

A LIFE COURSE APPROACH TO CHRONIC DISEASE EPIDEMIOLOGY

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■ **Abstract** A life course approach to chronic disease epidemiology uses a multidisciplinary framework to understand the importance of time and timing in associations between exposures and outcomes at the individual and population levels. Such an approach to chronic diseases is enriched by specification of the particular way that time and timing in relation to physical growth, reproduction, infection, social mobility, and behavioral transitions, etc., influence various adult chronic diseases in different ways, and more ambitiously, by how these temporal processes are interconnected and manifested in population-level disease trends. In this review, we discuss some historical background to life course epidemiology and theoretical models of life course processes, and we review some of the empirical evidence linking life course processes to coronary heart disease, hemorrhagic stroke, type II diabetes, breast cancer, and chronic obstructive pulmonary disease. We also underscore that a life course approach offers a way to conceptualize how underlying socio-environmental determinants of health, experienced at different life course stages, can differentially influence the development of chronic diseases, as mediated through proximal specific biological processes.

INTRODUCTION

A life course approach to chronic disease epidemiology explicitly recognizes the importance of time and timing in understanding causal links between exposures and outcomes within an individual life course, across generations, and on population level disease trends. The importance of time is illustrated by the fact that chronic conditions such as cancers and cardiovascular diseases have long latency periods—i.e., they develop over time (166). Time lags between exposure, disease initiation, and clinical recognition (latency period) suggest that exposures early in life are involved in initiating disease processes prior to clinical manifestations. Similarly, many important adult risk factors for chronic diseases (poverty, smoking, diet, physical activity) have their own natural histories, e.g., what people eat or do not eat in adulthood may be sensitive to the dietary habits they established in

early life. The importance of timing is illustrated by knowledge that the particular stage of life when an exposure occurs can be important in understanding its later effects. For example, evidence is mounting that human papilloma virus (HPV) is a necessary cause of cervical cancer (148). The infection is acquired through sexual intercourse, and there is some evidence that younger age at sexual debut increases the effect of infection on the risk of developing cervical cancer (169).

Adopting a life course approach should not be construed as suggesting that the recognition of important early-life influences on chronic diseases implies deterministic processes that negate the possibility of later-life intervention (196). One illustration is that *Helicobacter pylori* infection, which is acquired mainly in early life (81), has relatively recently been confirmed as the predominant cause of cardia and noncardia gastric cancer (1, 20)—a disease that is rare below age 50. Gastric (stomach) cancer was the single leading cause of cancer mortality in the United States and many industrialized countries through the 1940s and is still a leading cause of cancer death in Asia. The recent identification of this crucial early-life exposure has led to successful treatment in adulthood, which helps eradicate *H. pylori* infection and dramatically reduces the risk of developing stomach cancer (29, 187). This also provides additional justification for what we already know about ensuring adequate housing and hygiene conditions, especially for poor children. The bulk of adult chronic diseases is unlikely to be explained as the predetermined outcome of inevitable trajectories of exposures in utero or infancy, but rather as longer-term consequences of the albeit complex accumulation and interaction, across generations, of early and later-life exposures. The relative importance, however, of early and later-life exposures will differ by health outcome (34).

A life course perspective on chronic disease epidemiology relies on a multidisciplinary framework for understanding how early- and later-life biological, behavioral, social, and psychological exposures affect adult health (16). However, although general theorizing about these interconnected and multi-faceted processes is important (87), a life course approach to chronic disease epidemiology is enriched by specification of the particular way that time and timing in relation to physical growth, reproduction, infection, social mobility, and behavioral transitions, etc., influence various adult chronic diseases in different ways (112), and by how these temporal processes are interconnected within the life course of one cohort. More ambitiously, a life course approach also attempts to understand how such temporal processes across the life course of one cohort occur in previous and subsequent birth cohorts and are manifested in disease trends that are observed over time at the population level.

THE DEVELOPMENT OF A LIFE COURSE APPROACH IN EPIDEMIOLOGY

The appreciation of life course processes is hardly a new idea. In 1667, Milton wrote in *Paradise Lost*,

“The childhood shows the man,
As the morning shows the day.” (144a, lines 220–21)

Life course thinking has been prominent in disciplines such as psychology, sociology, neurodevelopment, and anthropology (113), and there are important historical examples in epidemiology. For instance, in 1934, Kermack (107) showed cohort patterns in mortality declines in Britain between 1850 and the 1930s (Figure 1), which suggests that each successive generation carried with it, from birth, the potential for a longer life (44). In a study of Maryland school children, Ciocco commented in 1941 that “disease in adulthood is often brought about by the cumulative effects over a long period of time of many pathological conditions, many incidents, some of which take place and are even perceived in infancy” (26, p. 2375). In the 1960s there were papers on the role of early-life influences on chronic diseases (96), and Dubos discussed the long-lasting effects of early environmental exposures under the intriguing title of biological Freudianism (54). Even in the 1970s, there was recognition by chronic disease epidemiologists of the importance of early-life influences on coronary heart disease (CHD) (104). Nevertheless, from the 1960s, chronic disease epidemiology came increasingly to focus on adult lifestyles, and interest in the childhood origins of disease understandably waned with the identification, among adults, of the major CHD risk factors of

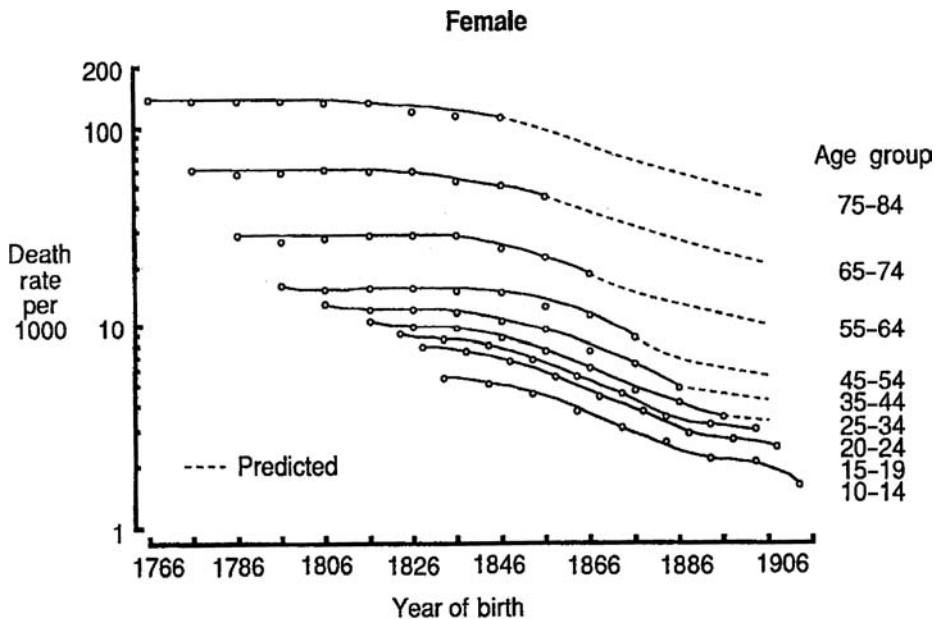


Figure 1 Changes in generation mortality (England and Wales). An example of birth cohort effects in female mortality declines in Britain (106).

smoking, hypertension, and cholesterol. The revival of life course approaches to chronic diseases was stimulated by the work of Forsdahl beginning in the early 1970s (68). Forsdahl suspected that adverse environmental conditions in infancy and early childhood could increase the risk of CHD in adult life. He analyzed aggregate data from Norway and demonstrated that infant mortality rates early in the twentieth century correlated strongly with CHD mortality rates 70 years later (66). Forsdahl speculated that permanent damage may be caused by nutritional deficits in early life that rendered individuals less able to tolerate particular forms of fat in their adult diet, so early-life social disadvantage might interact with affluence in later life to increase CHD risk (67).

