	0.169	0.023	0.186	0.157	0.037
Emotional problems	0.087	0.076	0.344	0.045	0.039	0.621
Conduct Problem	0.040	0.035	0.582	0.012	0.010	0.833
At Home (Conners' Mother self completion)						
Impulsive	0.020	0.018	0.782	-0.003	-0.003	0.977
Hyperactive/Inattention	0.078	0.068	0.372	0.063	0.054	0.491
Clumsy	0.015	0.013	0.818	0.004	0.003	0.900
Poor Motor Coordination	-0.046	-0.040	0.730	-0.070	-0.060	0.593
At School (Child Development Behaviour)						
Antisocial Behaviour	0.100	0.084	0.273	0.139	0.112	0.126
Disorganised activity	0.149	0.124	0.119	0.155	0.126	0.124
Neuroticism/Anxiety	0.133	0.111	0.129	0.175	0.141	0.047
Clumsiness	0.103	0.086	0.273	0.127	0.103	0.183
Poor hand-Eye Coordination	-0.141	-0.118	0.124	-0.150	-0.121	0.121
Hyper/Kinesis	-0.031	-0.026	0.832	-0.003	-0.003	0.928
Introversion/Extroversion	0.140	0.116	0.170	0.100	0.081	0.336
Behavioural Trauma	0.046	0.038	0.354	0.059	0.048	0.257
Dressing	-0.172	-0.142	0.033	-0.131	-0.106	0.119
At School (Self Completion)						
Locus of Control+	-0.034	-0.029	0.669	-0.026	-0.022	0.756
Self Esteem‡	-0.227	-0.192	0.012	-0.214	-0.177	0.026
Psychological factors at age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.167	0.142	0.101	0.191	0.160	0.068
Hyperactive	0.101	0.088	0.293	0.116	0.099	0.247
Emotional problems	0.037	0.032	0.733	0.077	0.066	0.516
Conduct Problem	0.194	0.165	0.016	0.204	0.172	0.014

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

† Adjusted for the effect of maternal smoking, social class of the father, birth weight and smoking by age 16 years

+ Higher scores indicate greater internalization; ‡ Higher score indicate higher self-esteem.

* For all the other psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

Table B 4: Standardized coefficients for the effects of childhood psychological measures on the risk of cervical cancer between ages 17 and 30 years old in the BCS70 for both the unadjusted and the confounder adjusted model.

	Age-adjusted			Age & confounder adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
Psychological factors at age 5*						
Child Behaviour at Home (Rutter A)						
Total Score	0.350	0.293	0.005	0.254	0.193	0.044
Hyperactive	0.327	0.275	0.016	0.291	0.219	0.041
Emotional problems	0.139	0.121	0.248	0.086	0.066	0.482
Conduct Problem	0.330	0.277	0.005	0.207	0.157	0.070
Psychological factors at age 10						
Child Behaviour at Home (Rutter A)						
Total Score	0.151	0.130	0.236	0.106	0.083	0.438
Hyperactive	0.313	0.263	0.015	0.292	0.226	0.029
Emotional problems	0.005	0.004	0.931	-0.026	-0.020	0.909
Conduct Problem	0.072	0.063	0.546	0.009	0.007	0.883
At Home (Conners' Mother self completion)						
Impulsive	0.141	0.122	0.301	0.103	0.082	0.467
Hyperactive/Inattention	0.309	0.260	0.012	0.267	0.208	0.035
Clumsy	-0.114	-0.099	0.696	-0.134	-0.106	0.652
Poor Motor Coordination	-0.096	-0.084	0.712	-0.126	-0.100	0.640
At School (Child Development Behaviour)						
Antisocial Behaviour	0.391	0.323	0.001	0.383	0.276	<0.001
Disorganised activity	0.460	0.373	0.001	0.421	0.300	0.003
Neuroticism/Anxiety	0.357	0.297	0.001	0.362	0.262	0.001
Clumsiness	0.245	0.210	0.030	0.268	0.197	0.018
Poor hand-Eye Coordination	-0.290	-0.245	0.010	-0.303	-0.221	0.014
Hyper/Kinesis	0.146	0.126	0.113	0.124	0.093	0.184
Introversion/Extroversion	0.092	0.081	0.540	0.093	0.070	0.555
Behavioural Trauma	0.045	0.040	0.312	0.036	0.027	0.396
Dressing	-0.282	-0.239	0.005	-0.246	-0.181	0.019
At School (Self Completion)						
Locus of Control+	-0.243	-0.206	0.027	-0.173	-0.126	0.164
Self Esteem‡	-0.327	-0.275	0.005	-0.307	-0.224	0.013
Psychological factors at age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.462	0.353	<0.001	0.470	0.321	<0.001
Hyperactive	0.411	0.323	<0.001	0.413	0.294	<0.001
Emotional problems	0.373	0.294	0.015	0.371	0.262	0.019
Conduct Problem	0.436	0.335	<0.001	0.457	0.312	<0.001

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

† Adjusted for the effect of maternal age at delivery, maternal smoking and social class of the father.

+ Higher scores indicate greater internalization; ‡ Higher score indicate higher self-esteem.

* For all the other psychological measures, higher scores indicate worse conditions of behavioural maladjustment.

Standardized estimates for Type 2 diabetes analysis

Table B 5: Standardized estimates for the effect of childhood psychological factors on self reported diabetes in midlife in the NCDS.

	Age-adjusted			Age & Confounder adjusted†		
	StdX	StdXY	Sig	StdX	StdXY	Sig
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	0.049	0.023	0.653	-0.019	-0.009	0.900
Hyperactive	0.012	0.006	0.917	-0.041	-0.019	0.786
Emotional problems	-0.067	-0.031	0.555	-0.057	-0.026	0.620
Conduct Problem	0.072	0.034	0.505	-0.033	-0.015	0.802
Child Behaviour at School (BSAG)						
Emotional problems	0.281	0.132	0.001	0.193	0.091	0.013
Conduct problems	0.258	0.122	0.002	0.192	0.091	0.009
Miscellaneous Nervous Syndrome	0.152	0.072	0.075	0.110	0.052	0.133
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	0.166	0.089	0.124	0.120	0.056	0.256
Hyperactive	0.163	0.087	0.121	0.121	0.057	0.220
Emotional problems	0.066	0.035	0.559	0.081	0.038	0.474
Conduct Problem	0.117	0.063	0.288	0.037	0.018	0.718
Child Behaviour at School (BSAG)						
Emotional problems	0.340	0.193	<0.001	0.274	0.141	0.002
Conduct problems	0.377	0.213	<0.001	0.263	0.135	0.001
Miscellaneous Nervous Syndrome	0.251	0.144	<0.001	0.206	0.106	0.004
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	-0.013	-0.008	0.912	-0.085	-0.041	0.538
Hyperactive	0.089	0.051	0.420	0.034	0.017	0.680
Emotional problems	-0.090	-0.052	0.489	-0.087	-0.043	0.623
Conduct Problem	0.117	0.068	0.293	0.002	0.001	0.884
Child Behaviour at School (Rutter B)-Tota score						
Well adjusted						
With behavioural disorder	0.339	0.181	<0.001	0.271	0.121	0.010
Subscales						
Neurotic	0.202	0.108	0.044	0.110	0.049	0.257
Antisocial	0.136	0.074	0.156	0.016	0.007	0.734

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.
StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds
Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

† Adjusted for the effect of maternal smoking, and reading score

Table B 6: Standardized estimates for the effect of childhood psychological factors on prevalence with HbA1c ≥ 6 and or Type 2 diabetes in midlife in the NCDS.

