From Developmental Origins of Adult Disease to Life Course Research on Adult Disease and Aging: Insights from Birth Cohort Studies

Chris Power,[1] Diana Kuh,[2] and Susan Morton[3]

[1]MRC Center of Epidemiology for Child Health/Center for Pediatric Epidemiology & Biostatistics, University College London Institute of Child Health, London WC1N 1EH, United Kingdom; email: christine.power@ucl.ac.uk

[2]MRC Unit for Lifelong Health and Ageing, London WC1B 5JU, United Kingdom

[3]Centre for Longitudinal Research—He Ara ki Mua, University of Auckland Tamaki Campus, Glen Innes, Auckland 1743, New Zealand

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Abstract

Maturation of long-running birth cohort studies has fostered a life course approach to adult health, function, and disease and related to conceptual frameworks. Using broad concepts of human development including physical, cognitive, and emotional function, birth cohorts provide insights into the processes across the life course and between generations that link to adult outcomes. We discuss findings on the determinants and health consequences of lifetime trajectories of body size, cognitive and emotional function, and socioeconomic position. Findings from the studies suggest that, for some adult health outcomes, explanations will be incomplete unless exposures and processes from across the life course are taken into account. New birth cohort studies are poised to delineate further the nature and timing of life course relationships in contemporary generations of children.

INTRODUCTION

CVD: cardiovascular disease

Research on the developmental origins of adult disease is broad in scope, embracing many scientific disciplines, exposures, and outcomes. Such research recognizes the potential for influences on early-life development to lead to changes that impact on disease risk decades later in adulthood. This developmental perspective is long-established within some disciplines, for example, those concerned with emotional and cognitive function, but for other disciplines it is relatively recent. A major impetus to developmental origins research was provided in the early 1980s by a series of studies linking low birth weight, as a proxy for poor prenatal growth, to increased risk of chronic diseases in adulthood, including cardiovascular disease (CVD) and diabetes (the fetal origins hypothesis) (2). Earlier in the past century, investigators were interested in early environmental influences on the individual's constitution that might affect later mortality risk (52). Nonetheless, the fetal origins hypothesis represented a shift in emphasis for research on adult chronic disease, which had focused largely on adult lifestyles. Emerging research over the past three decades has led to a convergence of evidence on the wide-ranging effects of early environment and associated development for later health outcomes (50, 99) and to establishment of the International Society for Developmental Origins of Health and Disease in 2003.

Birth cohort studies established some decades ago have been well positioned to investigate developmental origins hypotheses, and in turn, these hypotheses have provided a stimulus for the establishment of new cohorts. There are now several birth and infancy cohorts in Britain, New Zealand, Finland, and elsewhere, including those established in the past few years and longer-running studies with follow-up in some instances of five or more decades. Basic details of some of these studies are given in **Table 1**; the list is far from comprehensive but illustrates the range of birth dates, length of follow-up, and original study purposes. Both younger and older studies alike have tended to collect information on parental characteristics and social and family background, as well as conditions during pregnancy and in early childhood. In addition, many older studies have assessed the physical, cognitive, behavioral, and emotional development of their participants and collected information on social destinations, lifestyles, and other putative influences on later disease risk. In recognition of the importance of charting early developmental milestones and trajectories (see sidebar on Trajectories), some younger cohorts have been instigated during pregnancy rather than at or soon after birth and also have more frequent contacts early in childhood than did some older studies. Longer-running studies have been able to investigate influences across developmental domains (physical, cognitive, emotional) in relation to health in later life, and with information collected at different life stages, these maturing birth cohorts have fostered a life course approach to adult disease. The objective of a life course approach in epidemiology is to establish how social and biological factors operating at different stages of life and across generations contribute to the development of adult health and disease over time (52). With its consideration of different ages, life course research seeks to understand influences of early-life exposures and development on later disease outcome and the processes occurring in the intervening years of life that link them. Thus, life course epidemiology extends the developmental origins of adult disease perspective by focusing attention on potentially sensitive

TRAJECTORIES

"A trajectory provides a long-term view of one dimension of an individual's life over time. These may be social states (such as work, marriage, socioeconomic position), psychological states (such as depression) or physiological states (such as lung function). Implicit is the idea of a normative trajectory around which individuals deviate" (52). For health function, a trajectory may include a period of gain to a peak followed by a period of decline (e.g., for lung function).

Table 1   Selected birth (or infancy) cohorts[a]

Cohort name/country	Year of birth	Selection/design	N at baseline	Follow-ups (timing)	N at last sweep (%)	Initial reason for/focus of study
National Survey of Health and Development/Britain (54, 108)	1946	Socially stratified sample of singleton babies born in one week, March 1946, to married women	5,362	Birth, 2, 4, 6, 7, 8, 9, 10, 11, 13, 15, 19, 20, 22, 23, 26, 31, 36, 43, 47(F), 48(F), 49(F), 50(F), 51(F), 52(F), 53, 54(F), 60–64 years	2,661	To consider cost of and care in pregnancy and childbirth. Social class differences in maternal and child mortality and morbidity
National Child Development Study/Britain (77)	1958	All born in one week, March 1958	17,638	Birth, 7, 11, 16, 23, 33, 42, 45, 46, 50 years	9,790	To identify social and obstetric factors linked to stillbirth and neonatal death
Aberdeen Children of the 1950s Study/Britain (62)	1950–1956	All primary-school children in Aberdeen in 1962	12,150	Perinatal[b] (linked), 7, 9, 11, 45–50 years	7,655	To understand predictors of low childhood cognition
Northern Finnish Birth Cohort Study/Finland (87)	1966	Live born, European descent, with expected birth dates in 1966, Oulu and Lapland (northern Finland)	12,058	Pregnancy, birth, 1 year, 14 years, 31 years	8,690	To examine risk factors for childhood mortality and morbidity in a geographically defined population
1970 British Birth Cohort Study/Britain (20)	1970	All born in one week, April 1970	16,571	Birth, 5, 10, 16, 26, 30, 34, 42 years	9,656 at 34 years	To examine the social and biological characteristics of mothers in relation to neonatal morbidity
Dunedin Multidisciplinary Health and Development Study/New Zealand (98)	1972	All births in Dunedin March 1972–April 1973 enrolled at 3 years	1,037	3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32 years	972	To conduct a longitudinal population-based multidisciplinary study of child health, development, and behavior
Christchurch Health and Development Study/New Zealand (24)	1977	Children born April–early August 1977 in Christchurch	1,265	Annually from birth to 16, 18, 21, 25, 30 years	934	To conduct a longitudinal birth cohort focused on child health and development
Avon Longitudinal Study of Parents and Children (ALSPAC)/England (7)	1991–1992	Offspring of all pregnant women in the county of Avon, estimated delivery date April 1, 1991—December 31, 1992	15,247 eligible pregnancies enrolled	68 time points, birth to 18 years	7,729[c]	To investigate modifiable influences on child health and development

