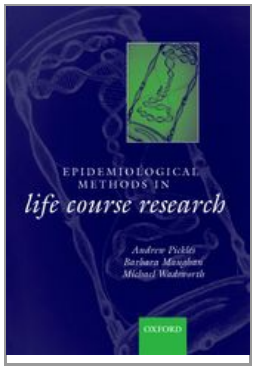

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Andrew Pickles, Barbara Maughan, and Michael Wadsworth

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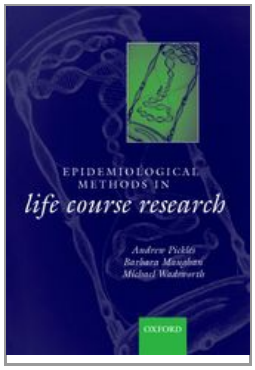

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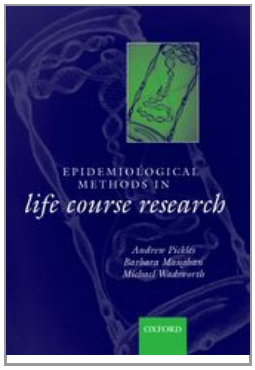

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(p.xi) Preface

Although we tend to think of life course epidemiology as a recent development, in practice, pointers to life course effects began to emerge from some of the earliest epidemiological studies of individual differences in health. Widdowson, for example, asked why children having identical diets in two orphanages gained height at different rates, and found the adverse effect on height growth of a negative emotional environment.[1] Dubos *et al*. showed that 'when newborn animals are nursed by mothers fed diets that are slightly inadequate, their size remains subnormal throughout their lifespan, even though the young are fed an adequate diet after weaning. A similar depression of growth can be produced by subclinical infections shortly after birth'.[2] Reid presented evidence suggesting that the beginnings of adult-onset bronchitis might lie in childhood,[3] while Illsley and Kincaid noted in the findings from the first British national perinatal mortality study the 'strong implication that physical growth and development are related to later obstetric performance'.[4] In an article entitled *Biological Freudianism*, Dubos *et al*. concluded that 'socially and individually, the response of human beings to the conditions of the present is always conditioned by the biological remembrance of things past'.[2]

What distinguishes these researchers as forerunners of what is now called life course epidemiology is their pursuit of answers across different kinds of data sources and investigative methods, including ecological studies that looked at risk in age cohorts as

children and adults, natural experiments, migration studies and follow-up studies. Like their predecessors, today's life course epidemiologists, whose scope, concepts and findings are brought together by Kuh and Ben-Shlomo in the first volume of this series,[5] use a wide range of investigative methods, have ingeniously sought new opportunities for quasi-experimental design and have patiently developed new sources of life course data. Our intention in this volume is to describe the methods now used and being developed to study individual differences in reaction to adverse exposures across the life course, and the mechanisms by which risk factors may influence present but, in particular, future health, that is the essential temporal and developmental aspect of life course epidemiology. A second, and equally strong theme is that of the permeability of health domains: the pervasive effects of stress on both psychological and physical health, the widespread occurrence of co-morbidity and the frequent co-occurrence of risk factors of varied kinds and environments that are toxic for a wide range of health outcomes. A third and increasingly important theme is the incorporation of genetics into aetiological models and analysis—and in particular in a form that progresses beyond the unproductive antithesis of nature versus nurture to investigate gene–environment interplay. The demands presented by these last two themes result in an **(p.xii)** additional distinctive feature of much of life course epidemiology, namely its highly interdisciplinary character—an appreciation that an understanding of disease aetiology will not come from any one discipline alone, and a recognition of the need to be familiar with the concepts and putative aetiological mechanisms of disciplines beyond one's own.

As a consequence, we have neither disease-specific chapters nor chapters concerning single disciplines, such as methods for genome-wide screening for disease loci. Instead, for the most part, each chapter focuses on a cross-cutting theme elaborating issues such as measurement, design and analysis likely to be important in interdisciplinary studies of almost any disease.