	Age-adjusted			Confounder adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	0.079	0.079	0.163	0.033	0.031	0.570
Hyperactive	0.082	0.082	0.152	0.039	0.036	0.506
Emotional problems	-0.039	-0.039	0.522	-0.045	-0.042	0.481
Conduct Problem	0.116	0.115	0.033	0.045	0.042	0.434
Child Behaviour at School (BSAG)						
Emotional problems	0.200	0.196	<0.001	0.189	0.176	<0.001
Conduct problems	0.175	0.172	<0.001	0.149	0.139	0.002
Miscellaneous Nervous Syndrome	0.116	0.116	0.010	0.108	0.102	0.022
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	0.092	0.092	0.093	0.076	0.071	0.197
Hyperactive	0.064	0.064	0.224	0.048	0.045	0.394
Emotional problems	0.002	0.002	0.963	0.002	0.002	0.956
Conduct Problem	0.134	0.133	0.013	0.092	0.086	0.113
Child Behaviour at School (BSAG)						
Emotional problems	0.204	0.200	<0.001	0.210	0.195	<0.001
Conduct problems	0.216	0.211	<0.001	0.176	0.164	<0.001
Miscellaneous Nervous Syndrome	0.083	0.083	0.087	0.092	0.087	0.073
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.072	0.072	0.198	0.021	0.020	0.717
Hyperactive	-0.013	-0.013	0.901	-0.076	-0.072	0.367
Emotional problems	0.094	0.094	0.102	0.099	0.094	0.107
Conduct Problem	0.076	0.075	0.165	0.039	0.037	0.508
Child Behaviour at School (Rutter B)-Total score						
Well adjusted						
With behavioural disorder	0.169	0.166	0.001	0.186	0.174	0.001
Subscales						
Neurotic	0.137	0.136	0.007	0.174	0.163	0.001
Antisocial	0.107	0.107	0.019	0.100	0.095	0.033

* For all the psychological measures, higher scores indicate worse conditions of behavioural maladjustment.
StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds
Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors
† Adjusted for the effect of sex, family history of diabetes, social class of the father, and maternal smoking

Standardized estimates for asthma analysis

Table B 7: Standardized estimates for the effect of childhood psychological measures on adult onset (age 17-42) asthma or wheezy bronchitis in the 1958 birth cohort (NCDS).

	Unadjusted			Adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	0.128	0.127	<0.001	0.136	0.128	<0.001
Hyperactive	0.067	0.067	0.053	0.067	0.064	0.064
Emotional problems	0.055	0.055	0.118	0.051	0.048	0.166
Conduct Problem	0.083	0.083	0.018	0.104	0.098	0.005
Child Behaviour at School (BSAG)						
Emotional problems	0.041	0.041	0.250	0.043	0.041	0.239
Conduct problems	0.081	0.080	0.020	0.111	0.104	<0.001
Miscellaneous Nervous Syndrome	0.034	0.034	0.336	0.033	0.031	0.363
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	0.141	0.140	<0.001	0.147	0.138	<0.001
Hyperactive	0.068	0.068	0.052	0.073	0.069	0.044
Emotional problems	0.069	0.069	0.050	0.068	0.065	0.060
Conduct Problem	0.132	0.131	<0.001	0.145	0.136	<0.001
Child Behaviour at School (BSAG)						
Emotional problems	0.029	0.029	0.421	0.026	0.024	0.499
Conduct problems	0.129	0.128	<0.001	0.156	0.147	<0.001
Miscellaneous Nervous Syndrome	-0.007	-0.007	0.856	0.001	-0.001	0.976
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.127	0.126	<0.001	0.119	0.112	<0.001
Hyperactive	0.103	0.103	0.002	0.113	0.106	<0.001
Emotional problems	0.030	0.030	0.391	0.024	0.023	0.504
Conduct Problem	0.177	0.174	<0.001	0.170	0.159	<0.001
Child Behaviour at School (Rutter B) total score						
Well adjusted						
With behavioural disorder	0.147	0.145	<0.001	0.124	0.116	0.001
Subscales						
Neurotic	0.141	0.140	<0.001	0.117	0.110	0.002
Antisocial	0.138	0.137	<0.001	0.132	0.124	<0.001
Childhood Adversity Score **	0.232	0.226	<0.001	0.208	0.195	<0.001

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

† Model adjusted for the effect of sex, maternal smoking, parity, pneumonia at age 7, social class of the father at 7 years, history of hay fever at seven or 11 years, history of eczema at seven or 11 years, and smoking at age 16 for

* For all the psychological measures, higher scores indicate worse conditions of behavioural

** Retrospective childhood adversity score (Path through life scale) assessed at age 44-45.

Table B 8: Standardized estimates for the effect of childhood psychological measures on the 12-month period prevalence of asthma or wheezy bronchitis at age 42 years in the NCDS.