(*Continued*)

Table 1 *(Continued)*

Cohort name/country	Year of birth	Selection/design	N at baseline	Follow-ups (timing)	N at last sweep (%)	Initial reason for/focus of study
Southampton Women's Survey/England (44)	1998–2007	Births to recruited 12,583 prepregnant women	3,156	Prepregnancy, pregnancy (multiple), 6 months, 1, 2, 3, 4, 6, 8 years	1,477 at 6 years	To understand perinatal and early life determinants of children's growth and development
Millennium Cohort Study (MCS)/United Kingdom (14)	2001	Nationally representative sample across United Kingdom recruited during infancy	19,244	9 months, 3, 5, 7, 11 years	15,590 at 7 years	To understand the biological and environmental determinants of contemporary child development

[a]Note: This list of studies is not exhaustive. Birth cohorts documented have collected perinatal information and have existed for long enough to provide sufficient longitudinal data to inform the areas addressed in this article. The success of older cohorts has provided the impetus for many new birth cohort studies begun around or after the turn of the millennium. Newer studies include those in the European Child Cohort Network (EUCCONET), as well as studies in Australia (Growing Up in Australia—LSAC) and New Zealand (Pacific Island Families Study and Growing Up in New Zealand). EUCCONET includes the Norwegian Birth cohort (MoBa), Danish National Birth cohort, Generation R Study (The Netherlands), Born in Bradford (United Kingdom), Millennium Cohort study (MCS), Growing Up in Scotland (GUS), Growing Up in Ireland (GUI), ELFE (France) and will include a newly planned UK study.

[b]The Aberdeen Children of the 1950s Study is included here because it has birth information for the 14,932 children who were part of this cohort. However, they were enrolled between ages 5 and 11 years (in 1962), and perinatal data were linked for the cohort at that time.

[c]Completing ≥1 item during the transition to adulthood.

periods in childhood and adolescence as well as in the prenatal period. It extends the adult lifestyle theories of chronic disease by focusing attention on the early acquisition of lifestyle and its cumulative effects. It extends social causation theories of adult chronic disease by drawing attention to the impact of the socioeconomic environment in childhood as well as adulthood. It also extends both developmental origins and adult theories of disease causation by considering the joint action of early and later exposures.

With an increasing number of studies and duration of follow-up, birth cohorts are now charting new territories. Some recently established cohorts are focusing on understanding early development in the wider neighborhood and societal context (69). Older birth cohort studies, often with decades of information, are examining influences on the population range of functional capacities and disease risk into later adulthood, and an agenda on life course influences on aging is already emerging. Many birth cohorts now incorporate genetic factors

and are contributing to the discovery of genetic variants associated with important phenotypes (e.g., obesity) through consortia for genome-wide association studies. Moreover, the cohorts offer the prospect of advancing understanding of (epi)genetic influences on developmental trajectories and how these relate to the potentially modifiable environmental context.

At a time when birth cohort studies are evolving to address a range of social, economic, and health questions, it is timely to critically review their contributions and identify future challenges. This article does not purport to provide a comprehensive summary of the vast literature from these cohorts, but it considers some main themes of relevance to public health. Specifically, we consider examples of where birth cohorts have stimulated thinking about the life course frameworks that might guide research on pathways to adult disease and where, in this regard, they have added new knowledge. Evidence from the studies has been informative on many important themes,

e.g., on the natural history of some conditions, long-term outcomes of specific pregnancy exposures/characteristics, and determinants of healthy lifestyles, but we do not cover these themes in any detail here. Instead, we summarize some of the work on the following in relation to adult function and disease: lifetime socioeconomic position (SEP), lifetime growth trajectories, and cognitive and emotional development at different life stages. For each of these research areas the birth cohorts have contributed a substantial body of empirical evidence. With the exception of lifetime SEP, which to some extent can be investigated retrospectively, associations for growth, cognition, and mental health can be assessed only with prospectively obtained measures at different life stages.

CONCEPTUAL FRAMEWORKS

Conceptual frameworks have been developed to guide research on the life course processes leading to adult disease. Investigators have proposed various general models that have then been adapted and applied to different health outcomes. Although such frameworks have been used in other contexts (e.g., record linkage studies), they are particularly relevant in the investigation of birth cohorts.

Figure 1 provides an example of a general framework, with main components that are often considered in life course research. This simplified representation incorporates intergenerational factors, developmental domains (cognitive, emotional, and physical), social identities and health behaviors, and environmental influences that potentially act at all life stages to affect later health. **Figure 1** is presented to highlight five main points. First, birth cohort studies, in general, can focus on determinants of the full spectrum of both health and disease in a population. Second, life course trajectories for body functions (e.g., muscle function, lung function) are a dynamic way to study lifetime influences on health and disease; these trajectories capture the natural history of biological systems that grow and develop rapidly

LIFE COURSE MODELS OF ADULT DISEASE OUTCOMES

The critical period model (also called biological programming or latency model) refers to exposures acting during a critical window of development that affect the structure or function of organs, tissues, or body systems and which, in turn, affect later disease risk. This model underpins the fetal origins of adult disease hypothesis. Sensitive-period models are similar, with exposures exerting greatest effects during times of rapid development, but there is greater scope for modification by other influences than there is with a critical period model.

The accumulation of risk model refers to the adverse effect on later disease of exposures accumulating over the life course. It thereby focuses on total burden of insults, i.e., the number, duration, or severity of a range of health-damaging environmental, socioeconomic, and behavioral factors.

The chains of risk model (also pathways model) refers to sequences of events or exposures, whereby one exposure increases the likelihood that another will follow, leading to a final exposure(s) that is causally related to later disease. Links are not deterministic, and earlier exposures do not affect disease risk but often lead to a final link in the chain that does affect later disease risk. Social, biological, and psychological factors can be part of chains of risk models, possibly acting as mediating or modifying factors.