The book falls into two main parts, the first broadly concerned with design and measurement, the second with methods of analysis. Chapter 1 provides an overview of models of the development of risk throughout the life course, and how data sources to test these models are being developed. Chapter 2 deals with traditional and some new designs and measurement considerations for studies that focus on individual differences and processes. In contrast, Chapter 3 focuses on design and measurement in studies that examine mechanisms beyond the individual, where social interaction and context are key. Chapter 4 examines the promise of the very large (primarily cohort) studies, with designs that have been driven by the search for genetic effects, that are currently receiving heavy investment in a number of countries. Chapter 5 examines the conceptual background, potential scope and design of intervention studies of interest from a life course perspective.

The second part of the book deals with analytical issues. A common question for much life course analysis is how to analyse the effects of a time-varying exposure. Chapter 6 explains some of the complexities of this comparatively simple problem, and describes and illustrates simple and reliable solutions. Chapter 7 surveys alternative treatments for the

ubiquitous problem of missing data. Life course research questions frequently involve a profile of health outcomes (either over time, or over a set of outcomes), that have both shared and distinctive predictors. The research questions are also often developmental, with a concern to identify pathways that might involve precursor stages, mediating variables and chains of effect. A central theme of Chapter 8 thus concerns analysis of a multivariate outcome and of sets of linked equations. However, the traditional concern of epidemiology to take account of the effects of confounders remains, and although life course data allow some new possibilities for tackling this problem, they also bring additional complexities of their own. Thus this chapter is also concerned to outline the range of approaches, both new and older, some more conceptual others more technical, that tackle different versions of the problem of estimating causal, as distinct from mere associational, effects. These include structural equation modelling and marginal structural modelling. Chapter 9 surveys the range of approaches that can be used for the analysis of event data, from the various forms of survival analysis, to trajectory analysis that yields a typology of developmentally distinct patterns of onset.

Finally, in the light of the arguments put forward in this volume, in an Afterword we briefly review the methodological challenges and difficulties of life course epidemiology, describing both the progress achieved thus far, and the work that remains to be done.

(p.xiii) Preparation of this volume has been very much a joint enterprise. First and foremost, our thanks are due to our contributors, who responded so willingly to the request to share their expertise in life course research. In addition, we are grateful to the Series Editors for their encouragement and constructive guidance; to colleagues at the University of Manchester, the Institute of Psychiatry and the MRC National Survey of Health and Development for discussions that have shaped our thinking on life course issues over many years; to Angela Butterworth, Helen Liepman and Georgia Pinteau of OUP, for their expert help in smoothing our way through the production process; and to Sally Cartwright and Wendy Lamb, who assisted in several unenviable tasks with such care and good humour.

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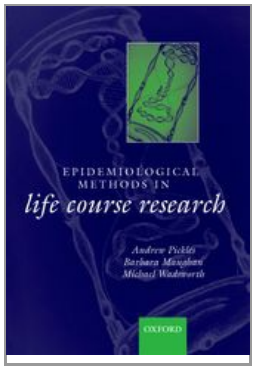

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Introduction: development and progression of life course ideas in epidemiology

Michael Wadsworth
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[–] Abstract and Keywords

Increasing demand for life course data and life course findings requires developments in methods of modelling life course trajectories and analysis of life course data. This chapter illustrates the progression of ideas in epidemiological life course studies, and the main strands of thinking about how risk develops and is modified. Innovative methods for obtaining life course data are described, and the reasons for development of new sources of life course data are outlined.

Keywords: life course concepts, causal models, data sources, life course trajectories

Abstract

Increasing demand for life course data and life course findings requires developments in methods of modelling life course trajectories and analysis of life course data. In this

chapter, we illustrate the progression of ideas in epidemiological life course studies, and the main strands of thinking about how risk develops and is modified. Innovative methods for obtaining life course data are described, and the reasons for development of new sources of life course data are outlined.