	Unadjusted			Adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
At Age 7*						
Child Behaviour at Home (Rutter A)						
Total Score	0.152	0.151	<0.001	0.146	0.131	<0.001
Hyperactive	0.106	0.105	0.003	0.119	0.107	0.002
Emotional problems	0.109	0.108	0.003	0.070	0.064	0.085
Conduct Problem	0.085	0.085	0.020	0.122	0.110	0.003
Child Behaviour at School (BSAG)						
Emotional problems	0.025	0.025	0.492	0.020	0.019	0.622
Conduct problems	0.100	0.100	0.003	0.144	0.130	<0.001
Miscellaneous Nervous Syndrome	0.082	0.082	0.013	0.085	0.077	0.025
At Age 11						
Child Behaviour at Home (Rutter A)						
Total Score	0.179	0.176	<0.001	0.177	0.158	<0.001
Hyperactive	0.151	0.149	<0.001	0.169	0.152	<0.001
Emotional problems	0.104	0.104	0.005	0.079	0.071	0.056
Conduct Problem	0.133	0.132	<0.001	0.149	0.134	<0.001
Child Behaviour at School (BSAG)						
Emotional problems	0.097	0.096	0.006	0.083	0.075	0.042
Conduct problems	0.144	0.143	<0.001	0.170	0.152	<0.001
Miscellaneous Nervous Syndrome	0.002	-0.002	0.961	0.036	0.033	0.392
At Age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.186	0.183	<0.001	0.152	0.136	<0.001
Hyperactive	0.138	0.137	<0.001	0.160	0.143	<0.001
Emotional problems	0.118	0.117	0.002	0.046	0.042	0.311
Conduct Problem	0.175	0.172	<0.001	0.167	0.149	<0.001
Child Behaviour at School (Rutter B) total score						
Well adjusted						
With behavioural disorder	0.157	0.155	<0.001	0.130	0.117	0.002
Subscales						
Neurotic	0.161	0.159	<0.001	0.118	0.106	0.005
Antisocial	0.116	0.115	0.001	0.122	0.110	0.003
Childhood Adversity Score **	0.213	0.208	<0.001	0.174	0.157	<0.001

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

† Model adjusted for the effect of sex, maternal smoking, parity, pneumonia at age 7, social class of the father at 7

* For all the psychological measures, higher scores indicate worse conditions of behavioural

** Retrospective childhood adversity score (Path through life scale) assessed

Table B 9: Standardized estimates for the effect of childhood psychological measures on adult onset (age 17-30) asthma or wheezy bronchitis in the 1970 birth cohort.

	Unadjusted			Adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
Psychological factors at age 5*						
Child Behaviour at Home (Rutter A)						
Total Score	0.025	0.025	0.415	0.025	0.023	0.448
Hyperactive	0.013	0.013	0.680	0.019	0.017	0.567
Emotional problems	0.015	0.015	0.632	-0.019	-0.018	0.556
Conduct Problem	0.001	0.001	0.970	0.035	0.033	0.285
Psychological factors at age 10						
Child Behaviour at Home (Rutter A)						
Total Score	-0.021	-0.021	0.497	-0.006	-0.005	0.867
Hyperactive	0.002	0.002	0.946	0.035	0.033	0.305
Emotional problems	0.005	0.005	0.856	-0.016	-0.015	0.633
Conduct Problem	-0.062	-0.061	0.047	-0.040	-0.038	0.260
At Home (Conners' Mother self completion)						
Impulsive	-0.005	-0.005	0.857	-0.001	-0.001	0.971
Hyperactive/Inattention	0.000	0.000	0.997	0.039	0.036	0.265
Clumsy	0.011	0.011	0.719	0.018	0.017	0.597
Poor Motor Coordination	-0.050	-0.050	0.112	-0.062	-0.058	0.089
At School (Child Development Behaviour)						
Antisocial Behaviour	0.092	0.092	0.002	0.137	0.127	<0.001
Disorganised activity	0.036	0.036	0.237	0.097	0.090	0.008
Neurotism/Anxiety	0.079	0.079	0.009	0.100	0.093	0.004
Clumsiness	0.073	0.073	0.014	0.120	0.111	<0.001
Poor hand-Eye Coordination	-0.033	-0.033	0.278	-0.080	-0.075	0.026
Hyper/Kinesis	0.052	0.052	0.083	0.137	0.127	<0.001
Introversion/Extroversion	0.020	0.020	0.515	0.018	0.016	0.626
Behavioural Trauma	0.048	0.048	0.088	0.074	0.069	0.018
Dressing	-0.044	-0.044	0.148	-0.073	-0.068	0.035
At School (Self Completion)						
Locus of Control‡	-0.052	-0.052	0.094	-0.055	-0.051	0.129
Self Esteem+	-0.090	-0.090	0.003	-0.082	-0.076	0.021
Psychological factors at age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.054	0.054	0.126	0.092	0.085	0.020
Hyperactive	0.063	0.062	0.074	0.115	0.107	0.003
Emotional problems	0.021	0.021	0.559	0.037	0.035	0.364
Conduct Problem	0.008	0.008	0.830	0.037	0.035	0.362

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

†Adjusted for sex, family histoty of atopy, history of childhood eczema up to age 10, history of hayfever up to age 10, mother's age at birth, maternal smoking during pregnancy , and birthweight.

‡ Higher scores indicate greater internalization; +Higher score indicate higher self-esteem.

* For the rest of the psychological measures, higher score indicate worse conditions of behavioural maladjustment.

Table B 10: Standardized estimates for the effect of childhood psychological measures on 12-months period prevalence of asthma or wheezy bronchitis at age 30 in the BCS70.

	Unadjusted			Adjusted†		
	StdX	**StdXY**	**Sig**	**StdX**	**StdXY**	**Sig**
Psychological factors at age 5*						
Child Behaviour at Home (Rutter A)						
Total Score	0.038	0.038	0.313	-0.006	-0.006	0.876
Hyperactive	-0.007	-0.007	0.864	-0.024	-0.022	0.546
Emotional problems	0.060	0.060	0.104	0.006	0.005	0.886
Conduct Problem	0.010	0.010	0.786	0.005	0.005	0.902
Psychological factors at age 10						
Child Behaviour at Home (Rutter A)						
Total Score	0.036	0.036	0.317	0.003	0.003	0.943
Hyperactive	0.045	0.045	0.217	0.040	0.035	0.338
Emotional problems	0.006	0.006	0.876	-0.053	-0.047	0.201
Conduct Problem	-0.009	-0.009	0.805	-0.022	-0.020	0.606
At Home (Conners' Mother self completion)						
Impulsive	0.036	0.036	0.322	0.005	0.004	0.904
Hyperactive/Inattention	0.040	0.040	0.264	0.043	0.038	0.307
Clumsy	0.003	0.003	0.934	-0.020	-0.018	0.634
Poor Motor Coordination	-0.016	-0.016	0.672	0.022	0.019	0.596
At School (Child Development Behaviour)						
Antisocial Behaviour	0.142	0.140	<0.001	0.145	0.128	0.001
Disorganised activity	0.131	0.130	<0.001	0.147	0.130	0.001
Neurotism/Anxiety	0.140	0.139	<0.001	0.123	0.108	0.005
Clumsiness	0.099	0.099	0.006	0.084	0.075	0.047
Poor hand-Eye Coordination	-0.068	-0.068	0.073	-0.033	-0.029	0.464
Hyper/Kinesis	0.075	0.074	0.039	0.097	0.086	0.026
Introversion/Extroversion	-0.071	-0.071	0.062	-0.029	-0.026	0.512
Behavioural Trauma	0.036	0.036	0.299	0.039	0.035	0.326
Dressing	-0.055	-0.055	0.143	-0.040	-0.036	0.362
At School (Self Completion)						
Locus of Control‡	-0.044	-0.044	0.250	-0.038	-0.034	0.404
Self Esteem+	-0.101	-0.101	0.008	-0.106	-0.093	0.015
Psychological factors at age 16						
Child Behaviour at Home (Rutter A)						
Total Score	0.078	0.078	0.061	0.087	0.077	0.066
Hyperactive	0.076	0.076	0.066	0.112	0.099	0.014
Emotional problems	0.094	0.094	0.027	0.083	0.073	0.085
Conduct Problem	0.011	0.011	0.811	0.021	0.018	0.680

StdX-semi-standardized; StdXY-fully standardized coefficients of the log odds

Variables having larger standardized beta weights (in absolute value) are considered to be stronger predictors

†Adjusted for sex, family history of atopy, history of childhood eczema up to age 10, history of hayfever up to age 10, mother's age at birth, maternal smoking during pregnancy , and birthweight.