Sources: adapted from Hertzman et al. (38), Keating & Hertzman (50), Ben-Shlomo & Kuh (4), and Kuh et al. (52)

during the prenatal, prepubertal, and pubertal periods, reaching a peak or plateau at maturity and gradually declining with age (**Figure 2**). The progressive, generalized deterioration in function postmaturity can be thought of as biologically aging; the generally accepted disposable soma theory of aging suggests this is caused by increasing molecular and cellular damage from environmental insults and chance (51). Third, influences over the life course might operate in several ways to affect adult function and disease. Researchers have identified models for the alternative processes that might be involved; main models including critical period, accumulation, or chains of risk are shown in the sidebar, Life Course Models of Adult Disease Outcomes. Although these life course models

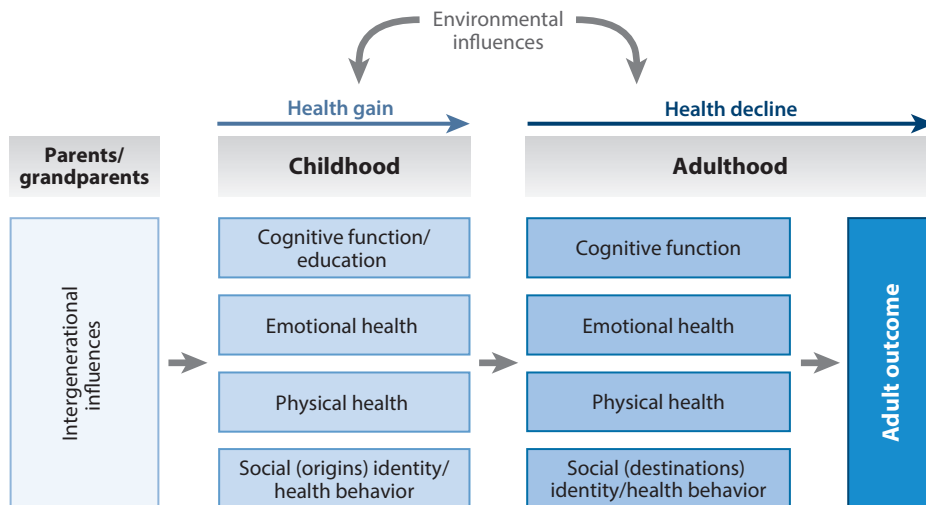**SEP:** socioeconomic position

Figure 1

Simplified framework linking early-life exposures with adult outcome.

can be seen as distinct, they are not necessarily mutually exclusive, and one can envisage variations of basic models. For example, an exposure that operates during a critical or sensitive period may also accumulate with other exposures over the life course, possibly through modification of earlier factors by those occurring later in life. Fourth, developmental domains may coevolve, e.g., between physical developmental characteristics such as height and emotional or cognitive development, whereas during adulthood, relationships between health and other factors (e.g., social circumstances, health behaviors and so forth) may be bidirectional. Hence, there are numerous links across the domains represented in **Figure 1**; birth cohort studies provide several examples of coevolution and bidirectional relationships. Fifth, developmental trajectories and subsequent health in adulthood can be affected by intergenerational influences. These intergenerational influences likely represent the effect of both genetic and environmental influences acting over time (12).

Although not specified in the simplified **Figure 1**, environmental influences can operate at many levels, including individual (micro), community and neighborhood (meso), or national and international (macro) levels (38). For example, smoking in a population can be influenced at the individual level in terms of behaviors relating to smoking initiation and maintenance (addiction), at the community level in terms of peer relationships and behavior as well as access and availability of tobacco, and also at the national level in terms of taxation or smoke-free legislation to prohibit smoking
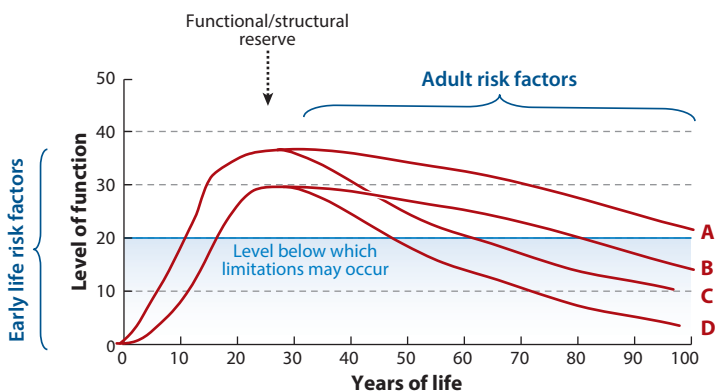

Figure 2

Life course functional trajectories. Line *A*, normal development and decline; line *B*, exposure during development reducing functional reserve at maturity; line *C*, exposure acting postmaturity, accelerating age-related decline; line *D*, combination of *B* and *C*. Figure modified from *A Life-Course Approach to Chronic Disease Epidemiology*, edited by Diana Kuh and Yoav Ben-Shlomo, 2nd edition, 2004, chapter 1, page 9, figure 1.2, by permission of Oxford University Press.
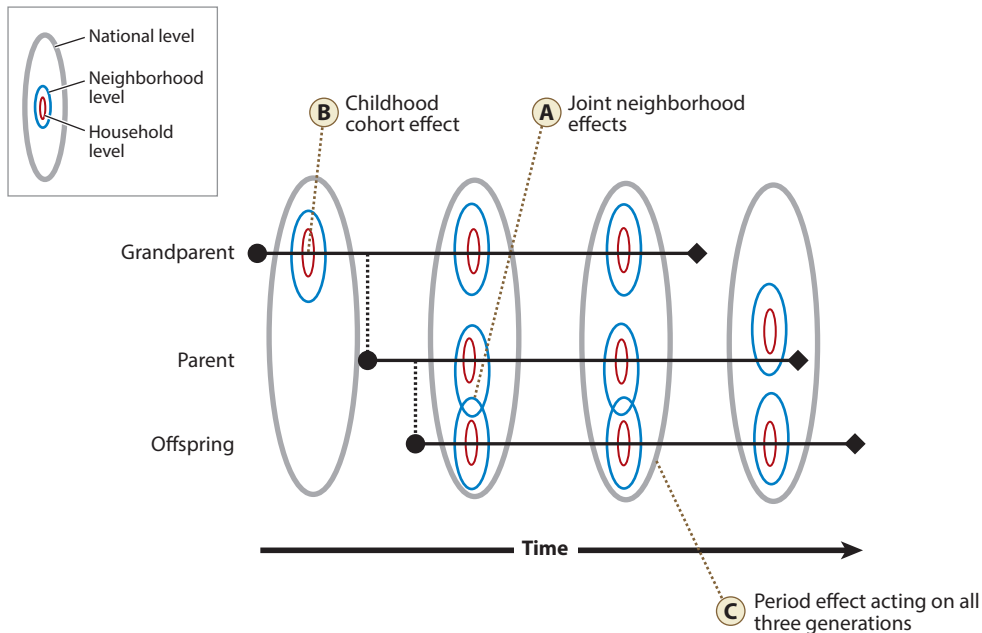
Figure 3