The most influential replication of this work was by Barker and colleagues in the United Kingdom (7). The Barker group interpreted their findings as indicating an influence of childhood nutrition, but the focus of their investigations quickly came to rest on exposures in the prenatal environment (8). From these initial observations, the now well-known fetal origins hypothesis was developed, which focused on the long-term effects of in utero biological programming associated with maternal and fetal undernutrition. A key problem with the initial studies in the fetal origins field was that when relating early-life exposures to health outcomes many decades later the intervening anthropometric, biological, behavioral, psychological, and social trajectories of individuals (which were largely unmeasured in the available data) were correlated with early-life exposures. Thus, because the processes affecting birth weight and postnatal growth may also influence subsequent weight in childhood, growth before puberty, and weight in adulthood, it was not clear whether early-life exposures were linked to adult disease only through their links with later-life exposures (14, 102, 130). After a decade of almost exclusive concentration on the independent effect of the prenatal period, studies by Barker and colleagues have also shown the importance of potentially modifying influences of experiences acting in later life (9, 59).

Research on early-life factors, in particular birth anthropometry, appeared against the backdrop of the huge amount of chronic disease epidemiology that was carried out during the second half of the twentieth century on adult behaviors (smoking, diet, exercise), physiological parameters (blood pressure, lipids, hemostatic factors), adult socioeconomic position (social class, income, occupation), and adult psychosocial factors (psychological dispositions, social networks, and work stress). The flurry of reports on the fetal origins of CHD during the 1990s produced somewhat polarized opinions; many epidemiologists emphasized the primacy of the already well-known adult risk factors (particularly as indicated by successful interventions on lowering blood pressure and cholesterol), whereas others focused almost exclusively on events happening very early during development. To counteract the increasing polarization of approaches that emphasized biological programming in utero and adult lifestyle approaches to chronic disease etiology, a partial synthesis under the rubric of life course epidemiology was built on the premise that various biological and social factors over the life course

independently, cumulatively, and interactively influence health and disease in adult life (16, 113). Life course epidemiology does not deny the importance of conventional chronic disease risk factors, such as smoking, diet, and hypertension, which were successfully identified by the early postwar adult cohort studies. Rather, its purpose is to bridge the perinatal and adult period by studying the contribution of early-life factors jointly with later-life factors to identify risk and protective processes across the life course. The fetal origins hypothesis provided a stimulus for broader thinking about a range of influences acting from before birth and then right across the life course. In 1997 [(111); second edition published in 2004 (112)] a book edited by Kuh & Ben-Shlomo, *A Life Course Approach to Chronic Disease Epidemiology*, collected contributions from across the disciplinary and disease spectrum and, for many researchers, helped re-establish life course thinking as important to the epidemiological endeavor.

THEORETICAL MODELS OF LIFE COURSE PROCESSES

Life course epidemiology examines a range of potential processes through which exposures acting at different stages of life can, singly or in combination, influence disease risk.

The critical period model emphasizes the timing of exposure, such that an exposure at a specific period in the life course has long-lasting effects on anatomical structure or physiological function that may eventually result in disease. The term critical period is usually reserved for exposures occurring during known periods of unalterable biological development. This is well understood in a variety of situations, such as with prenatal infections or drug exposure, where during a particular period of fetal development these can lead to devastating permanent developmental changes, whereas if they were experienced just a few days earlier or later they would have no long-term impact. The fetal origins hypothesis in its original formulation took this critical period approach. Other examples of processes where outcomes may depend on the time window at which an exposure acts are

- limb development in relation to maternal thalidomide use;
- fracture across the epiphysis (growth plate) when bone is growing during childhood and adolescence;
- very early postnatal infection with Hepatitis B and risk of adulthood liver cancer;
- congenital infections and environmental lead exposure that result only in serious neurodevelopmental deficits if occurring in infancy and childhood; and
- absence of certain infections or exposure to dirt in childhood, which may increase the risk of asthma, hay fever, Hodgkin's disease, non-Hodgkin's lymphoma, and type I diabetes.

Additionally, there may also be sensitive periods where the effect of an exposure is magnified more than the effect of the same exposure in another time period (113) (e.g., poverty during periods of important childhood social transitions such as school entry) (55), or energy imbalance and overweight just prior to puberty (144). The influence of exposures acting during critical or sensitive periods of susceptibility may also be modified by later-life exposures. This seems to be the case for the associations of birth weight with some chronic diseases in which associations are stronger (or only evident) among those who become obese during adolescence or adulthood (61, 69, 71).

The other main class of life course processes are those represented in accumulation of risk models, which focus on the total amount and/or sequence of exposure. Such models suggest that effects accumulate over the life course, although they also allow for developmental periods during which susceptibility may be greater (16) so that the sequence or trajectory of accumulation may also be important. The simplest model is dose-response, where health damage increases with the duration and/or number of detrimental exposures. Studies have shown this in relation to poor socioeconomic conditions, where additive effects of experiencing low socioeconomic position across different stages of the life course influence risk of several adult health outcomes (40, 132). Accumulation of risk can also be due to clustering of exposures. For example, children from poorer socioeconomic backgrounds are also more likely to be of low birth weight, to have poorer diets, to be more exposed to passive smoking and some infectious agents, and to have fewer opportunities for physical activity. Additionally, life course exposures may form chains of risk so that one negative exposure increases the subsequent risk of another negative exposure. For example, becoming overweight in childhood may cause reduced physical activity in adolescence. Chronic diseases likely result from the complex interplay of critical and sensitive period, and trajectory and accumulation processes. Although these general conceptual models are simplistic representations of life course processes that are likely very complex, even such simple models may be difficult to distinguish empirically (88). See Table 1.

EVIDENCE FOR LIFE COURSE PROCESSES AND CHRONIC DISEASES

Different types of epidemiological evidence may indicate the importance of life course processes for adult chronic diseases (Table 2). Readers should see Lawlor et al. (120) for a more thorough discussion of the strengths and limitations of different types of evidence in regard to cardiovascular diseases (CVD). Table 2 illustrates the ways in which epidemiological insights into life course processes have been gained from a variety of study types. This process of triangulation is important in life course epidemiology because it attempts to integrate knowledge gained about life course processes at the individual, generational, and population levels.