‡ Higher scores indicate greater internalization; +Higher score indicate higher self-esteem.

* For the rest of the psychological measures, higher score indicate worse conditions of behavioural maladjustment.

Results for Categorised Childhood Psychological Measures

As thresholds indicative of likely behavioural disorders were not available for most of the modified psychological measures instruments used in different sweeps of data collection, all the derived subscale scores were analysed in a continuous form as presented in the main results. The motivation for adopting the continuous rather than categorical measures during the analysis as well as the problems associated with categorisation are already discussed in Section 2.2.2. However, as a common practice in many epidemiological studies, arbitrary cut-offs are usually used to categorise the continuous variables during their analyses. The major reason for doing this is the common perception that categorization makes it easier to report and interpret final results.

On the basis of ease in interpretation of results, we have carried out supplementary analyses using the categorised childhood psychological measures. In categorising the variables, a score in the top 13% defined a severe case of maladjustment, the lowest 50% were considered normal, and the remainder were considered mild case of maladjustment (Ghodsian, 1983).

As shown in Tables B11-B16, many categorised measures followed the same significance pattern as the continuous variables, and would therefore have the advantage of easier interpretation. However, for a few cases (e.g. the neurotic subscale of Rutter B score, Table B11) the results derived from the categorical scales were different from those of the continuous scale in terms of their significance. For these measures when the cut-point chosen during the categorization were changed, the calculated odds ratios were also significantly changed. Also for such measures with different results in the continuous and categorical forms, the significant association with the outcomes repeatedly came and went depending on which cut-point was used to define the severe and the mild behavioural disorders. This is a common problem with categorisation using data-derived cut-points and has been experienced in other studies as well (Royston *et al.*, 2006).

Cancer results

Table B 11: The effects of childhood psychological measures on the risk of all cancers between ages 17 and 42 years old in the NCDS: Combined results of 10 multiply-imputed data.

Variable (Reference category)	N_C[1]	N_{CF}[2]	Age-adjusted			Age & confounder Adj.*		
			OR	(95% CI)	Sig	OR	(95% CI)	Sig
Age 7: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	89	4,291						
Mild	103	4,322	1.12	(0.85 , 1.48)	0.43	1.10	(0.83 , 1.46)	0.49
Severe	33	1,102	1.36	(0.92 , 2.01)	0.13	1.28	(0.86 , 1.91)	0.23
Emotional problems (Normal)	74	3,461						
Mild	98	4,292	1.08	(0.81 , 1.45)	0.61	1.07	(0.80 , 1.44)	0.65
Severe	53	1,969	1.22	(0.85 , 1.73)	0.28	1.20	(0.84 , 1.71)	0.31
Conduct Problem	107	3,920						
Mild	86	4,370	0.72	(0.54 , 0.96)	0.03	0.70	(0.52 , 0.93)	0.02
Severe	32	1,430	0.74	(0.50 , 1.09)	0.13	0.69	(0.47 , 1.01)	0.06
Age 7: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	95	4,592						
Mild	97	3,988	1.05	(0.80 , 1.37)	0.75	0.98	(0.75 , 1.29)	0.90
Severe	37	1,308	0.68	(0.44 , 1.05)	0.08	0.60	(0.38 , 0.93)	0.02
Conduct problems (Normal)	106	4,503						
Mild	99	3,860	1.13	(0.86 , 1.48)	0.37	1.10	(0.84 , 1.44)	0.50
Severe	24	1,525	1.32	(0.91 , 1.93)	0.15	1.23	(0.84 , 1.80)	0.30
Age 11: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	100	4,336						
Mild	79	3,950	0.96	(0.71 , 1.30)	0.79	0.94	(0.69 , 1.28)	0.70
Severe	38	1,157	1.59	(1.12 , 2.27)	0.01	1.52	(1.07 , 2.18)	0.02
Emotional problems (Normal)	52	2,638						
Mild	111	4,461	1.29	(0.91 , 1.83)	0.16	1.28	(0.90 , 1.82)	0.16
Severe	54	2,344	1.36	(0.94 , 1.96)	0.10	1.34	(0.93 , 1.93)	0.12
Conduct Problem (Normal)	94	4,350						
Mild	97	4,042	1.14	(0.87 , 1.49)	0.36	1.10	(0.84 , 1.44)	0.48
Severe	26	1,049	1.30	(0.86 , 1.95)	0.21	1.21	(0.80 , 1.82)	0.38
Age 11: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	96	4,303						
Mild	94	3,866	1.09	(0.82 , 1.45)	0.56	1.08	(0.80 , 1.48)	0.61
Severe	33	1,386	1.06	(0.72 , 1.58)	0.76	0.96	(0.62 , 1.50)	0.86
Conduct problems (Normal)	107	5,003						
Mild	69	3,125	1.06	(0.80 , 1.41)	0.68	1.03	(0.77 , 1.37)	0.84
Severe	47	1,427	1.57	(1.11 , 2.21)	0.01	1.46	(1.04 , 2.05)	0.03
Age 16: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	149	6,488						
Mild	19	993	0.95	(0.61 , 1.48)	0.82	0.89	(0.57 , 1.40)	0.62
Severe	24	729	1.49	(1.00 , 2.22)	0.05	1.30	(0.88 , 1.93)	0.19
Emotional problems (Normal)	59	2,719						
Mild	90	3,856	1.10	(0.81 , 1.50)	0.54	1.13	(0.82 , 1.54)	0.45
Severe	43	1,641	1.25	(0.86 , 1.82)	0.24	1.28	(0.88 , 1.88)	0.20
Conduct Problem (Normal)	91	4,343						
Mild	71	3,121	1.10	(0.83 , 1.46)	0.49	1.04	(0.78 , 1.37)	0.81
Severe	30	750	2.10	(1.40 , 3.15)	0.00	1.75	(1.16 , 2.63)	0.01
Age 16: Child Behaviour at School (Rutter B)								
Neurotic (Normal)	99	4,791						
Mild/Severe	103	3,838	1.32	(0.98 , 1.77)	0.07	1.24	(0.92 , 1.67)	0.17
Antisocial (Normal)	144	6,742						
Mild	35	1,125	1.40	(0.94 , 2.06)	0.09	1.16	(0.77 , 1.76)	0.47
Severe	24	766	1.56	(1.03 , 2.37)	0.03	1.13	(0.73 , 1.76)	0.59

1 Cancer cases; 2 Non-cancer cases

* Adjusted for the effect of maternal smoking, social class of the father, birth weight and smoking for the age 16 psychological measures.