Multigenerational schema: influences of hierarchical and life course exposures on disease risk across three related individuals. Intergenerational links, which can be common genetic and/or social influences, are shown between grandparents, parents, and offspring. Life course links are represented by exposures occurring at different life stages and at differing (household, neighborhood, and national) levels. Ben-Shlomo & Kuh (4) illustrate influences acting across time and across individuals with the example of adverse neighborhood conditions affecting a mother and her child (*A*), and with national exposures (e.g., war-time rationing) as either specific to a single population cohort (*B*) or experienced by all individuals (*C*). Modified from Ben-Shlomo Y, Kuh D, 2002, "A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and inter-disciplinary perspectives," *Int. J. Epidemiol.* 31(2):285–93, by permission of Oxford University Press (4). Adapted from Hertzman et al. (38).

indoors. Influences acting at these different levels might affect successive generations at different points in their lives, with consequent variations in impact: An exposure could occur at a critical or sensitive period for one generation with attendant effects over the life course, but with lesser impact when experienced at a later life stage for another generation. **Figure 3** illustrates the links between generations and life stages, with influences from different levels (individual, neighborhood, and national) of the broader social environment, as successive generations live through different periods of time.

The general frameworks in **Figures 1** and **3**, and other such schemas (29, 69), are not intended to be comprehensive, and when they are adapted and refined to investigate particular life course relationships, details of lifetime exposures and outcomes can be elaborated. For example, a study of body mass index (BMI) at different life stages considered exposures from the prenatal period (maternal age, BMI, blood pressure, and smoking in pregnancy), adolescence, and adulthood (physical activity, diet, smoking, alcohol consumption, and SEP) and found that life course factors (e.g., physical activity) had strong associations, separate from genetic factors, with BMI at age 31 years (49). In view of the complexity of elaborated models, many initial life course studies focus on SEP at different life stages, which, although a broad, nonspecific, and distal measure, has been used to indicate when related exposures might be operating.

BMI: body mass index

LIFETIME SOCIOECONOMIC POSITION AND ADULT DISEASE

SEP is a long-established determinant of health and disease, whereby better outcomes are generally seen with increasing socioeconomic advantage; i.e., generally, the association is graded with health benefits for each increase in SEP. From their earliest days, many birth cohort studies have had a particular interest in SEP, and they have shown a typical trend whereby

Figure 4

Associations of child and adult social class with disease risk factors at age 45 years in the 1958 British birth cohort. Disease risk factors at 45 years include systolic and diastolic blood pressure (SBP and DBP), body mass index (BMI), HbA1c, total and HDL cholesterol, triglycerides, fibrinogen, one-second forced expiratory volume (FEV1), total immunoglobulin E (IgE), hearing threshold at 4 kHz. Risk factors are converted to standard deviation (SD) scores to allow comparison of associations for child and adult social class across different outcomes. Estimated effects are differences per unit increase in social class (on a six-point scale from professional to unskilled manual) adjusted for sex and mutually adjusted for child and adult class. Filled circles [95% confidence interval (CI)], child social class; unfilled circles (95% CI), adult social class. From Power et al. (76).

exposures cluster by the individual's or family of origin's SEP. In different countries and at different times, birth cohorts have demonstrated that SEP associations are evident at all life stages with indicators of prenatal and postnatal development and reproductive, functional, and disease biomarkers as well as morbidity and mortality (5, 20, 41, 42, 75, 77, 108).

To provide clues about whether exposures in early as well as later life have long-term effects, birth cohorts have been used to establish whether childhood SEP is associated with later health, independent of adult SEP. Childhood SEP has predicted many (but not all) later outcomes, including poor cardiorespiratory fitness and dental health at 26 years (75), self-rated health at 33 years (83), literacy and numeracy at 42–43 years (90), obesity (75, 76, 78), CVD risk factors [blood pressure, inflammatory and endothelial markers (75, 76, 103), metabolic syndrome (59)], hearing thresholds (17), chronic widespread pain (76), IGF1 (insulin-like growth factor) at 45 years (56), cognitive (91) and physical function at 53 years (102) and older ages (5), timing of menopause (33), and premature mortality (55). **Figure 4** illustrates the independent associations for child and adult SEP with several but not all disease risk factors in midlife; it suggests that for a range of biomarkers the estimated associations for childhood are often as strong as those for adulthood SEP. In addition, birth cohort studies suggest that SEP associates with reproductive outcomes and offspring birth weight across generations. Specifically, they suggest that a mother's own growth in early life, which is influenced by her parents' SEP, influences her ability to nourish her offspring (12, 68, 70). Findings for these multiple health and disease indicators add to evidence from a wider range of studies, e.g., with retrospective recall of childhood SEP, showing associations with mortality from specific causes, such as CVD.