TABLE 1 Conceptual life course models (16)

Critical period models (focus on the importance of timing of exposure)
<ul style="list-style-type: none"> ■ with or without later-life risk factors ■ with later-life effect modifiers
Accumulation of risk models (focus on the importance of exposure over time and the sequence of exposure)
<ul style="list-style-type: none"> ■ with independent and uncorrelated insults ■ with correlated insults <ul style="list-style-type: none"> - risk clustering - chains of risk with additive or trigger effects

LIFE COURSE RISK FACTORS FOR CHRONIC DISEASES

Table 3 summarizes putative life course exposures for CHD, hemorrhagic stroke, type 2 diabetes, breast cancer, and chronic obstructive pulmonary disease (COPD) by arranging known risk factors according to life course stage and including evidence for early-life exposures. Space limitations preclude full discussion of each of these, and readers should consult more comprehensive sources (34, 38, 45, 85, 111, 112, 115, 137, 150, 152). Additionally, it is important to recognize that many of the life course risk factors discussed here—birth weight, growth, nutrition, smoking, obesity, etc.—are socially patterned and are thus important mechanisms in generating social inequalities in adult health (11, 38, 46, 74). Table 3 is intended to be illustrative of the scope of research on the life course epidemiology of chronic diseases and underscores how early- and later-life processes may differentially contribute to different chronic diseases.

Coronary Heart Disease

CHD remains a major cause of death in many industrialized countries and is rising alarmingly in developing countries (197, 198). Adopting a life course approach to CHD prevention (82) may have some of its most important public health applications in developing countries (2). Here, we discuss CHD and ischemic stroke together because their associations with life course risk factors appear similar. Several lines of evidence converge around the idea that both early and later-life exposures are important in CHD and ischemic stroke. This begins with recognition that the precursors of atherosclerosis—fatty streaks—are already evident in the arteries of children (17, 18). Evidence from autopsy studies of young male U.S. war fatalities in the 1950s and 1960s demonstrated high prevalence of atherosclerosis and coronary artery narrowing (58, 143).

BIRTHWEIGHT AND GROWTH There is now good evidence that early-life anthropometry and growth are linked to CHD in adulthood. In their review, Lawlor et al.

TABLE 2 Types of epidemiological evidence of life course processes*

Type of data	Evidence of life course processes
Birth cohort effects (107, 184) (for example see Figure 1)	Cohort effects in health trends have been used as indirect evidence for the importance of early-life exposures.
Historical, area-level infant and maternal mortality rates (10, 67, 126)	Because past infant and maternal mortality rates in an area may indicate childhood social conditions for those born at that time, associations between these historical rates and current chronic disease rates (net indicators of current social conditions) provide indirect evidence of early-life exposures and by examining differences in associations with different indicators (e.g., maternal mortality, perinatal mortality, or postneonatal mortality) may provide insight into more specific mechanisms.
Place of birth (63, 94)	When those who migrate (especially as children) have different adult disease rates than does the population into which they migrate, this may indirectly suggest the importance of early-life exposures, although such studies are hard to interpret because of selection and intervening behavioral, socioeconomic, and other adult differences in exposure among migrants.
Adult recall of events and circumstances at birth and in childhood (13, 28, 64)	Associations between recalled age at menarche, parental occupation, or adverse childhood experiences and chronic disease risk may implicate early-life exposures but are potentially subject to recall biases and greater measurement error.
Objectively measured events and circumstances at birth and in early childhood (27, 70, 146)	Indicators of social circumstances, such as socioeconomic position, family structure, number of siblings, and crowding measured in early life, when associated with disease risk in adulthood (net relevant adult risk factors), provide direct support for life course processes.
Anthropometry at birth and during childhood collected from objective sources such as birth, obstetric, school records, and childhood growth studies (71, 127, 153)	Weight and height taken from records collected at birth, postnatally, or in childhood associated with chronic diseases in adulthood provide direct evidence for early-life processes, but interpretation relies on the adequacy of control for adult risk factors.
Adult height and leg length (37, 85)	As adult height is largely attained by the end of adolescence, associations between height and chronic diseases in middle age reflect factors driving growth processes early in life. Leg length is a more specific measure of growth period as it is largely determined before puberty (76). Nevertheless, such studies are unable to capture the relative importance for later chronic diseases of the determinants of different stages and pace of growth in utero through adolescence.

(Continued)

TABLE 2 (Continued)

Type of data	Evidence of life course processes
Birth anthropometry of offspring (42, 160)	When birth anthropometry of offspring predicts similar or different maternal and paternal adult health outcomes, this may help distinguish between early-life intergenerational processes involving in utero environment and/or genetic effects.
Objective measurement of infectious, biological, behavioral, socioeconomic, and psychosocial risk factors at birth and during childhood and adolescence (4, 49, 109, 141, 149)	Associations between risk factors, such as blood pressure, lipid levels, socioeconomic position, or psychological disposition measured in early-life and adult chronic diseases (net of relevant adult risk factors) provide important evidence for early-life exposures. Many studies of this type, however, involve younger cohorts in which there are few cases of chronic diseases.

*Adapted from Lawlor et al. (120).

(120) found 11 studies that examined associations between birth size and CHD. They concluded that there was generally an inverse association between birth weight and CHD, but associations with other anthropometric measures, such as ponderal index (thinness) at birth, were not consistent (120). Furthermore, it is not birth size per se but rather growth rate in utero that seems most relevant (61, 127), and additionally, evidence is converging on the important role of postnatal growth, such that long-term effects of in utero growth retardation are modified by postnatal and childhood growth, or obesity in adulthood (61, 71). Associations between birth weight and CHD appear nonlinear so that higher CHD is associated with both lower and higher birth weights (127), suggesting different mechanisms of in utero nutritional influences for growth retardation but altered glucose metabolism and insulin resistance subsequent to gestational diabetes for babies of high birth weights (170).

It is important to distinguish maternal and fetal nutrition in considering influences on in utero growth retardation (89). There is relatively little human evidence on alterations to maternal nutrition during pregnancy and effects on later chronic diseases or risk factors (98). There have, however, been several studies of pregnant women who suffered severe nutritional deprivation during World War II (167, 178). These studies were able to examine the effects of maternal nutritional deprivation in different pregnancy trimesters on the basis of assumptions that most fetal length is gained in the second trimester, whereas weight is gained mainly in the third trimester. However, even this basic understanding of the tempo of in utero growth has been questioned recently (118); so in hindsight, it is perhaps less surprising that the results of these studies are inconsistent, especially when they are based on small numbers of events. The results of long-term follow-up of dietary trials during pregnancy will be especially important in better understanding the role of

TABLE 3 Putative life course risk factors for selected chronic diseases*

Life course stage	CHD	Hemorrhagic stroke	Type 2 diabetes	Breast cancer	COPD
Trans-generational	Parental history Maternal health, behavior, stress, and diet before pregnancy Low SEP	Parental history Maternal health, behavior, stress, and diet before pregnancy Low SEP	Parental history Maternal health, behavior, stress, and diet before pregnancy Low SEP Gestational diabetes	Parental history	Parental history
In utero	Maternal health, behavior, stress, and diet during pregnancy Growth retardation Low birth weight	Maternal health, behavior, stress, and diet during pregnancy Growth retardation Low birth weight	Maternal health, behavior, stress, and diet during pregnancy Low and high birth weight	High birth weight	Low birth weight
Infancy	Infant feeding Maternal attachment Catch-up growth Poor growth Low SEP	Infant feeding	Infant feeding Catch-up growth	Infant feeding	Infections Crowding ETS
Childhood	Low SEP Poor growth Poor prepubertal growth Shorter leg length Diet Obesity	Low SEP Poor growth High number of siblings Obesity	Low SEP Low SEP Shorter leg length Adiposity rebound Obesity Insulin resistance Diet	High SEP Height velocity BMI velocity Longer leg length Calorie restriction	Low SEP Low SEP Shorter leg length Crowding ETS Obesity Indoor/outdoor air quality
	Certain infections				