Table B 12: The effects of childhood psychological measures on the risk of cervical cancer between ages 17 and 42 years old in the NCDS: Combined results of 10 multiply-imputed data.

Variable (Reference category)	N_C[1]	N_{CF}[2]	Age-adjusted			Age & confounder Adj.*		
			OR	(95% CI)	Sig	OR	(95% CI)	Sig
Age 7: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	36	2,329						
Mild	29	2,149	0.85	(0.49 , 1.47)	0.56	0.83	(0.48 , 1.45)	0.52
Severe	14	510	1.60	(0.84 , 3.04)	0.15	1.45	(0.76 , 2.77)	0.27
Emotional problems (Normal)	23	1,721						
Mild	35	2,203	1.09	(0.66 , 1.79)	0.74	1.05	(0.64 , 1.74)	0.83
Severe	21	1,065	1.20	(0.68 , 2.13)	0.53	1.17	(0.65 , 2.09)	0.60
Conduct Problem	32	2,390						
Mild	33	2,025	1.15	(0.69 , 1.89)	0.59	1.07	(0.64 , 1.79)	0.80
Severe	14	574	1.66	(0.90 , 3.06)	0.10	1.44	(0.77 , 2.67)	0.25
Age 7: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	28	2,625						
Mild	38	1,942	1.79	(1.14 , 2.81)	0.01	1.62	(1.03 , 2.57)	0.04
Severe	13	509	0.87	(0.37 , 2.06)	0.76	0.76	(0.32 , 1.78)	0.52
Conduct problems (Normal)	30	2,582						
Mild	43	1,813	1.73	(1.08 , 2.77)	0.02	1.66	(1.04 , 2.65)	0.03
Severe	6	681	2.34	(1.23 , 4.47)	0.01	2.06	(1.08 , 3.93)	0.03
Age 11: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	37	2,391						
Mild	23	1,924	0.87	(0.52 , 1.47)	0.61	0.85	(0.51 , 1.43)	0.55
Severe	16	503	2.50	(1.41 , 4.45)	<0.01	2.33	(1.31 , 4.16)	<0.01
Emotional problems (Normal)	16	1,308						
Mild	40	2,291	1.27	(0.70 , 2.32)	0.43	1.27	(0.70 , 2.32)	0.44
Severe	20	1,220	1.43	(0.75 , 2.72)	0.28	1.40	(0.73 , 2.66)	0.31
Conduct Problem (Normal)	31	2,541						
Mild	35	1,878	1.54	(0.93 , 2.55)	0.09	1.45	(0.88 , 2.41)	0.15
Severe	10	399	2.35	(1.17 , 4.70)	0.02	2.04	(1.03 , 4.04)	0.04
Age 11: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	30	2,387						
Mild	35	1,856	1.52	(0.93 , 2.49)	0.10	1.40	(0.86 , 2.28)	0.18
Severe	11	633	1.47	(0.74 , 2.91)	0.27	1.30	(0.66 , 2.56)	0.45
Conduct problems (Normal)	32	2,903						
Mild	27	1,470	1.79	(1.06 , 3.03)	0.03	1.72	(1.02 , 2.90)	0.04
Severe	17	503	3.46	(1.93 , 6.20)	<0.01	2.98	(1.69 , 5.27)	<0.01
Age 16: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	50	3,451						
Mild	5	440	1.03	(0.45 , 2.37)	0.95	0.83	(0.36 , 1.91)	0.66
Severe	10	314	2.35	(1.24 , 4.45)	0.01	1.70	(0.88 , 3.27)	0.11
Emotional problems (Normal)	13	1,282						
Mild	33	2,002	1.42	(0.80 , 2.52)	0.23	1.55	(0.86 , 2.79)	0.14
Severe	19	924	1.77	(0.93 , 3.35)	0.08	1.86	(0.97 , 3.56)	0.06
Conduct Problem (Normal)	28	2,113						
Mild	20	1,672	1.05	(0.61 , 1.79)	0.87	0.86	(0.50 , 1.47)	0.58
Severe	17	422	3.21	(1.59 , 6.47)	<0.01	1.97	(0.94 , 4.13)	0.07
Age 16: Child Behaviour at School (Rutter B)								
Neurotic (Normal)	32	2,355						
Mild/Severe	38	2,095	1.35	(0.85 , 2.14)	0.21	1.12	(0.70 , 1.80)	0.63
Antisocial (Normal)	41	3,659						
Mild	15	513	2.48	(1.37 , 4.50)	<0.01	1.48	(0.81 , 2.71)	0.20
Severe	15	278	4.31	(2.43 , 7.63)	<0.01	1.99	(1.07 , 3.70)	0.03

1 Cancer cases; 2 Non-cancer cases

* Adjusted for the effect of maternal smoking, social class of the father, high blood pressure/eclampsia, mathematic score and smoking for the age 16 psychological measures.

Diabetes results

Table B 13: The effect of childhood psychological factors on self reported diabetes in midlife in the NCDS: Combined results of 10 multiply-imputed data.