We can identify several points of interest. First, the observation that associations of childhood SEP with functional measures or biomarkers (intermediate phenotypes) are
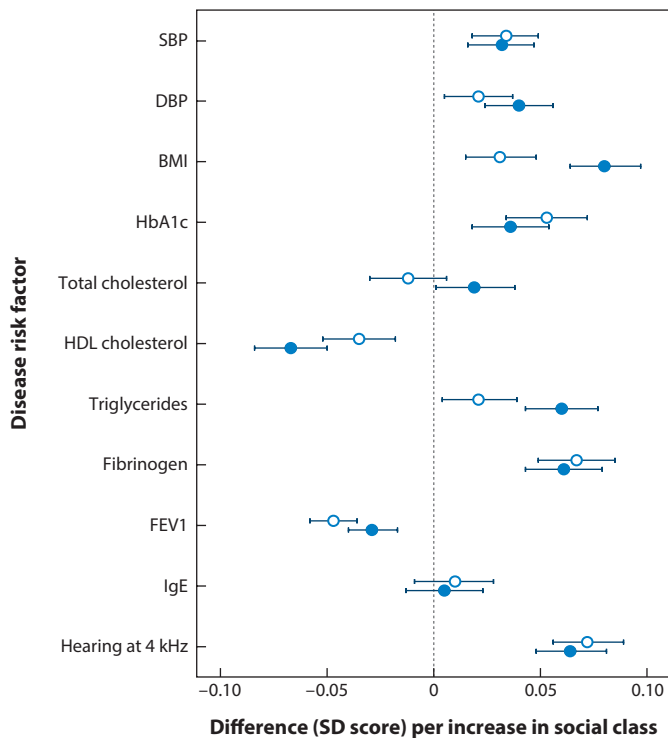
evident well before clinical manifestation of disease serves to highlight the role of earlier life influences. Many outcomes are related to early-life SEP, but some are not, providing specificity for those adult conditions for which there may be a contribution of early-life exposures. Second, the fact that associations for childhood SEP mentioned above are independent of adult SEP suggests that an accumulation of exposures at different life stages may be operating (accumulation model). Reinforcing this point, effects on adult health have been observed of SEP accumulation across multiple ages (83). Such findings do not preclude critical or sensitive-period effects, or variations in importance of influences at different life stages for different outcomes. Third, many studies of childhood SEP were from generations who experienced considerable hardship by today's standards, and we might expect that with increasing affluence, socioeconomic adversity in childhood had lessened to the point that it is no longer relevant to adult health. Yet, later-born cohorts, such as the Dunedin (New Zealand) study, provide little support for this expectation, given findings that poorer SEP in childhood had a detrimental effect on the cardiorespiratory fitness and dental health of 26-year-olds born in 1972–1973, irrespective of their adult SEP (75). Such observations imply that, even in a developed modern society, the socioeconomic conditions in which children are born and raised influence their health in adult life. Fourth, findings from birth cohort studies have stimulated the development of theory on how childhood disadvantage leads to impaired later health outcomes (e.g., as in the models outlined in the sidebar, Life Course Models of Adult Disease Outcomes); they have provided empirical evidence on whether and when alternative models apply and, in addition, have been used to inform policy development (see below).

Empirical evidence is available to suggest the processes through which childhood disadvantage leads to poorer health outcomes. For example, in one study, links between childhood SEP and midlife physical performance were partially mediated by growth, development, childhood home environment, and adult SEP (102). In a second study, childhood SEP was associated with all-cause mortality among women (though not men): Women from manual origins had about double the risk of death between 26 and 60 years compared with women from nonmanual origins (55). The study tested the hypothesis that childhood SEP influences adult mortality via cognitive development and its subsequent link to health behavior (specifically adult smoking). Associations for child SEP remained, although attenuated after allowing for mediation by cognition and smoking, and were in addition to those seen for adult SEP (55). Thus, part of the explanation for a link between childhood SEP and adult mortality appeared to be due to the influence of childhood SEP on cognitive development and subsequent lifestyles, but with a role for additional processes. Further opportunities exist to unravel the processes linking child SEP to later outcomes. Of relevance here are recent epigenetic studies, for example, showing associations of SEP with methylation changes in blood samples taken in mid-adulthood, suggesting that SEP-related factors contribute to general DNA methylation variation (6). Both child and adult SEP had distinct epigenetic signatures (indicated by differentially methylated promoters); i.e., there was little overlap of their signatures. This finding opens up the prospect that early-life exposures change gene expression, possibly programming genes critical for human health, such as those involved in cardiovascular and behavioral pathologies (6).

In addition to providing clues on the timing of influences on later health outcomes, research on the birth cohorts has improved our understanding of the origins of social inequalities in health. As mentioned above, the cohorts demonstrate social inequalities from early- to later-life stages, across a range of health indicators (5, 20, 41, 42, 75, 77, 108). They also provide some evidence for a link between health status and social mobility: Poor health is associated with downward mobility, and better health is associated with upward mobility (28, 75). Yet, in general, evidence from the birth

cohorts suggests that health-related social mobility is not a major explanation for social inequalities in adult health (75, 77, 103).

LIFETIME GROWTH TRAJECTORIES AND ADULT DISEASE

The fetal origins hypothesis stimulated much controversy on whether the prenatal or postnatal period was most influential for adult chronic disease. The growth acceleration hypothesis was subsequently proposed, which argued for detrimental effects of rapid postnatal growth on later disease risk (99). Such perspectives have fostered an appreciation of the early timing of some influences on adult disease and have directed attention toward a range of potentially relevant anthropometric measurements, including birth weight, height, and BMI. With serial measurements of body size onward from birth, as well as information on adult outcomes, the older birth cohort studies show that growth trajectories over decades of life are associated with particular adult outcomes. In addition, against a backdrop of secular trends in height and adiposity, both younger and older cohorts have had a major focus on the putative influences at different life stages on the anthropometric (e.g., low birth weight or obesity) characteristics of their populations.

Cohort studies show the well-established associations between body size (low birth weight, shorter height, and higher BMI) and unfavorable CVD risk factors, such as blood pressure and lipids, at different life stages. As expected, current size in adulthood has been of paramount importance for many CVD risk factors. More uniquely, findings from the older cohorts suggest that the growth trajectory leading to adult height, weight, and BMI is highly relevant to adult disease risk.

Starting with growth early in life, several cohorts show that low birth weight is linked to elevated blood pressure (35, 45, 64), lipids (10, 100), and glucose metabolism (104) in adulthood. Birth cohorts have contributed to systematic reviews that aim to establish the consistency and overall magnitude of associations, for example, of lower birth weight or accelerated postnatal growth with adult outcomes such as elevated blood pressure or type 2 diabetes (43, 109). In some instances the magnitude of effect is modest; nonetheless, findings are consistent with the fetal origins hypothesis. Support for a growth acceleration effect is available also. For example, faster weight gain in infancy predicts childhood obesity (16), body fat, timing of menarche (71), and higher adult blood pressure (45), and factors associated with catch-up growth in infancy (such as maternal smoking in pregnancy) are associated with elevated risk of adult obesity (45, 79). The birth cohorts show that it is not just weight gain in infancy that is detrimentally associated with adult CVD risk factors (e.g., blood pressure) but also excessive gain across life stages from child, adolescence, and adulthood (35, 39, 64, 112). Moreover, individuals who are thinner in childhood/adolescence appear to be more vulnerable to the effects of gains in BMI for blood pressure (64) and lipids (74). Excessive BMI gain is also adversely associated with glucose metabolism; however, in this instance, effects are stronger for those who were heavier rather than thinner in childhood, consistent with the finding that longer duration of obesity adversely affects risk of type 2 diabetes (86). This latter finding for longer duration (or earlier onset) of obesity seems to be due largely to the greater adiposity in adulthood of those with earlier onset. Indeed, the birth cohorts show strong tracking of obesity from child to adulthood (82, 111).