Adolescence	Low SEP Diet	Low SEP Blood pressure	Low SEP Diet	Height velocity Early age at menarche Weight gain Calorie restriction	Low SEP Shorter leg length Smoking Obesity
	Physical activity Obesity Blood pressure Cholesterol Parity (women)		Physical activity Obesity Insulin resistance		
	Low SEP Short height Quitting smoking	Low SEP Short height Quitting smoking	Low SEP Short height Diet	High SEP Greater height	Low SEP Shorter height Quitting smoking Diet Obesity
	Diet Physical activity	Blood pressure Offspring birth weight	Physical activity Obesity	Obesity Later age at first birth	Physical activity Occupational exposures Indoor/outdoor air quality
Adulthood	Obesity Cholesterol	Obesity Alcohol	Alcohol Insulin resistance	Contraceptive use	
	Blood pressure Binge drinking Insulin resistance Work factors		Offspring birth weight Work factors Psychosocial factors	Diet Alcohol Physical activity Later age at menopause Hormone replacement therapy	
	Psychosocial factors				
	Offspring birth weight				

* Abbreviation: SEP, socioeconomic position; ETS, environmental tobacco smoke.

maternal nutrition during pregnancy and later chronic diseases in her offspring (120).

The small number of studies that have examined offspring birth weight in relation to parents' CHD risk (42, 48) show both increased maternal and paternal CHD risk with lower offspring birth weight, although maternal risk seems somewhat more strongly associated (161). Although there are nongenomic mechanisms for intergenerational effects of in utero influences (53), these studies also provide some support for genetic mechanisms driving both growth retardation and CHD risk (33); definitive interpretation of these findings awaits further investigation.

Various studies have confirmed the inverse association between height and CHD in both men and women in countries that have experienced high rates of CHD (43, 165, 194). However, recent contradictory evidence from Korea—a low CHD country—suggests that associations between height and CHD risk depends on the presence of other factors, perhaps high levels of dietary fat (173). The association between height and CHD risk appears to be independent of birth weight (165), and the leg length component of total stature seems especially important (37). Leg length is particularly influenced by nutrition and possibly infection in infancy and prepubertal childhood (191).

MAJOR CHD RISK FACTORS Several CHD risk factors are already present during childhood and adolescence. Cholesterol, blood pressure, and overweight measured at young ages track, albeit imperfectly, into adulthood (5, 117, 119, 134), but physical activity in childhood or adolescence is only modestly correlated with physical activity in adulthood (23, 186). For example, the Bogalusa Heart Study showed that 77% of obese children became obese adults with worse CHD risk factor profiles (73). In an extensive review (137), blood cholesterol, blood pressure, and body mass index (BMI) measurements taken in adolescence or early adulthood were found to be predictive of CHD up to 50 years later. The incidence of CHD over a 40-year follow-up of young men in the Johns Hopkins Precursor study showed gradients between cholesterol level measured at young ages and later incidence of CHD (109). Studies that measured cholesterol in childhood demonstrated that this predicts carotid artery intima-media thickness (a marker of atherosclerosis) at least as strongly as cholesterol measured in adulthood, and that the childhood measures remain predictors after adulthood measures are taken into account (158). Long-term exposure to circulating cholesterol is a stronger risk factor than are single measures in either childhood or adulthood (128). This observation is in accord with evidence from other sources. Rose (166) demonstrated that ecological correlations between cholesterol levels and CHD were stronger for cholesterol measured many years before CHD was assessed than if contemporaneous cholesterol measures were used (166). Additionally, clinical trial results have shown that the relative reduction in CHD risk among those allocated to cholesterol-lowering drugs increases with duration of treatment (93). Furthermore, evidence from Mendelian randomization approaches demonstrates that the lifetime differences in cholesterol

levels generated by genetic polymorphisms are consistent with greater effects of lifetime cholesterol exposure than are seen with single cholesterol measures in adulthood (36). All this evidence suggests that accumulation over the life course of exposure to high levels of cholesterol is important in CHD risk. High fat diets and cholesterol seem to be the crucial risk factors for CHD (177) because there are no examples of CHD epidemics in countries that have low-fat diets.

For blood pressure, the situation is somewhat different. Although blood pressure measured in early adulthood predicts CHD risk 50 years later (138), the effects appear no greater than those seen for blood pressure measured in adulthood (145). Cholesterol measured during early life reflects long-term exposure that is not influenced by early stages of CHD. Thus, cholesterol measured in early life generally produces greater prediction than do such measurements taken in later life because they may reflect long-term accumulative atherosclerotic process. In contrast, blood pressure levels in early life, though influencing later disease, do not show the enhanced association seen for cholesterol.

The situation described for blood pressure is similar to that observed for smoking, where smoking among adolescent or young adults is strongly related to later disease risk but no more strongly than is adult smoking (142). The age at smoking cessation is the key to reducing risk, which declines fairly rapidly after cessation (51, 105, 154, 193). Whether earlier age of initiation and smoking intensity in early life strongly influence the amount smoked over the life course and age at quitting is unclear; but given the generally narrow age range of initiation compared with the much broader age range for quitting, adult factors that more directly influence earlier age at quitting seem to be most important.

STROKE Stroke is a heterogeneous outcome comprising mainly ischemic and hemorrhagic subtypes, although accurate classification is uncertain using routinely collected death certificate data. Epidemiological investigations of stroke in Western industrialized countries are dominated by ischemic strokes (~70%–80% of all strokes), which involve similar atherosclerotic/thrombotic processes as in ischemic/coronary heart disease. Thus, the associations of CHD and life course risk factors described above also apply largely to ischemic stroke. Many studies have identified shared adult risk factors for CHD and stroke, such as hypertension, obesity, smoking, lipids, etc., so they are often combined into a single category of CVD. There are several reasons, however, to distinguish different subtypes when considering etiology and the potential for life course exposures to influence stroke. There are generally weak international correlations between stroke and CHD such that Japan and Korea have high stroke rates (especially hemorrhagic) but low levels of CHD. Historical ecological studies show stronger correlations between infant mortality and stroke than with CHD 70 years later (126). Stroke and CHD have different epidemiological profiles; stroke has undergone continuous decline and CHD has shown an epidemic rise and fall over the course of the twentieth century. Lawlor and colleagues (121) showed that when the hemorrhagic component

of total stroke was removed, trends in ischemic stroke parallel trends in CHD. A major difference in the epidemiology of ischemic and hemorrhagic stroke is that circulating cholesterol levels are positively related with the risk of ischemic stroke and are either unrelated or negatively related to hemorrhagic stroke (91). Similarly BMI shows a stronger and more consistent association with ischemic than with hemorrhagic stroke (175).