Variable (Reference category)	N_D[1]	N_{ND}[2]	Age-adjusted			Age & confounder Adj.*		
			OR	(95% CI)	Sig	OR	(95% CI)	Sig
Age 7: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	39	4,299						
Mild	34	4,363	0.82	(0.51 , 1.32)	0.42	0.83	(0.52 , 1.33)	0.45
Severe	9	1,115	0.94	(0.47 , 1.88)	0.86	0.86	(0.43 , 1.74)	0.68
Emotional problems (Normal)	33	3,466						
Mild	33	4,330	0.84	(0.53 , 1.33)	0.45	0.76	(0.47 , 1.24)	0.27
Severe	16	1,988	0.83	(0.45 , 1.55)	0.57	0.81	(0.45 , 1.47)	0.49
Conduct Problem	29	3,957						
Mild	40	4,384	1.18	(0.75 , 1.87)	0.47	1.09	(0.68 , 1.75)	0.72
Severe	13	1,441	1.19	(0.62 , 2.28)	0.59	1.00	(0.52 , 1.94)	0.99
Age 7: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	24	4,548						
Mild	35	3,888	1.73	(1.05 , 2.85)	0.03	1.54	(0.90 , 2.62)	0.12
Severe	21	1,512	2.47	(1.41 , 4.33)	<0.01	1.90	(1.03 , 3.53)	0.04
Conduct problems (Normal)	28	4,619						
Mild	30	4,020	1.29	(0.79 , 2.11)	0.31	1.11	(0.65 , 1.88)	0.70
Severe	22	1,309	2.87	(1.65 , 4.97)	<0.01	2.16	(1.21 , 3.83)	0.01
Age 11: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	29	4,369						
Mild	36	3,960	1.37	(0.87 , 2.15)	0.17	1.37	(0.83 , 2.26)	0.22
Severe	11	1,177	1.51	(0.76 , 3.01)	0.24	1.35	(0.68 , 2.67)	0.40
Emotional problems (Normal)	18	2,642						
Mild	38	4,501	1.04	(0.62 , 1.75)	0.89	0.99	(0.56 , 1.76)	0.98
Severe	20	2,363	1.04	(0.58 , 1.87)	0.88	1.07	(0.58 , 1.98)	0.83
Conduct Problem (Normal)	31	4,377						
Mild	31	4,071	1.07	(0.67 , 1.71)	0.78	1.01	(0.61 , 1.65)	0.98
Severe	14	1,056	1.83	(0.98 , 3.42)	0.06	1.60	(0.86 , 3.00)	0.14
Age 11: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	28	4,332						
Mild	26	3,909	1.03	(0.60 , 1.76)	0.92	1.04	(0.59 , 1.85)	0.89
Severe	22	1,382	2.45	(1.40 , 4.28)	<0.01	2.03	(1.08 , 3.82)	0.03
Conduct problems (Normal)	29	5,040						
Mild	27	3,142	1.60	(0.96 , 2.67)	0.07	1.39	(0.82 , 2.36)	0.22
Severe	20	1,441	2.68	(1.53 , 4.68)	<0.01	1.97	(1.13 , 3.45)	0.02
Age 16: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	50	6,527						
Mild	8	999	1.23	(0.63 , 2.39)	0.55	1.04	(0.50 , 2.20)	0.91
Severe	7	739	1.27	(0.63 , 2.54)	0.50	1.14	(0.56 , 2.31)	0.72
Emotional problems (Normal)	26	2,728						
Mild	30	3,881	0.82	(0.47 , 1.46)	0.51	0.82	(0.44 , 1.56)	0.55
Severe	9	1,662	0.60	(0.28 , 1.31)	0.20	0.58	(0.26 , 1.31)	0.19
Conduct Problem (Normal)	34	4,365						
Mild	22	3,137	1.02	(0.63 , 1.67)	0.92	1.12	(0.68 , 1.85)	0.65
Severe	9	767	1.39	(0.69 , 2.80)	0.36	1.09	(0.49 , 2.39)	0.83
Age 16: Child Behaviour at School (Rutter B)								
Neurotic (Normal)	30	4,821						
Mild/Severe	36	3,864	1.34	(0.83 , 2.15)	0.23	1.15	(0.67 , 1.96)	0.62
Antisocial (Normal)	47	6,777						
Mild	12	1,133	1.45	(0.78 , 2.71)	0.24	1.29	(0.67 , 2.47)	0.44
Severe	7	780	1.31	(0.59 , 2.90)	0.50	0.90	(0.37 , 2.24)	0.83

1 Diabetes cases- those who reported having diabetes by age 42 years; 2 No diabetes cases reported

* Adjusted for the effect of maternal smoking, and reading score

Table B 14: The effect of childhood psychological factors on prevalence with HbA1c ≥ 6 and or Type 2 diabetes in midlife in the NCDS: Combined results of 10 multiply-imputed data.

Variable (Reference category)	N_D[1]	N_{ND}[2]	Age-adjusted			Age & confounder Adj.*		
			OR	(95% CI)	Sig	OR	(95% CI)	Sig
Age 7: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	140	2,945						
Mild	134	2,979	0.96	(0.76 , 1.22)	0.74	0.93	(0.74 , 1.18)	0.57
Severe	42	710	1.20	(0.85 , 1.70)	0.30	1.12	(0.79 , 1.59)	0.51
Emotional problems (Normal)	118	2,368						
Mild	141	2,961	0.91	(0.71 , 1.18)	0.48	0.91	(0.71 , 1.17)	0.45
Severe	57	1,311	0.85	(0.60 , 1.19)	0.33	0.85	(0.61 , 1.19)	0.34
Conduct Problem	108	2,725						
Mild	166	2,978	1.37	(1.07 , 1.74)	0.01	1.27	(0.99 , 1.62)	0.06
Severe	42	935	1.14	(0.80 , 1.61)	0.47	0.99	(0.69 , 1.40)	0.94
Age 7: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	123	3,180						
Mild	124	2,612	1.22	(0.93 , 1.59)	0.15	1.14	(0.87 , 1.50)	0.33
Severe	71	961	1.83	(1.32 , 2.53)	<0.01	1.65	(1.19 , 2.28)	<0.01
Conduct problems (Normal)	123	3,222						
Mild	142	2,724	1.35	(1.03 , 1.77)	0.03	1.30	(0.99 , 1.70)	0.06
Severe	53	807	1.71	(1.23 , 2.37)	<0.01	1.55	(1.11 , 2.16)	0.01
Age 11: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	127	3,019						
Mild	143	2,706	1.28	(1.01 , 1.62)	0.04	1.23	(0.97 , 1.56)	0.08
Severe	40	780	1.34	(0.94 , 1.91)	0.10	1.23	(0.86 , 1.76)	0.25
Emotional problems (Normal)	86	1,870						
Mild	144	3,043	1.03	(0.77 , 1.39)	0.83	1.04	(0.77 , 1.39)	0.81
Severe	80	1,591	1.10	(0.81 , 1.49)	0.53	1.10	(0.81 , 1.49)	0.53
Conduct Problem (Normal)	123	3,053						
Mild	148	2,776	1.33	(1.04 , 1.71)	0.02	1.24	(0.97 , 1.59)	0.08
Severe	39	674	1.59	(1.14 , 2.22)	0.01	1.41	(1.01 , 1.98)	0.05
Age 11: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	124	3,106						
Mild	129	2,589	1.22	(0.92 , 1.61)	0.17	1.14	(0.86 , 1.52)	0.36
Severe	57	855	1.62	(1.17 , 2.24)	<0.01	1.48	(1.07 , 2.05)	0.02
Conduct problems (Normal)	133	3,572						
Mild	111	2,092	1.41	(1.09 , 1.84)	0.01	1.33	(1.02 , 1.74)	0.03
Severe	66	886	1.92	(1.40 , 2.65)	<0.01	1.71	(1.23 , 2.37)	<0.01
Age 16: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	216	4,557						
Mild	36	699	1.11	(0.77 , 1.58)	0.59	1.05	(0.73 , 1.51)	0.79
Severe	19	484	1.15	(0.77 , 1.74)	0.49	1.06	(0.70 , 1.61)	0.77
Emotional problems (Normal)	82	1,941						
Mild	127	2,680	1.05	(0.81 , 1.36)	0.71	1.09	(0.84 , 1.41)	0.51
Severe	62	1,122	1.15	(0.83 , 1.58)	0.40	1.21	(0.88 , 1.67)	0.25
Conduct Problem (Normal)	137	3,118						
Mild	103	2,134	1.08	(0.83 , 1.40)	0.56	1.05	(0.81 , 1.36)	0.72
Severe	31	491	1.42	(0.97 , 2.10)	0.07	1.36	(0.91 , 2.03)	0.13
Age 16: Child Behaviour at School (Rutter B)								
Neurotic (Normal)	148	3,412						
Mild/Severe	144	2,573	1.23	(1.00 , 1.53)	0.05	1.24	(1.00 , 1.53)	0.05
Antisocial (Normal)	215	4,757						
Mild	44	746	1.28	(0.95 , 1.73)	0.11	1.17	(0.87 , 1.58)	0.31
Severe	33	485	1.52	(1.05 , 2.21)	0.03	1.32	(0.90 , 1.93)	0.15