Birth cohorts are experiencing the obesity epidemic at different life stages. A comparison of two UK cohorts showed major shifts in prevalence of overweight and obesity, even for generations born just 12 years apart (1946 and 1958 cohorts) (63). Differing trajectories for these populations are evident, with steeper gains in BMI and longer duration of overweight or obesity for the younger generation (63). Such differences in trajectories of adiposity are likely to have implications for disease burden in adulthood. Several studies have therefore been

concerned to identify exposures associated with hazardous BMI trajectories (i.e., rapid BMI gain or young age of obesity onset). Notably, across several cohorts, less advantaged childhood SEP has been associated with more rapid gain in BMI at different life stages: within childhood (42), from child to adulthood (84, 106), and within adulthood (34). The higher BMI in childhood of those with less advantaged SEP appears to have become more pronounced in younger compared with older generations, suggesting that there is a widening social gap (73).

Several other factors have been linked to rapid BMI gain or high BMI in childhood, including high parental BMI, maternal smoking in pregnancy, lone parenthood, others smoking in the same room as the child, more frequent television viewing, and short sleep duration (30, 88). Some factors continue to show associations with BMI at later-life stages. For example, frequent television viewing and low activity levels in adolescence and early adulthood are associated with greater central adiposity, BMI, or gains in BMI through to midlife (32, 72, 106), while fast-food consumption and dieting to lose weight also show associations with faster BMI gain (106). Earlier timing of puberty (58, 82) and genetic factors have also been linked to higher BMI or BMI gain at later-life stages. Using the growing knowledge of genetic variants associated with adiposity, one study showed that factors at different life stages, such as physical activity, had strong associations with BMI at 31 years independent of adiposity-related gene (FTO) variants (49). The association of FTO with adult BMI appeared to operate in part via its effects on earlier BMI development. Similarly, a risk score of several adiposity-related gene variants was associated with weight gain in infancy and throughout childhood to 11 years (19), and when investigators considered weight gain over a longer period of the life course, the combined effect of adult obesity susceptibility variants was confined to childhood (18). This latter finding is consistent with earlier research on parent-offspring associations showing that parental obesity has a more limited effect on offspring obesity after age 10 years than it does in earlier childhood (110). Intergenerational associations for adiposity are well established; offspring of obese parents have an elevated risk of overweight/obesity. Lifestyle and sociodemographic factors for offspring did not explain parent-offspring BMI associations; however, Power et al. (85) have shown variations in the intergenerational association over successive generations and also by social class, which suggests that intergenerational transmission of adiposity at a population level is not immutable. Intergenerational transmission of adiposity may be due in part to greater nutrient transfer from obese mothers to the fetus, leading to permanent changes in appetite, metabolism, and other functions, as envisaged by the fetal origins hypothesis. The observation that high maternal weight gain in early pregnancy increases the risk of offspring obesity in adolescence (57) is consistent with such prenatal effects. However, others have argued that if there were a specific maternal effect, through intrauterine programming, the maternal-offspring adiposity association would be stronger than the paternal-offspring association; yet differential associations have not been found (11). Although such observations do not discount intrauterine effects due to maternal characteristics or exposures, they do shift attention to postnatal influences on adiposity or at least to the interaction of pre- and postnatal conditions.

Intergenerational associations have also been documented for size at birth: Offspring's birth weight increases in relation to increases in the mother's own birth weight (21) or height (1). Intergenerational studies, usually reliant on record linkage with birth cohort data, have additionally demonstrated the influence of maternal lifetime anthropometry on her offspring's size at birth (70). Comparing across a normal population distribution, mothers who were large at birth themselves, and who grew most rapidly in early childhood, tended to have the largest babies themselves. Moreover, rapid growth after early childhood further increased the likelihood of mothers delivering heavier

infants (13, 67). One birth cohort study showed maternal but not paternal birth weight and weight gain in early childhood to be positively associated with next-generation birth weight (40). These data suggest that the capacity to nourish infants in utero is influenced by a mother's own growth throughout her life, rather than solely by her adult size, current behaviors, and health status (67). Other multi-generational studies of size at birth suggest that the correlations in size at birth between parents and their children while being determined in part by shared genes are also considerably influenced by shared environments across generations (12). Among other influences associated with impaired prenatal growth, some (e.g., maternal smoking in pregnancy) observed decades ago in older cohorts are seen still in more recent studies.

Key themes can be identified from the growing birth cohort literature on intergenerational and lifetime relationships with anthropometric characteristics, for which the above provides only a partial account. First, with regard to the health burden associated with adiposity, many studies highlight the importance of current BMI for adult CVD risk but emphasize also the importance of gain in BMI throughout the life course. They also suggest that there are additional associations for prenatal body size, as indicated by birth weight. The cohort studies suggest that for particular CVD biomarkers how individuals arrive at the BMI they have in adulthood, i.e., their BMI trajectories, matters. Second, factors related to the development of adiposity are observed across different life stages, including three periods suggested as being particularly influential for the development of obesity: the prenatal period, the period of adiposity rebound (at about 5–7 years), and puberty (15). Many of the influences identified are modifiable. Third, the intergenerational relationships observed for birth weight, height, and adiposity suggest that, in some instances, causes and health consequences associated with these physical characteristics are more than lifelong and extend across previous and subsequent generations.

COGNITIVE AND EMOTIONAL DEVELOPMENT AT DIFFERENT LIFE STAGES AND ADULT DISEASE

Cognitive and emotional development are key domains for which long-term associations with adult health have been documented in birth cohort studies; moreover, these studies have also offered insights on the intervening life course pathways (**Figure 1**). Continuities between child development and function in adult life are strong: Poor cognitive function in childhood predicts poor educational qualification and literacy and numeracy levels in adulthood (90, 97) and faster decline in memory, speed, and concentration in midlife (92); in addition, for emotional development, childhood psychological problems are associated with increased risk of anxiety and affective disorder in adulthood (9, 23). Cognitive and emotional development also influence adult SEP (28, 90) and are associated with several adult health outcomes. For example, cognition in childhood predicts self-rated health at 33 years (65); long-term sickness absence (unable to work) in adulthood (37), obesity and weight gain (8), and other biomarkers for CVD (blood pressure, lipids, and glucose metabolism) at 45 years (80); hyposecretion of postwaking cortisol at 45 years (26); and timing of menopause (66), physical performance (53), and premature mortality (55). In general, those with poor cognitive scores in childhood have the least favorable outcomes, in some instances even when studies control for family background and other relevant factors. Likewise, worse emotional status in childhood predicts adult outcomes, such as obesity at 26 years (93), poor self-rated health at 33 years (65), sickness or disability at 46–51 years (36), injury risk through to 42 years (48), and premature mortality (47). Several studies to date suggest that health behavior and adult social destinations are important mediators in associations of childhood cognition or emotional status with adult health (37, 80). However, for some outcomes, such as timing of menopause, physical performance, and psychological disorders,

effects of childhood cognition are not mediated by social and behavioral risks and may instead reflect common CNS pathways.