1.1 Introduction

For centuries there has been a fascination with the processes of human development and the extent to which early life influences adulthood. It is, however, only of relatively recent times that the subject has been systematically addressed. The social sciences and psychology have taken a broad approach to lifespan influence and development, ranging from Freud to Terman and Oden[1] to Elder.[2] The life sciences concerned with human mental health and development also have a long history of systematic research into life course effects,[3–7] as do those concerned with human physical health.[8–11]

Over the last 25 years, epidemiological thinking about life course processes has developed considerably. Studies of physical health have progressed from ecological comparative investigations of health and mortality in specific geographic areas at different historical times,[12,13] to identification of pathways over long periods of life,[11,14] and to hypotheses that suggest biological processes that may explain how the effects of environmental exposures and individual characteristics appear to affect biological function and disease risk.[15] In mental health, these kinds of studies have, in addition, shown direction and reversibility of effect, particularly in childhood[16] and in later life.[17]

These new insights have been facilitated by, and have also prompted, new approaches to data acquisition. New sources of data have been found for opportunistic use, for **(p.2)** example follow-up of individuals who experienced serious difficulties likely to impact on health,[18,19] and the follow-up of populations identified from routine health or demographic records.[20,21] Life course studies that accrue new data have also greatly improved. The objective is no longer solely to identify illness and risk of illness, but also to measure function in order to study pathways to functional change with age.[7,11] For example, clinically validated scales have been developed that allow reliable identification of minor mental health problems, and screening for more severe ones, in large-scale studies.[22–24] Scales to measure memory and other aspects of cognitive function have been developed for use in studies of cognitive ageing,[25] and measures of well-being are being developed.[26] Improved measures of the social environment have been devised to capture, for example, the extent of social integration and support at the individual level[27] and in international comparisons.[28] More easily useable, valid and reliable biological measures have also been developed, for example of cardiovascular function,[29] and the collection of source material for making DNA can now be undertaken at home visits by data collectors with little training, or by self-administration.

During the same period, life course analysis methods used by epidemiologists have progressed from basic regression-based methods to those concerned specifically with the requirements of long-term epidemiological studies. Identification of life course pathways has been helped by development of methods such as latent class analysis,[30] and by multilevel modelling, sensitivity methods and Cox modelling.[31,32] Missing cases

and missing values, that tend to become an increasing problem as long-term studies continue, are no longer simply omitted from analyses. Instead, as discussed in Chapter 7, cases are weighted, values multiply imputed or partial records included using increasingly sophisticated analysis methods that allow for varying degrees of selective loss.[32–34]

New demands for life course epidemiological studies of health, and new approaches to study design, are being driven essentially by three sources of influence. First is the increasing pressure to understand the processes of development of disease risk and of physical and mental ageing as the demographic structure changes, and as the care of chronic illness and disability, and the drive to prevent them early in the disease risk process, become dominant health activities. Second is the general acceptance that early life physical and mental development play a part in relation to most if not all outcomes of epidemiological concern, and need to be taken into account in life course approaches. Third is the new accessibility of genetic information about individuals.

The aim of much new life course epidemiological research is to replicate findings and re-test them in other social, geographical and historical contexts, and to investigate the roles that gene–environment interplay and gene–gene interactions play in life course pathways to disease risk and disease. Most of the existing data sources that have genome and good phenome characterization are on the margins of statistical viability because of their sample size.[35],[36] Consequently, studies of this kind now need to pool existing life course data resources, and in the long run also to use the new and much larger sample size data resources in study samples currently in childhood or adolescence or in studies that are just beginning.[37]

The concern of this book is to show how life course epidemiology is handling the implications of the new demands through development of methods of measurement, and of data management and analysis. This first chapter sets the scene by outlining **(p.3)** the development of life course thinking using examples from research on physical and mental health, and summaries of work on the measurement of the development of risk and resilience, and of how research has coped with the reality of less than perfect measures.

The second section of the book is concerned with study design in terms of measurement, dealing first with methods of studying individual differences, next with measurement of the effects of the social environment, and then with the new large-scale study designs, with genetically informed designs, and with the methods used in life course intervention epidemiology.

The third section reviews both conventional methods used in analysis of life course epidemiological data and the innovative methods required when using data covering many years of life.