1 Diabetes cases- those who reported having diabetes by age 42 years; 2 No diabetes cases reported

* Adjusted for the effect of sex, family history of diabetes, social class of the father, and maternal smoking

Asthma results

Table B 15: The effect of childhood psychological factors on adult onset asthma in the NCDS.

Variable (Reference category)	AW[1]	AW_F[2]	Age-adjusted			Age & confounder Adj.*		
			OR	(95% CI)	Sig	OR	(95% CI)	Sig
Age 7: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	485	1,257						
Mild	491	1,259	1.01	(0.87 , 1.17)	0.89	1.01	(0.87 , 1.18)	0.90
Severe	139	276	1.31	(1.04 , 1.64)	0.02	1.32	(1.04 , 1.68)	0.02
Emotional problems (Normal)	408	1,005						
Mild	464	1,238	0.92	(0.79 , 1.08)	0.32	0.91	(0.77 , 1.07)	0.25
Severe	243	550	1.09	(0.90 , 1.32)	0.38	1.08	(0.89 , 1.32)	0.45
Conduct Problem	467	1,196						
Mild	477	1,277	0.96	(0.82 , 1.11)	0.56	0.99	(0.85 , 1.16)	0.92
Severe	172	319	1.38	(1.11 , 1.71)	<0.01	1.42	(1.13 , 1.78)	<0.01
Age 7: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	502	1,391						
Mild	463	1,042	1.01	(0.87 , 1.18)	0.86	1.07	(0.91 , 1.25)	0.41
Severe	134	298	1.12	(0.90 , 1.39)	0.30	1.13	(0.90 , 1.42)	0.28
Conduct problems (Normal)	531	1,347						
Mild	413	1,033	1.23	(1.06 , 1.43)	0.01	1.26	(1.08 , 1.47)	<0.01
Severe	155	351	1.25	(0.99 , 1.57)	0.06	1.35	(1.06 , 1.71)	0.01
Age 11: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	518	1,352						
Mild	464	1,149	1.05	(0.91 , 1.22)	0.49	1.03	(0.88 , 1.20)	0.71
Severe	136	297	1.20	(0.95 , 1.50)	0.12	1.22	(0.96 , 1.54)	0.10
Emotional problems (Normal)	298	845						
Mild	539	1,306	1.17	(0.99 , 1.38)	0.06	1.14	(0.96 , 1.35)	0.14
Severe	281	648	1.23	(1.01 , 1.49)	0.04	1.22	(1.00 , 1.49)	0.05
Conduct Problem (Normal)	486	1,401						
Mild	512	1,163	1.27	(1.10 , 1.47)	<0.01	1.29	(1.11 , 1.50)	<0.01
Severe	120	233	1.48	(1.16 , 1.89)	<0.01	1.53	(1.18 , 1.98)	<0.01
Age 11: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	489	1,308						
Mild	428	1,000	1.14	(0.98 , 1.33)	0.08	1.16	(0.99 , 1.36)	0.07
Severe	135	341	1.06	(0.85 , 1.33)	0.62	1.05	(0.83 , 1.33)	0.68
Conduct problems (Normal)	553	1,546						
Mild	343	823	1.17	(0.99 , 1.37)	0.06	1.21	(1.03 , 1.43)	0.02
Severe	156	280	1.56	(1.25 , 1.94)	<0.01	1.69	(1.34 , 2.12)	<0.01
Age 16: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	871	2,286						
Mild	155	317	1.28	(1.04 , 1.58)	0.02	1.25	(1.01 , 1.56)	0.04
Severe	91	195	1.22	(0.94 , 1.59)	0.13	1.27	(0.98 , 1.67)	0.08
Emotional problems (Normal)	373	929						
Mild	524	1,373	0.95	(0.81 , 1.11)	0.53	0.95	(0.81 , 1.12)	0.57
Severe	220	497	1.10	(0.90 , 1.35)	0.34	1.09	(0.89 , 1.34)	0.41
Conduct Problem (Normal)	550	1,609						
Mild	462	1,022	1.32	(1.14 , 1.53)	<0.01	1.31	(1.13 , 1.53)	<0.01
Severe	105	167	1.84	(1.41 , 2.39)	<0.01	1.78	(1.36 , 2.34)	<0.01
Age 16: Child Behaviour at School (Rutter B)								
Neurotic (Normal)	530	1,437						
Mild/Severe	450	971	1.26	(1.08 , 1.46)	<0.01	1.23	(1.05 , 1.43)	0.01
Antisocial (Normal)	771	2,018						
Mild	135	270	1.31	(1.05 , 1.64)	0.02	1.24	(0.98 , 1.57)	0.07
Severe	75	125	1.57	(1.17 , 2.12)	<0.01	1.54	(1.12 , 2.10)	0.01

1 Adult onset asthma or wheezy bronchitis cases; 2 With no reported cases of adult onset asthma or wheezy bronchitis

* Model adjusted for the effect of sex, maternal smoking, parity, pneumonia at age 7, social class of the father at 7 years, history of hay fever at seven or 11 years, history of eczema at seven or 11 years, and smoking at age 16 for the 16 year old measures.