Identification of adult health associations for cognitive and emotional development underscores the importance of understanding the determinants of these child developmental domains, a valuable goal in its own right. However, if impaired cognitive and emotional development generate adverse trajectories for adult health outcomes, then additional questions are raised, such as whether there are common early-life causes of these child developmental domains and adult health outcomes. Evidence on the determinants of cognitive and emotional development from the birth cohorts spans parental characteristics as well as prenatal, early postnatal, and later childhood/adolescent environments.

Links with lower childhood cognitive ability have been observed for less advantaged social classes around the time of birth, as have younger maternal age and high parity, poor maternal physical condition, birth of the child outside of marriage, prematurity, poor intrauterine growth, short childhood height, parenting style, and less stimulating home learning environment (46, 61, 81, 89, 96, 97, 101). The birth cohort literature suggests that socioeconomic environment has particularly strong associations; other factors such as birth weight, have had a lesser impact. Moreover, although the socioeconomic environment in early life appears to be important in shaping cognitive development, additional contributions are evident for accumulated disadvantage (or poverty) over different ages in childhood/adolescence (96). Greater benefits to childhood cognitive ability of an enriched home/learning environment, as indicated by more frequent parental reading to the child and interest in education, are seen among the least advantaged socioeconomic groups (81).

Adversities in the social environment during childhood have also been associated with emotional development and adult mental health, including being reared in an institution, physical and sexual abuse, parental psychopathology or substance abuse, family conflict, parental divorce, childhood neglect, and other facets of parental style (22, 23, 94). Of particular note is the accumulation of such factors, both during childhood and also from childhood to adulthood. Pathways between childhood stressors and adult mental ill-health have been identified including cumulative adversity, or additive strain models, influences on vulnerability via the development of self-esteem, mastery and other psychological attributes, and influences on the individual's social trajectory, e.g., future employment/education opportunities, social support, and life events (94).

Three main points are highlighted here from birth cohort study findings on cognitive/emotional development and later health. First, for both cognitive and emotional development, strong continuities into adulthood and links with adult lifestyles and social destinations (mentioned here in brief) (3, 28, 90) provide pathways from development in childhood to adult health and disease. For cognitive development, some evidence suggests that part of the explanation for associations with later health outcomes may be due to common early-life causes, as indicated for example by social class at birth or by birth weight, although common causes do not appear to play a major role. By comparison, studies examining life course relationships suggest that adult lifestyles and social destinations are important intermediaries, accounting for much of the associations with later health. Such findings may be interpreted as indicating the primacy of chains of risk or accumulation models (see sidebar, Life Course Models of Adult Disease Outcomes) underlying cognitive ability (or emotional development) and later health relationships. However, given current knowledge, critical- or sensitive-period (latent) effects cannot be excluded. Second, findings from the birth cohorts tend to support experimental and other evidence suggesting that early life is a sensitive period for cognitive and emotional development; they also suggest that later influences, for example, during adolescence, may affect trajectories of development in these domains.

This latter point is relevant to the argument that adolescence may provide a second sensitive developmental period when brains mature rapidly and new behaviors and capacities evolve (107). Lifelong enhancement and preservation of mental capacities are recognized as vital to meet future challenges for aging societies (25); hence, clarification of life course relationships and comorbidity with physical health remain important research priorities for birth cohorts.

INSIGHTS AND CHALLENGES

One major insight from birth cohorts is that for several adult chronic diseases and functional outcomes, such as obesity, CVD biomarkers, and respiratory, cognitive, and mental function, adult factors alone provide only a partial explanation. This observation is supported by research showing that factors from early-life stages (e.g., SEP, adiposity, mental health) are associated with later health and disease, even after controlling for adult factors. The tracking from earlier to later life of some functional and health indicators and health behaviors also suggests that influences on later outcomes are set in train earlier in life. Even when proximal factors in adulthood are paramount, the life course relationships leading to adulthood may, in some instances, be highly relevant. Thus, from a public health perspective, it matters for risk of type 2 diabetes that an adult has been obese for long periods of his or her lifetime (86) or, for lipid profile, that the obese adult was lighter, relatively, at earlier life stages (74). Likewise, from the standpoint of several health and disease markers, including physical capability at older ages, the duration of disadvantaged SEP throughout life is likely to matter for outcome. A focus solely on adulthood may not only provide incomplete or partial explanations for later health and disease, but in some instances lead to inflated estimates for adult factors. For example, adult psychosocial work stress and night working have been linked to adverse CVD risk factors, but associations diminish after taking account of factors occurring before adult working life commences (because of the different backgrounds of individuals entering certain types of work) (105). Similarly, associations documented for adult cortisol and memory in later life attenuate when allowance is made for cognitive ability in childhood (most likely because of associations between cortisol and cognition earlier in life) (26). Such findings do not negate the role of adult life factors, which may compound influences from earlier in life, but they draw attention to the need to understand the impact of childhood and the intervening years to adult outcome.

Despite the rich data on development, function, health, and disease, few if any birth cohorts have the repeated measures needed to characterize life course trajectories of health/functional gain, peak, and decline, and the influences that drive them (**Figures 1** and **2**). They can, however, be combined to show how aspects of health and function change over the life course. Findings from birth cohorts provide important clues, for example, on the full lifetime impact of SEP. At early stages of life, associations for SEP with several developmental, functional, and health indicators show delayed or poor development (e.g., for height as well as for emotional and cognitive ability), suggesting a failure to reach optimum or peak functioning among less socioeconomically advantaged groups even before advancing age-related declines occur. (The pattern is more commonly the reverse in terms of reproductive and many social careers, such as earlier school leaving, parenthood, and labor-market entry, for which less advantaged groups typically have accelerated trajectories compared with more advantaged groups.) Birth cohort study findings suggest that later in life there is earlier deterioration of physical capacity, faster health decline, and premature mortality among those from less advantaged SEP. Taken together, findings for different life stages of birth cohorts underscore the shorter healthy lifetimes of less advantaged SEP groups; contributions to this shortening healthy life appear to emanate from both earlier and later in life.