1.2 Three summary examples of the development of life course ideas

1.2.1 A biological example

The biological example concerns cardiovascular health. Since this problem usually becomes evidently symptomatic in later middle life or the later years, and is manifest earlier in men than in women, the original British epidemiological prospective research into cause used samples of men and began in middle life, as did some important successor studies;[38,39] in the USA, the Framingham study was at that time a notable exception.[40] Risk was sought in obesity, current habits of diet, exercise and smoking, and in personality and temperament. Later, two ideas suggested the possible earlier beginnings of risk of cardiovascular disease, each concerned with exposure to a changing environment. Forsdahl[12] wondered whether children born in times of scarcity who did not grow well were then in effect programmed to handle poor diets. If they lived their adult lives in times of plenty, they would be more inclined than others to become obese adults and at risk earlier than others of raised cholesterol levels. Barker[13] observed in demographic statistical data that geographical areas of high premature heart disease mortality also had high infant mortality, and wondered whether the two phenomena were related. Migration studies showed that those born in low risk geographical areas tended to carry that level of risk, even after migrating to higher risk areas,[41] although that was not true of all kinds of risk.[42] Then came long-term follow-up studies that showed indicators of poor growth in early life (usually using low weight at birth) to be associated with raised risk of adult heart disease.[10,43] The biological programming hypothesis developed from that work stated that the lifetime resource of biological functional capacity was established in pre-natal and early post-natal life, and that subsequent challenges to that resource conditioned disease onset.[10] Subsequent work then asked what affected growth in early life, and what made the individual vulnerable initially to poor growth and to later challenge.[21] Consequent modification of the programming hypothesis was achieved by showing that the pathway from poor growth and poor socio-economic circumstances in early life to the disease outcome was influenced by other forms of risk, particularly that involving chronic exposure to stressful psychological and socio-economic circumstances in childhood and **(p.4)** also in adult life.[44–46] Now new life course hypotheses about the development of heart disease risk have been developed that propose biologically plausible links between growth, the socio-economic environment and in particular exposure to chronic stress, using the hypothalamic–pituitary–adrenal (HPA) axis.[15] This is one of the first working examples of programmed progression. It helped to progress understanding of an apparent discontinuity between early life effects and later outcomes, and to explain individual variation in risk impact. Similarly Whincup *et al*.[47] point out the imprecision of earlier blood pressure measures in explaining intra-individual variation. New current work that is concerned with genetic sources of risk and their interaction with environmental exposures will continue that work.[37]

1.2.2 A psychological example

In contrast to much chronic physical disease, many severe psychiatric disorders—such as autism and hyperactivity—onset early in childhood; rates of others—such as depression—rise sharply in adolescence. We take depression as our ‘psychological’ example here. Like most psychiatric disorders, depression is now considered to be multifactorially determined: heritable influences are important, cognitive/psychological vulnerabilities are often evident, and many episodes are immediately precipitated by

exposure to adverse life events or stress. From Freud onwards, however, theorists have also posited that early experience is a key determinant of vulnerability. Over time, empirical studies have tested and refined models deriving from this approach. In part, these efforts have focused on identifying the *source* of early risk: notions that parental loss might be the key element, for example, have gradually given way to an awareness that inadequacies in parental care are likely to constitute one core feature. Secondly, investigators have attempted to clarify the *mechanisms* whereby early adversity contributes to later risk. Brown and his colleagues,[48] for example, have proposed two pathways, one 'internal', operating via psychological vulnerabilities laid down in childhood, the second 'external', whereby adverse childhood social conditions operate via environmental or behavioural pathways to increase risks of later exposure to adult stress. Where childhood exposures are severe—as, for example, in the case of physical or sexual abuse—evidence now suggests that biological systems, including HPA function, may also be affected. Though depression *per se* is rare in childhood, it is now clear that depressed adults have often shown other emotional and/or behavioural difficulties earlier in development,[49] and prospective studies suggest that childhood risks may be especially salient for early onset of depression, beginning in the early to mid teens.[50] As with many physical disorders, the experience of a first episode of depression may also influence later risk: evidence suggests, for example, that associations with 'triggering' life events are stronger in first episodes than for recurrences, suggesting either a 'kindling' effect, whereby sensitivity to stressors is reduced as time goes on, or an increased stress sensitivity such that with repeated episodes, much more minor stressors are sufficient to trigger effects.[51]