Table B 16: The effect of childhood psychological factors on 12-months period prevalence of asthma or wheezy bronchitis at age 42 in the NCDS.

Variable (Reference category)	AW[1]	AW_F[2]	Age-adjusted			Age & confounder Adj.*		
			OR	(95% CI)	Sig	OR	(95% CI)	Sig
Age 7: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	307	4,076						
Mild	356	4,070	1.15	(0.98 , 1.35)	0.09	1.16	(0.98 , 1.37)	0.08
Severe	112	1,023	1.47	(1.17 , 1.84)	<0.01	1.43	(1.13 , 1.81)	<0.01
Emotional problems (Normal)	253	3,282						
Mild	339	4,055	1.13	(0.96 , 1.33)	0.16	1.08	(0.92 , 1.28)	0.36
Severe	184	1,838	1.34	(1.07 , 1.67)	0.01	1.20	(0.96 , 1.51)	0.11
Conduct Problem	307	3,720						
Mild	334	4,125	1.00	(0.86 , 1.17)	0.99	1.07	(0.91 , 1.26)	0.40
Severe	135	1,328	1.27	(1.02 , 1.57)	0.03	1.33	(1.07 , 1.66)	0.01
Age 7: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	344	4,344						
Mild	311	3,775	1.03	(0.86 , 1.24)	0.71	1.06	(0.88 , 1.27)	0.52
Severe	130	1,216	1.03	(0.84 , 1.27)	0.75	1.05	(0.85 , 1.29)	0.67
Conduct problems (Normal)	347	4,263						
Mild	316	3,645	1.04	(0.88 , 1.23)	0.63	1.09	(0.93 , 1.29)	0.29
Severe	122	1,427	1.31	(1.06 , 1.62)	0.01	1.44	(1.17 , 1.79)	<0.01
Age 11: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	287	4,150						
Mild	334	3,698	1.32	(1.12 , 1.57)	<0.01	1.30	(1.09 , 1.54)	<0.01
Severe	114	1,081	1.59	(1.26 , 2.00)	<0.01	1.57	(1.23 , 2.00)	<0.01
Emotional problems (Normal)	188	2,502						
Mild	333	4,244	1.06	(0.88 , 1.27)	0.53	1.01	(0.84 , 1.22)	0.89
Severe	214	2,183	1.28	(1.04 , 1.58)	0.02	1.19	(0.96 , 1.46)	0.11
Conduct Problem (Normal)	304	4,142						
Mild	326	3,814	1.19	(1.01 , 1.40)	0.04	1.25	(1.06 , 1.46)	0.01
Severe	105	971	1.51	(1.20 , 1.90)	<0.01	1.61	(1.27 , 2.03)	<0.01
Age 11: Child Behaviour at School (BSAG)								
Emotional problems (Normal)	307	4,092						
Mild	314	3,649	1.15	(0.98 , 1.36)	0.08	1.19	(1.01 , 1.41)	0.04
Severe	130	1,290	1.36	(1.10 , 1.68)	0.01	1.40	(1.13 , 1.74)	<0.01
Conduct problems (Normal)	352	4,761						
Mild	245	2,949	1.12	(0.88 , 1.43)	0.34	0.20	(0.94 , 1.54)	0.13
Severe	154	1,321	1.52	(1.25 , 1.85)	<0.01	1.74	(1.41 , 2.13)	<0.01
Age 16: Child Behaviour at Home (Rutter A)								
Hyperactive (Normal)	486	6,153						
Mild	80	932	1.09	(0.85 , 1.39)	0.50	1.11	(0.87 , 1.41)	0.40
Severe	81	671	1.48	(1.17 , 1.88)	<0.01	1.54	(1.22 , 1.96)	<0.01
Emotional problems (Normal)	193	2,586						
Mild	301	3,645	1.05	(0.87 , 1.27)	0.58	1.00	(0.82 , 1.21)	1.00
Severe	155	1,529	1.37	(1.09 , 1.72)	0.01	1.21	(0.97 , 1.51)	0.09
Conduct Problem (Normal)	305	4,128						
Mild	245	2,949	1.19	(1.01 , 1.41)	0.04	1.16	(0.99 , 1.37)	0.07
Severe	98	682	2.00	(1.50 , 2.66)	<0.01	1.91	(1.42 , 2.56)	<0.01
Age 16: Child Behaviour at School (Rutter B)								
Neurotic (Normal)	335	4,557						
Mild/Severe	343	3,597	1.28	(1.10 , 1.49)	<0.01	1.22	(1.05 , 1.42)	0.01
Antisocial (Normal)	500	6,387						
Mild	95	1,065	1.09	(0.86 , 1.38)	0.46	1.14	(0.90 , 1.44)	0.26
Severe	82	708	1.50	(1.19 , 1.89)	<0.01	1.68	(1.32 , 2.15)	<0.01

1 Adult onset asthma or wheezy bronchitis cases; 2 With no reported cases of adult onset asthma or wheezy bronchitis

* Adjusted for sex, maternal smoking, history of pneumonia by age 7, hay fever by age 7 or 11 and eczema by age 7 or 11.

Population-attributable Fraction

The population-attributable fraction (also known as the population etiologic fraction or population-attributable risk) is an important epidemiological measure which attempts to quantify the proportion of disease incidence which is due to a particular factor (or "exposure"). We computed the population-attributable fraction for all the childhood psychological factors that had significant direct effect in the mediation model, adjusting for all the possible confounders. Estimating the attributable fraction from within a logistic regression framework enables confounders to be taken into account and allows estimation of the summary attributable fraction for a set of exposures. The population-attributable fraction were calculated using the methods described by Buzzi *et al*. (1985) with slight modification including computation of the confidence interval as presented by Greenland and K. Drescher (1993), and implemented in Stata program, `aflogit` (Brady, 1998).

Table B 17: The population-attributable fraction (AF) with 95% CIs for the effect of childhood psychological factors on self reported diabetes and adult onset asthma from age 17 to 42 years in the NCDS.

Disease	Psychological factor	AF	95 % CI
Self Reported Diabetes	Age 11 (BSAG)		
	Emotional problems	0.169	[0.080 , 0.252]
	Conduct problems	0.237	[0.157 , 0.315]
Adult-onset asthma	Age 11 (Rutter A)		
	Conduct Problem	0.053	[0.025 , 0.080]
	Age 11 (BSAG)		
	Conduct problems	0.071	[0.038 , 0.103]
	Age 16 (Rutter A)		
	Conduct Problem	0.110	[0.068 , 0.150]
	Age 16 (Rutter B)		
	Neurotic	0.056	[0.020 , 0.091]
	Antisocial	0.033	[0.014 , 0.052]