Notwithstanding challenges for birth cohort studies mentioned below, the wealth

of information available from large groups of children and families repeatedly from birth and over time notionally provides relevant evidence about health and function across the life course with utility for the development of policy to improve population health and well-being. Some changes to policy have been attributed to findings from birth cohorts, for example, in the New Zealand policy context relating to safety standards for children (e.g., compulsory wearing of cycle helmets) (98); in the United Kingdom, reassurance of supine sleeping position in babies was provided to support the Back to Sleep campaign (7), and evidence on the influence of socioeconomic position on life chances has been provided from several studies. However, many challenges impede the attribution of policy changes directly to findings from birth cohort studies. In the United Kingdom, the body of evidence in the developmental origins field, often utilizing birth cohorts to demonstrate links between early-life and later outcomes, has not been directly credited with explicit policy development; however, it has been acknowledged as leading to an emphasis, in policy rhetoric at least, to the importance of early prevention strategies and has joined up intersectoral policy solutions to complex developmental issues (60). The ability of birth cohort studies to inform public health policy by providing evidence about the determinants of trajectories that lead to health and disease for a group of individuals as well as the ability to examine these trajectories in the context of the wider social and environmental conditions in which a particular population exists have perhaps been somewhat underutilized or underreported (113), although life course models often make this dimension explicit.

Among future challenges for birth cohort studies are the conceptual and analytic methods for handling the complexities of life course information together with neighborhood and macrolevel data. This general challenge embraces several related issues, including adequacy and historic relevance of measures, disentangling the direction of associations, causality, and related methodological approaches.

BIOLOGICAL EMBEDDING

Biological embedding, or embodiment, refers to the processes through which extrinsic factors experienced at different life stages "get under the skin," i.e., alter the body's biological functions or structures. These processes may involve development associated with critical periods, habituation, learning, damage, or repair.

- Critical- or sensitive-period effects or biological embedding (see sidebar, Biological Embedding) will be difficult to establish firmly without innovative biomarker or functional indicators to assess biological alterations. Ideally, indicator measures need to be appropriate for different ages to facilitate comparison across life stages and so that understanding can be advanced of individual health trajectories of gain and decline. Indicator measures for older birth cohorts that span childhood to adulthood include body size (birth weight, height, and weight) and cognitive, emotional, and sensory function; additional markers will be useful for younger cohorts. Likewise, accurate measurement of exposures and their timing is a challenge to existing and future studies, for example, to discriminate between influences on health gain and decline. A particular requirement, given the long-term design of birth cohorts, is that the meaning and social context of exposures are transparent many years after they are recorded. For example, infant feeding method may be recorded accurately as duration of breastfeeding, and yet decades later changes to infant formulas may be overlooked; the past meanings or associated motivations of maternal smoking in pregnancy or being born into and brought up in a large family may also differ from today. The historic conditions of childhood that inevitably envelop long-term studies with follow-up from early life need to be understood and can affect interpretation

but do not necessarily negate study findings or relevance to today.

- An agenda for life course research, to which birth cohort studies can contribute, includes addressing what the mechanisms are by which early-life events have long-term effects, and whether pathways can be altered or reversed; what the postnatal windows of plasticity are; the extent of intergenerational transmission of disease risk; the importance of developmental processes in generating the burden of disease in different populations; and what approaches are possible to intervene in individuals and in populations during different stages of the life course (27). Particularly important from a policy perspective is the identification of whether pathways from adverse early-life exposures to unfavorable outcomes can be altered and the life stages at which interventions might be most effective. Research on birth cohorts could contribute relevant knowledge, and, particularly with exploration of multiple cohorts born in different times or places, opportunities to examine issues of sensitivity to context are available. Methodological approaches to address questions about life course relationships are important to consider, given that exposure measures often correlate over time (13). Yet, despite rich data available for birth cohort studies, their observational designs raise the difficulty of inferring causality. Novel methodological approaches have been devised to shed light on causality, notably by using instrumental variables. Genetic instrumental variables, in particular, are now widely used to discriminate between causal and noncausal associations (95), and their use is likely to extend with further genetic discoveries. Not all exposures can be investigated using genetic instrumental variables, and further methodological development is needed to address causality. Meanwhile, birth cohorts can add to the totality of the evidence base, given that they are often better placed to take account of confounding than are other observational studies. In the context of research on healthy aging, investigators have argued that findings from longitudinal studies can add value by identifying problems to be addressed, can justify the need for a clinical trial, can suggest effect sizes on which to base the size of a trial and information to be collected, can indicate whether a risk factor affects some people more than others, and can provide a set of intermediate outcomes that predict onset of outcomes such as disability (31). Thus, an agenda on life course influences on aging is already emerging, which, given demographic trends in high-income countries, will be of enormous relevance to policy in forthcoming years.

CONCLUDING REMARKS

Findings from the maturing birth cohorts have fostered a life course approach to adult health, function, and disease, and in some instances have suggested the processes involved. Advances in knowledge on unraveling life course relationships are not restricted to birth cohorts; i.e., other studies have contributed, although birth cohorts uniquely contain information from around the time of birth, have a broad range of data, and often follow up over several ages through childhood into adult life. Because birth cohort studies are observational, they provide information on associations rather than establish causality; hence, findings need to be considered together with evidence based on differing study designs. The growing number of cohorts born in different places and at different times provides increasing opportunities to establish the conditions under which life course relationships vary, providing further insights for public health. The birth cohorts suggest that broader socioeconomic conditions have a long-term impact across generations and throughout life. Researchers need to undertake a more complete exploration of the extent to

which such risks to health acquired at earlier-life stages can be ameliorated by later protective factors. Further possibilities exist to test the extent to which adult health, function, and disease are affected by factors acting at different life stages, as well as the alternative processes through which life course relationships arise. In particular, the roles of developmental trajectories for life chances have been explored to some extent but will be important to consider for health outcomes later in life as cohorts age. New cohorts will address gaps in knowledge and assess whether relationships seen for previous generations apply to children of today.

DISCLOSURE STATEMENT

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