Regarding early-life factors, there is evidence that height, greater number of siblings, and early-life socioeconomic disadvantage are more strongly associated with hemorrhagic stroke than with ischemic stroke or CHD (90, 139, 173). Few studies have examined the role of birth anthropometry on stroke risk, but available evidence suggests that associations with low birth weight are stronger for hemorrhagic than ischemic stroke (99). Given that hemorrhagic strokes are more strongly linked to hypertension than are ischemic strokes (176), one hypothesis states that associations with birth weight reflect the influence of in utero and early-life growth and nutrition processes on the development of hypertension. Breast-feeding is associated with lower offspring blood pressure (136) and randomized controlled trials of restricting sodium intake in infants resulted in lower blood pressure at the age of 6 months (95) and at age 15 (75). Sodium levels are lower in breast milk than in most formula feeds, and the sodium content of formula feeds has decreased across the century. Although this is only one possible hypothesis, this individual-level mechanism is consistent with evidence from the population level, where hemorrhagic stroke has declined continuously over the twentieth century in the United States and United Kingdom; there have also been strong birth cohort declines in blood pressure (79, 138, 140). Additionally, there is intriguing evidence linking hemorrhagic stroke and stomach cancer, both ecologically and through their strong individual-level associations with numbers of siblings, and thus infection risk in early life. For stomach cancer, *H. pylori* is clearly key, but the same processes that lead to *H. pylori* infection could be related to other early-life infection (or *H. pylori* itself) that increases risk of hemorrhagic stroke. A recent systematic review of studies linking *H. pylori* to stroke unfortunately contained no useful data regarding hemorrhagic stroke (31). In summary, this evidence suggests that the hemorrhagic component of stroke is more directly sensitive to early-life conditions than is either ischemic stroke or CHD, which involve contributions from both early- and later-life exposures.

TYPE 2 DIABETES Type 2 diabetes is an increasing public health problem in the United States (147), in other rich countries, and especially in parts of the developing world, where rates will likely double over the next two or three decades (108). It is a condition characterized by elevated levels of blood glucose, resulting from insufficient insulin production in the beta cells of the pancreas and/or from cellular (mainly muscle) resistance to insulin that controls glucose uptake. In the natural history of type 2 diabetes it appears that insulin resistance—with concomitant increased insulin secretion—proceeds an end-stage failure in insulin production and that early-life exposures are more strongly associated with the insulin resistance

than with the insulin production mechanism (150). A premorbid condition, known as insulin resistance syndrome, is characterized by the clustering of adverse levels of blood pressure, triglycerides, lipids, insulin, glucose, and central obesity. Because these are also some of the main risk factors for CHD, insulin resistance syndrome has been proposed as the common patho-physiological disturbance behind both CHD and type 2 diabetes (162); thus some similar associations are observed between life course exposures and CHD and diabetes.

A systematic review identified 48 studies examining associations between birth weight and diabetes or impaired glucose tolerance (IGT) in young adulthood and later life (150). Overall there was consistent evidence, especially among middle-age cohorts, linking in utero growth to diabetes/IGT risk. Inverse associations between birth weight and risk of diabetes/IGT were found generally in populations where overall diabetes risk was relatively low. In the United States, where diabetes is more common, the largest study on U.S. nurses showed a U-shaped association between birth weight and type 2 diabetes that became linearly inverse after control for maternal diabetes history or adult obesity (164). Thus, associations between higher birth weight and increased diabetes/IGT risk may reflect the effects of higher birth weight on later-life obesity and/or the effects of an in utero environment affected by maternal gestational diabetes, which is itself linked to maternal low birth weight (100).

Both genetic and environmental mechanisms have been proposed to explain links between birth weight and diabetes/IGT risk. The thrifty phenotype hypothesis suggests that impaired in utero growth and later-life obesity may lead to insulin resistance (86). In contrast, the fetal insulin hypothesis suggests that because insulin promotes fetal growth, it is possible that a genetic mechanism generating resistance to insulin lies behind both reduced fetal growth and insulin resistance in later life (92). Evidence in support of this hypothesis comes from the fact that paternal type 2 diabetes risk and insulin resistance are associated with lower offspring birthweight (47, 192).

The results from studies of birth weight and IGT at younger ages underscore the importance of differential patterns of postnatal growth (65) including associations between lower leg: trunk length ratio (determined prepubertally) and higher insulin resistance (37, 122) and adiposity rebound (the age after infancy when body mass begins to rise) (60). Higher risk of IGT has been observed among children with low BMI until age 2 years, but who then experienced adiposity rebound at younger ages and sustained a higher rate of weight gain through childhood (19). According to current guidelines, only 3% of these individuals were overweight and none were obese at age 12; thus these findings from India reflect processes—the temporal dynamics of early growth—rather than simply the outcome of childhood overweight and obesity. In rich countries, where the whole distribution of BMI in children has a much higher mean, it is uncertain how growth processes like early adiposity rebound may affect later diabetes/IGT risk.

Recognition of the role of in utero factors on diabetes risk provides motivation to appreciate more broadly the importance of physical growth processes in utero,

across infancy, childhood, adolescence, and into adulthood. Childhood and adult obesity are by far the most important risk factors for diabetes in rich countries such that very few cases of diabetes occur among nonoverweight adults. Thus, child and adulthood obesity and maternal gestational diabetes remain the most important avenues for public health interventions. Nevertheless, in utero, early-life growth processes and energy balance in childhood and adolescence are important pathways to the development of obesity and insulin resistance in later life.

BREAST CANCER Breast cancer is one chronic disease for which the main established reproductive and menstrual risk factors are already considered within a temporal framework consistent with a life course approach. Although possibly differentially associated with pre- and postmenopausal breast cancer, the main risk factors—parental history, younger age at menarche, younger age at first birth, lower parity, and later age at menopause—are temporally consistent with the basic understanding that breast cancer is related to cumulative and/or interactive exposures over the years of active ovarian function (52). In a systematic review of early-life breast cancer risk factors (prior to age 25), Okasha and colleagues (152) examined birth weight, infant and childhood growth, peak height velocity, height, childhood obesity, diet, age at menarche, and exercise in relation to breast cancer risk. They concluded that there was some evidence for an association between higher birth weight and breast cancer risk, strong evidence for an association between increased height (and possibly leg length), and inconsistent evidence for the role of weight in childhood or adolescence (despite their inverse associations with age at menarche), physical activity, diet, smoking, or alcohol consumption, and later breast cancer risk. They argued that exposures in the period from age at menarche to first birth may be critical because of the susceptibility of rapidly differentiating breast cells to carcinogenic exposures that may enhance cell proliferation.

Results of recent studies not included in the review by Okasha and colleagues (152) may add weight to their conclusions. First, the largest study of the association between birth weight and breast cancer risk among more than 100,000 women shows a clear association between higher birth weight and higher breast cancer risk after control for age at first birth and parity (3). Second, a study using the 1946 U.K. birth cohort found that after adjustment for several confounders, height velocity from ages 4–7 and 11–15, and BMI velocity from ages 2–4, were associated with increased premenopausal breast cancer risk, especially among girls with age at menarche less than 12.5 years. Thus, faster childhood growth leading to earlier attainment of adult height among girls with earlier age at menarche magnified breast cancer risk (50). Finally, a Swedish study showed that women who had been hospitalized for anorexia nervosa before age 40 had a more than 50% reduced risk of breast cancer, and this effect was even stronger among parous women. This suggests the importance of early-life diet and caloric restriction and their potentially interactive effects with known risk factors such as parity (144).