1.2.3 A social example

Studies of antisocial behaviour and crime provide a third example of the insights emerging from a life course approach. Here, age trends typically follow a different pattern from **(p.5)** that for chronic disease: in most Western societies, for example, rates of antisocial behaviour are relatively low in childhood, rise steeply in the teens, then fall again in the 20s and 30s. Cross-sectional studies in adolescence (the peak period for 'participation' in antisocial behaviour) have highlighted a plethora of potential risks. Criminologists were also, however, among the first to undertake long-term longitudinal studies, tracking outcomes for antisocial children later in life. These longitudinal data highlighted an apparent paradox. Looking backwards from adulthood, continuities in antisocial behaviour were strong: almost all severely antisocial adults have been antisocial in childhood. Looking forwards from childhood, in contrast, only about a third of antisocial children went on to have major criminal histories later in their lives,[52] although childhood exposure to parental separation has been show to be associated with a range of internalizing and externalizing outcomes.[53] Over time, attempts to reconcile these observations led to evidence that the overall 'pool' of antisocial individuals is made up of distinct subgroups, each with quite different developmental histories and sources of risk.[54] Childhood onset difficulties, for example, are often associated with both individual and environmental risks: neuropsychological deficits and adverse temperamental features appear to interact with adverse rearing environments to contribute to risk for 'life course persistent' antisocial behaviour. Adolescent onset difficulties, in contrast,

seem predominantly socially determined, with peer influences and the adolescent 'maturity gap' playing key roles. As these issues have been clarified, so new life course questions have emerged. At the time of writing, two such questions are attracting particular attention. First, what accounts for the well-nigh universal desistance from crime observed in most individuals at some stage in adult life? Do childhood risk factors still predict behavioural trajectories later in development, or, as some investigators[55] have argued, do new adult experiences constitute the crucial 'turning points' that redirect trajectories later in life? Secondly, what accounts for the high rates of *heterotypic continuity* to risk for other mental health problems—including phenomena as seemingly diverse as depression and schizophreniform disorders—now known to be later sequelae of childhood and adolescent conduct problems?[49]

1.3 The progression of ideas in epidemiological life course analysis

These three examples show how initially observation, both clinical and epidemiological, began the progression of development of life course hypotheses. Explanations were then sought at the individual level for the nature and development of risk, why risk varied with age, what were the 'drivers' and transmitters of risk, and what were the modifiers of risk. The main arguments concerned with the development of risk are now summarized.

1.3.1 Critical and sensitive periods

Explanation for why risk was greater at particular ages in life asked whether it was because these were life stages uniquely sensitive to the processes hypothesized to be the sources of risk, and if so whether that was the result of intrinsic processes (e.g. because cellular development has a unique developmental period), extrinsic influences (e.g. exposure to poverty), or an interaction between them.

(p.6) The concept of developmental stages is fundamental in both biology and psychology. It refers, in terms of age, to windows of opportunity during which a particular form of development normally occurs. Those windows are referred to as critical or sensitive periods: those terms are sometimes used interchangeably: critical in this context implies irreversibility.

Life course epidemiological studies of physical health in Britain initially suggested that factors that affected developmental progress *in utero*, particularly concurrent maternal health and the supply of nutrient to the fetus, were in effect also programming the future of the fetus in terms of functional capacity throughout the whole of life. This is known as the *biological programming hypothesis*.[13] The implication of determinism that the hypothesis originally carried was modified by the recognition that the environmental and social context of the critical or sensitive period was usually a defining aspect of the nature of the effect, and an indicator of how its effect was likely to continue. For example, poor maternal nutrition and exercise and maternal smoking that had adversely affected cardiovascular fetal development during a critical period of pre-natal development would also be likely to influence post-natal growth in adverse ways. Rutter *et al*.[16] further differentiated two kinds of developmental programming, experience-expectant and experience-adaptive. In experience-expectant developmental programming, 'normal