Insulin-like growth factor-1 (IGF-1) and its binding proteins may be important in understanding some of the findings linking birth weight, growth, height, and

diet to cancer risk (39). IGF-1 and its binding proteins are important mediators between growth hormone and growth and have been linked to prostate, colorectal, and premenopausal breast cancer (155, 163). Positive associations between height, leg length, childhood growth in relation to age at menarche, and breast cancer may reflect higher levels of IGF-1 and lower levels of binding proteins. Although adult height is not strongly linked to IGF-1 levels, it is associated with childhood growth (15, 103), and so childhood may be the period in which later cancer risk is increased. Additionally, childhood growth is influenced by diet, and both animal and human studies provide evidence that quality of diet and caloric restriction influence growth and cancer risk primarily through the action of IGF-1 (72). There are several possible pathways through which circulating IGF-1 levels could influence breast cancer risk. They could reflect activity of sex hormones, but this seems less likely because associations between IGF-1 and cancer are stronger than with directly measured sex hormones. As a growth promoter, IGF-1 levels may indicate greater cell proliferation and susceptibility to malignant transformation. Alternatively, IGF-1 may influence breast cancer risk through its negative effect on apoptosis.

Perhaps perversely, these same IGF-1 mechanisms may be implicated via greater height, leg length, etc. in decreased risk of cardiovascular diseases as noted above. Nevertheless, greater understanding of IGF-1 may provide insights into the growth mechanisms differentially linked to chronic diseases (39).

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) COPD is a heterogeneous outcome characterized by permanent airflow obstruction resulting from the destruction or remodeling of airways. Strachan & Sheikh (181) suggest that COPD results from a series of interacting processes potentially involving respiratory viral infections, atopic reactions (allergies), temporary airflow restrictions in response to irritants (asthma), and chronic secretion of mucous (bronchitis). Burrows and colleagues (22) argue that there are two major types of airway obstruction in adulthood: those related to smoking and those related to asthma and atopic allergy among nonsmokers. Clearly, the duration and intensity of smoking is the major cause of the population health burden of COPD at times when, and in countries where, smoking is common. However, COPD is sometimes prevalent in the absence of a large population smoking burden. For CHD or lung cancer, the age at smoking cessation was important in determining the extent to which disease risk declined over time (154). However, if COPD is related to early lung damage caused by smoking, then even lower levels of cumulative burden to the damaging effects of smoking may still be associated with poorer adult lung function many years later. Thus, the duration and intensity of smoking in early life may be more important for lung function in later life than it is for lung cancer or CHD (51, 80). Other influences over the life course such as birth weight (6), childhood respiratory infections (135), exposure to environmental tobacco smoke (30), outdoor and indoor air pollution (84), diet (97), physical activity and poorer socioeconomic circumstances (41, 101, 123, 135) in early and later life may also be important in COPD.

In terms of early-life influences, studies have suggested that low birth weight infants have an increased risk of respiratory disease in later life (6, 179), which could be owing to poor lung development in utero. Maternal but not paternal smoking has been associated with lower ventilatory function in adults; because maternal smoking during pregnancy is a strong predictor of birth weight, which could affect both in utero lung development as well as exposure to passive smoking in infancy (190). An interaction between maternal smoking and own smoking has been seen concerning adult lung function (189). Childhood respiratory infections of the chest especially before age 2 have been linked to poor adult lung function (135, 171), but these associations are difficult to interpret (180). Childhood chest infections may be associated with adult airflow obstruction for many reasons (181). Poor lung development in utero could increase susceptibility to both chest infections in childhood and adult respiratory disease, or childhood chest illness could cause lung damage, which then influences adult lung disease. Conversely, childhood chest illness and adult lung disease may be just a manifestation of an underlying asthmatic tendency, or both childhood and adult lung dysfunction may be related to the continuity of adverse exposures linked to poor socioeconomic circumstances.

Associations between life course exposures and obstructive airway disease in adulthood are further complicated by the possible role of early-life infections in allergic sensitization. Babies are born with immature immune systems and they develop responses partly on the basis of that to which they are exposed. Thus, there may be one or more critical periods in immune system development when exposure to certain infectious agents is important in programming an appropriate immune system response. Individuals who exhibit less allergic response tend to have greater thymus-derived helper 2 (Th2)-mediated responses, whereas those with atopy tend toward Th1-mediated responses (159) considered to be the normal response for bacterial and viral infections. In a recent review, Prescott (156) concluded that even though these processes affect immune system development, the effects are dependent on the timing of exposure, genetic factors, the nature of the infection, and possibly other factors in the prevailing environment (156). Although there is some support for this infectious-allergic response hypothesis, there is no direct evidence that reduced early-life infectious burden is responsible for documented increases in allergy and asthma (188, 195).

POPULATION LIFE COURSE PROCESSES

The life course approach may be useful when applied to considerations of population health. For example, Figure 2 demonstrates the strong correlation across countries between male stomach cancer mortality (1991–1993) and infant mortality 70 years earlier (126). It is difficult to understand why three countries—Japan, Russia, and Chile—should cluster together on this outcome. They share very little in terms of their current socio-environmental conditions, and historically they are very different countries culturally, economically, and socially. Yet they are

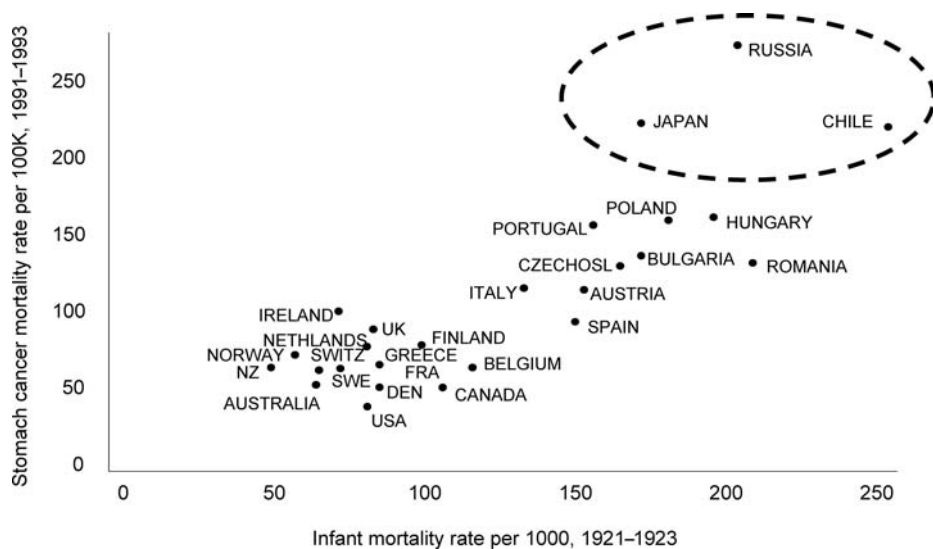


Figure 2 Infant mortality rate (1921–1923) and stomach cancer mortality rate (1991–1993) for men aged 65–74 (126).

all countries that had very high rates of infant mortality in the past, and the current generation dying of stomach cancer is that which, presumably, experienced the high rate of *H. pylori* infection, transmitted in the same way as the diarrheal diseases that killed infants in the past.

One of the more ambitious applications of a life course approach to chronic disease epidemiology is to integrate knowledge from individual level studies to help explain population-level trends in different diseases (32, 45, 116, 125). This means understanding how the array of life course risk factors, such as birth weight, height, diet, behaviors, etc., mentioned in Table 3 are configured across successive birth cohorts, and their long-term trends, and how these trends, given appropriate time lags, map onto trends in different diseases. For instance, if greater birth weight and height are both causally linked with lower CHD risk, then it is not simple to reconcile the consistent secular increases in birth weight and height over time, with the epidemic rise and fall of CHD observed in many countries during the twentieth century. If birth weight and height participate in causal mechanisms (168) sufficient to produce CHD, either these mechanisms must account for a relatively small number of cases or birth weight and height are complementary causes in other sufficient mechanisms involving major risk factors such as high blood lipid levels.

A counter example is smoking and lung cancer. We know that smoking is the most powerful risk factor for lung cancer, and in the United States we know the approximate birth cohort and age distribution of the uptake of smoking (62);

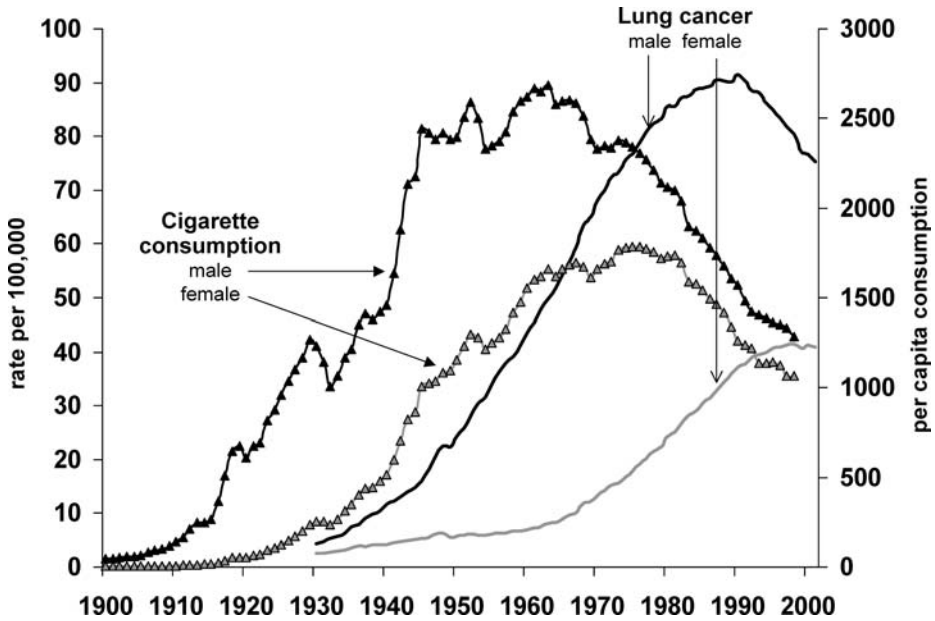


Figure 3 Sex-specific trends in smoking and lung cancer over the twentieth century in the United States.

we also know that the time lag between smoking and lung cancer is about 30–40 years. Although not by any means a perfect concordance, smoking explains most of the differences in lung cancer among individuals, between populations and within-population lung cancer trends (129). From individual-level U.S. data on sex-specific smoking prevalence by birth cohort (21, 62) and historical data on cigarette consumption, we have estimated sex-specific cigarette consumption trends over the twentieth century and show them in relation to sex-specific lung cancer trends in Figure 3 to illustrate this concordance between causation at the individual and population levels between smoking and lung cancer. A similar argument for consistency between individual- and population-level causes might be made for *H. pylori* infection and peptic ulcer and stomach cancer (184, 185), for HPV infection and cervical cancer, for alcohol and liver cirrhosis (151), and for hepatitis C infection and liver cancer (172). However, such examples will be most pertinent in situations where the bulk of cases arise from a small number of sufficient causes with relatively few component causes (168).

Outcomes that have more diverse pathways and more complicated interactions of risk factors make it more difficult to map trends in a single exposure across different birth cohorts onto trends in disease. However, if we had integrated measures based on knowledge of the major risk factors for outcomes such as CHD and how they interacted, then it is likely that a large part of the population-level

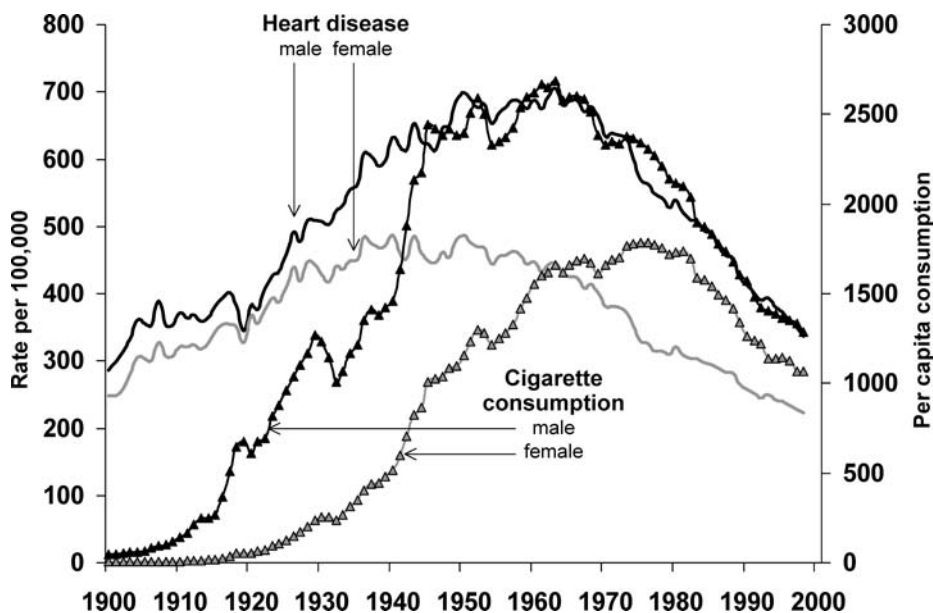


Figure 4 Age-adjusted heart disease mortality and estimated annual adult per capita cigarette consumption, males and females 1900–1998.

trend is explicable in terms of trends in combinations of major risk factors: lipids, hypertension, and smoking (12, 83, 133). Indeed, as we understand more about disease etiology, and about how many conditions that at first sight appear unitary—such as lymphoma—are in fact made up of many constituent diseases of distinct etiological processes and pathophysiology, we may discover that more diseases have a limited number of important sufficient causes. The clear multifactorial nature of CHD may, in fact, be an exception rather than the rule in this respect.

Figure 4 shows male and female heart disease in the United States from 1900–1998, demonstrating the twentieth-century epidemic pattern dominated by male heart disease mortality. An important limitation is that the category of “heart disease” used here is composed of a diverse set of pathological entities with potentially disparate causal mechanisms (131). The generic category of heart disease, which we are forced to use for temporal comparability, includes not only CHD but also congestive heart failure, rheumatic heart disease, arrhythmia, hypertensive heart disease, and others. In addition, the relative contributions of these subcomponents of the generic category of heart disease have changed over time. Nevertheless, it is reasonable to propose that the largest contributor to the rise and subsequent fall in the twentieth-century epidemic of heart disease was CHD.