somatic development *requires* particular experiences during the relevant sensitive phase of development if the somatic structure is to be laid down'.[56] Visual development is given as an example in which appropriate visual stimulation during early infancy is necessary for normal visual development. In contrast, in experience-adaptive developmental programming, 'somatic development, both structural and functional, is shaped by the specifics of experiences during a relatively sensitive phase of development in such a way that there is optimal adaptation to the specifics of that environment'.[57,58] This is exemplified by the effect of early life subnutrition that programmes the individual to function with low nutrition and thus for risk if richer diets are subsequently encountered.

Boyce and Keating (2004) describe sensitive and critical periods in neurological development in this way:[59]

> All the basic pathways involved in human emotion, volition, movement, and thought are already in place at birth, awaiting the experiential input that will propel latent pathways into the neural substrates of individual personalities, predispositions, talents and failings. Over the course of the next several postnatal months, this rich neural network is progressively 'pruned', selectively eliminating neurones (through apotosis, or programmed cell death) and synapses from the less utilised pathways and circuits. It appears that this process of neural elimination is as essential to the emergence of normal intelligence, behaviour, and mental functioning, as is the stage of neuronal proliferation that precedes it in fetal life.

Thus, a process of interaction between the developing organism and the environment, described by Boyce and Keating in the quotation above as 'experiential input', continues to affect the developmental course well after birth.[59] In some processes, such as height growth, that process continues until the late teenage years.

However, for some functions, one characteristic of early development continues to be detectable in the form of *tracking*. Tracking of some aspects of physical function (e.g. blood pressure, respiratory function) as well as cognitive function, refers to the likelihood **(p.7)** of the individual remaining in the same sector of the measurement distribution at the population level throughout adulthood. Tracking implies that biological programming, in its original sense, is a valuable concept. However, it does not necessarily imply that a function cannot be modified, as shown by the rapidly increasing prevalence of medication that effectively modifies blood pressure.

Similarly the childhood social environment can also have a long-term effect, but the processes by which it does so are greatly varied. The processes are likely to include adverse continuing circumstances that retard physical and cognitive growth and development, such as poor nutrition, emotional insecurity and inconsistency, low intellectual stimulation, and parental smoking. In the long run, not all effects of adverse childhood circumstances are irreversible, and some forms of intervention to counteract adverse childhood circumstances seem very effective.[18,47,60] Effects of early life interventions are not necessarily measurable on a short time scale, and long-term life course studies have yet to show whether apparent reversal or mitigation of adverse

childhood effects is sustained over many years of life.

Resilience is not yet a well-defined working concept in life course epidemiology. Resilience in the sense of resistance to vulnerability, has been shown to be associated, for example, with the quality of enduring relationships with partners and with high self-esteem. Childhood origins of such resilience have been found in habitual pro-social behaviour in the developmental period.[61] Examples of such resilience have been described by Rodgers,[62] Bifulco and Moran,[63] and Ryff *et al*.,[64] who showed that women vulnerable to adult depression because of emotionally disturbing experience in childhood were resilient to that risk if they were in a stable relationship in adult life. Resilience, in the sense of resistance to circumstances that are sources of health risk for many, has been shown in perceived high control of and reward from work circumstances,[65] but little is yet known about whether these perceptions originate in childhood. It has been suggested that chains of protection may develop from childhood 'that predispose towards the pursuit of health-protective developmental trajectories'.[59]

Pathways from early life to adult health have generally been modelled either in terms of a *latent effect* of an adverse impact in a critical or sensitive period, or in terms of a position on a *pathway* that begins at that time.[66] Latent effect models describe a source of vulnerability established during a critical period and eventually triggered into effect by an additional problem encountered later on in life, or by age. Pathway models, in contrast, describe the processes in terms of accumulating risk or cascades of risk, in which health risks or adverse social circumstances increase vulnerability to subsequent health risks and problems.