For males, these patterns suggest that at the population level, the effect of smoking on heart disease is rather immediate. However, the apparent simultaneity

of the rise and fall of smoking with heart disease in U.S. men has not been evident in all countries. For example, in the United Kingdom the zenith of smoking was about 10 years prior to the peak of the heart disease epidemic (25). In the United States there seems little or no time lag between the rapid rise of smoking in the population and the equally steep increase and decline in smoking and heart disease. This is not the case for women, where the peak in heart disease occurs 25–30 years before the zenith of smoking. There is clearly a need to examine these sex-specific links between smoking and CHD in more detail—especially concerning the age of initiation in various birth cohorts (78), age at smoking cessation, and their total exposure to smoking. The apparent sex difference in the causal immediacy between smoking and heart disease is not evident for lung cancer (Figure 3), where there is little sex difference in the time lag between the exposure of different birth cohorts to high rates of smoking and the subsequent population yield in lung cancer mortality.

There are three main processes implicated in CHD—development of atheroma, thrombo-embolic processes, and arrhythmia. Smoking may not only affect development of atheroma, but also operate through the thrombo-embolic and/or arrhythmic pathways, thus plausibly being able to influence, almost instantaneously, heart disease. This would be contingent on an underlying susceptibility owing to the development of vulnerable atherosclerotic plaque—itself associated with diet, blood lipids, and blood pressure. Data on blood pressure trends in the United States show strong birth cohort shifts in the whole distribution of blood pressure from the 1950s onward (79). This suggests that each successive generation born after the last decades of the nineteenth century carried with it a more favorable distribution of blood pressure. The U.S. epidemic of heart disease peaked in the 1960s for men—among cohorts born around the turn of the twentieth century. The rapid declines in heart disease after the 1960s are thus compatible with both period declines in smoking and cohort declines in blood pressure in the population. This implies different influences across successive birth cohorts in how both early- and later-life experiences of the conditions predisposing those particular cohorts to adverse risks for adopting (and maintaining) smoking and developing hypertension. With this complex mixture of cohort effects in the increases (and decreases) for some risk factors (hypertension), but period effects in others (smoking), combined with the generally multiplicative nature of the combined influence of CHD risk factors, (177) it is difficult to predict whether cohort or period effects in CHD should be seen. However, a reanalysis of U.K. data suggested that both were evident, but period effects were stronger (24).

The examples offered here of adopting a life course approach at the population level may be even more difficult to apply to other etiologically complex diseases. First, in some instances we have less knowledge of the main individual-level risk factors, so population-level trends in the known risk factors or their combinations do not map easily onto disease trends within and among populations (114); that said, some of the population trend is likely to be explained, even for breast cancer, by complicated interactions and trends in known risk factors. Nevertheless,

complex diseases like breast cancer do present something of a paradox in this regard, which awaits greater biological insights into their etiology (124).

Importantly, from a life course perspective, even if we can explain the bulk of the twentieth-century epidemic of chronic diseases like CHD, with the traditional risk factors, we still do not understand the socio-environmental determinants of the changing distributions of these risk factors across the life course of different birth cohorts and social groups over time (45, 110). One important implication for adopting a life course approach would be that apparently novel life course risk factors—such as poor in utero growth, early-life deprivation, or psychosocial factors in adulthood—are most likely to increase CHD risk through their links with conventional risk factors, both at the individual and population level (35). Thus, life course processes are likely to work mainly through the established major proximal adult risk factors (smoking, lipids, hypertension, diabetes). Connections between early- and later-life exposures might occur in several ways. Early-life exposures could modify the effects of adult exposures—as in lower birth weight, combined with higher adult BMI, and increased risk of diabetes and CHD (a critical period with later effect modification model according to the terminology in Table 1). Alternatively, early-life exposures may act as precursors—as in the tracking of blood pressure and obesity from childhood through adolescence (chain of risk model), or via the timing of exposure—where the amount of pre-pubertal weight gain and age at menarche affect health in adulthood (pathways model); or by accumulating negative exposure over time—as in the amount of smoking and COPD, or cholesterol and CHD.

METHODOLOGICAL CHALLENGES

Adopting a life course approach to chronic disease epidemiology presents multiple methodological and analytic challenges concerning study design, data collection, and interpretation. Fundamentally, investigating life course processes for chronic diseases requires measuring data at multiple time points from birth (or before) to middle and older ages (56, 182) and potentially across generations. Ideally, the timing of these data collections is informed by some knowledge of the relevant latency periods between particular life course exposures and outcomes. For some life course research questions, there are time lags of 50 or more years between exposures and outcomes of interest (e.g., *H. Pylori* infection and stomach cancer). That is why much of the current knowledge in the life course epidemiology of chronic diseases has been derived from reconstructed cohorts where information about early-life conditions and events was gathered from cohorts born in the late nineteenth and early twentieth centuries. One of the limitations of these data is that the life course processes studied in these cohorts are reflections of the past and may not in some cases be as applicable to current generations. Reconstructing early-life exposures from adult recall is limited because it introduces possibilities of bias and measurement error, so objective data collected at the relevant life course stage are

most desirable. Innovative designs that combine individual and routinely collected register information for exposures, confounders, and outcomes will be important in this regard. Future life course studies that attempt to collect a diverse array of information about early- and later-life exposures will have high respondent burden, so recruitment and retention over long periods of time will be a major challenge.

Life course exposures may operate through the timing of their action and/or through their accumulation. Testing critical and sensitive-period exposures requires that the exposure is measured at multiple points spanning the hypothesized time period. Such repeatedly measured exposure data are rare and expensive to collect. Similarly, if the exposure is thought to affect the outcome through accumulation, then the exposure needs to be measured at multiple time points. Multiple measures present analytic challenges in how best to represent the accumulation of exposure. Exposure can be averaged across time points, but it is conceptually inadequate to capture accumulation, especially when differences in the tempo or pattern of accumulation are thought to confer differential disease risk. It makes little sense to consider a measure of average growth rate from infancy to adolescence, and innovative methods are beginning to be applied to capture the dynamic trajectories of exposure accumulation (50).

Finally, long-term life course studies of chronic disease will make the problems of missing data even more acute than they are currently, and so advances in multiple imputation techniques are likely to be important (157). Additionally, innovative design through replenishment samples and analytic methods will need to be applied to avoid making inferences from overly selected study samples.

CONCLUSIONS

We have provided a necessarily selective overview of life course approaches to chronic disease epidemiology, in terms of its background, theories, and empirical evidence. Additionally, we have underscored that a life course approach offers a way to conceptualize how underlying socio-environmental determinants of health, experienced at different life course stages, can differentially influence the development of chronic diseases, as mediated through proximal specific biological processes. The life course perspective has a long history in sociological and psychological sciences (57), but it is still in its relative infancy within epidemiology. We are certain that the contents of this review will seem simplistic and naive within a relatively short time period, thus demonstrating the vitality that a life course approach can bring to epidemiology.

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