1.3.2 Development of risk

As these models imply, life course studies are also characterized by a focus on the development and elaboration of risk—whether biological, social, psychological or behavioural—throughout the life course. Effects associated with the biological processes of development, growth and ageing are considered in conjunction with the unfolding effects of life course variations in social circumstances, in psychosocial strengths, supports and vulnerabilities, **(p.8)** and in the development of health-relevant behaviours, to build a comprehensive picture of age-related influences on health and disease. This emphasis on the development or *accumulation* of risk across the life course has proved important in two complementary ways. First, exposures at critical or sensitive developmental periods may be modified by later exposures: research in coronary heart disease, for example, has shown that associations with low birth weight are especially marked, and sometimes only apparent, in individuals who become obese later in life.[67] Similarly Rodgers showed that in women, vulnerability to depression was established through childhood experience of parental separation that was only triggered into depression by adult experience of separation from a partner.[62] Secondly, even in the absence of critical or sensitive period effects, risks may cumulate across development, with the number and/or duration of exposures gradually incrementing the overall burden of risk. Figure 1.1 (adapted from Kuh *et al*.[68]) provides a schematic illustration of some of the differing patterns of risk accumulation that have been described.

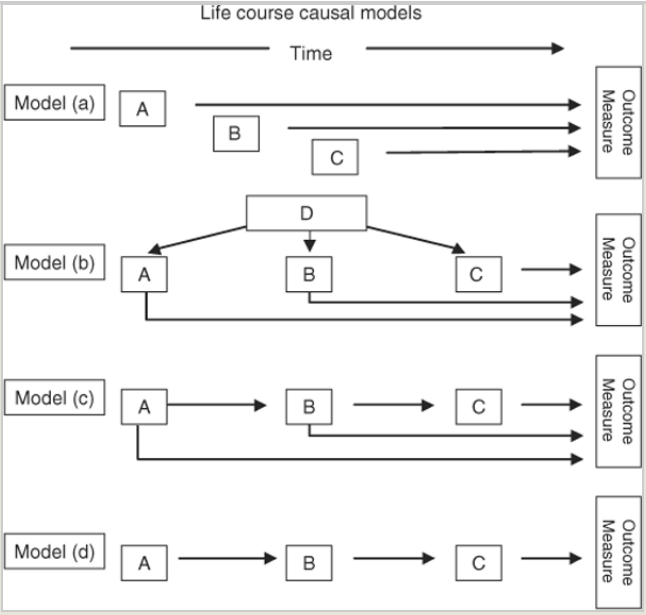

Fig. 1.1 Life course causal models.

(p.9) Model (a), the simplest account, shows differing sources of risk emerging at different stages in the life course, each exerting independent, additive effects. Though some risk effects doubtless follow this pattern, empirical findings suggest that the more complex scenarios illustrated in later models are in practice far more typical. Model (b) illustrates a *clustering* of risks, whereby an exposure at one life stage gives rise to a range of more specific risk processes. Poor social circumstances in childhood, for example, may contribute to risk for later respiratory disease through a variety of different processes, some environmental (through poor early nutrition, or exposure to effects of passive smoking), some biological (through effects of intrauterine growth on lung development and risk of early infection) and some behavioural (through increased risk of later smoking or poor diet).

In Model (b), each of these pathways has distinct and separable effects on disease outcome. Models (c) and (d) illustrate more complex patterns, whereby early risk factors impact not only on final disease outcome but also on the likelihood of later risk exposures. To pursue our socio-economic status (SES) example: poor childhood SES may contribute directly to risk for lung disease through exposure to early adverse environmental conditions. Low SES may also, however, influence progress on other risk pathways—constraining educational attainments, for example, or affecting the development of poor health behaviours—which, later in the life course, may contribute independently to risk. *Pathways* models of this kind have attracted increasing attention in charting the elaboration of risk processes for a wide range of both physical and mental health outcomes. In relation to mental health difficulties, behavioural styles set up in childhood may function to 'select' individuals into stress-prone environments (physical, social or relational) later in life. Severe antisocial behaviour in childhood, for example, is known to have wide-ranging effects on later social functioning, spanning problems in employment, in making and maintaining close relationships and in increased risks of alcohol and drug