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Epidemiological Study Designs: Traditional and Novel Approaches to Advance Life Course Health Development Research

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1 Introduction

1.1 Goals in Life Course Research

A life course approach to health and human development provides a conceptual and methodological framework to understand the multiple, multilevel, and synchronized (i.e. temporally integrated) determinants of health and disease across the lifespan. Theories underlying life course approaches are varied, but each emphasizes the importance of the occurrence and accrual of life events, plasticity, thriving, or risk over time and how these contribute to the development of particular outcomes of interest, including pathways associated with optimal health (George 1999; Kuh et al. 2003; Ben-Shlomo and Kuh 2002; Halfon et al. 2014). A number of key questions pertinent to the emergence of health development across the lifespan can be addressed using life course frameworks that would otherwise be difficult to ascertain. From furthering our understanding of familial and genetic contributions to the aetiology of health conditions to exploring the natural course of disorders in different populations and to examining the time-specific and cumulative impacts of social and environmental factors, the use of a life course framework has advanced our understanding of the systemic causes and course of multiple health conditions and positive health development.

The goal of the field of epidemiology is to advance the understanding of the determinants of health and disease among human populations. Consistent with the seven principles of LCHD (see Halfon and Forrest, Chap. 2), over the past few decades, there has been a growing recognition of the multiple determinants of most disorders and the need for a life course approach (Kuh et al. 2003; Ben-Shlomo and Kuh 2002; Halfon et al. 2014; Buka 2003; Buka and Lipsitt 1994; Angold and Costello 1995; Susser and Susser 1996). These developments in epidemiology were influenced by earlier and parallel advances in the field of human development (c.f., Baltes, Elder, Magnusson) (Baltes et al. 1998; Giele and Elder 1998; Magnusson 1996; Elder and Rockwell 1979). In epidemiology, as in other disciplines, we have come to understand that few, if any, events occur in isolation (Barker 2004; Elder and Shanahan 2007). Hence, the central focus in life course approaches to health development and life course epidemiology is on the complex process of occurrence and accrual of risks at multiple levels. For example, the probability that two identical twin infants will develop a substance use disorder may differ due to a number of subtle environmental differences

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that each encounters over the course of their life. In a recent editorial, Stephen Gilman described life course and developmental epidemiology as 'sharing the fundamental principles that health at any given point in time is substantially influenced by prior circumstances, and that disease processes unfold through a combination of risks operating at multiple levels—ranging from genetic inheritance and psychological vulnerability to social conditions' (Gilman 2002).

Epidemiological research shares basic goals with life course development concerning the origins, course, and prevention of health, disease, and disorder and, in turn, through the integration of the perspectives, the promotion of health development. Both advance through a variety of traditional and more recently developed study designs (Aschengrau and Seage 2008; Rothman et al. 2008). Each study design represents a different approach to common research questions and has implications for the ways in which study participants are selected and information is collected and analysed. The design chosen by an investigator is driven by the research question being posed along with considerations of cost, efficiency, and ethical and practical considerations (Aschengrau and Seage 2008; Woodward 2005). While many traditional epidemiological questions can be addressed through a number of alternative designs, some are of limited utility for issues at the core of a life course health development approach.

1.2 Framework for This Chapter

This chapter reviews the major design options for studying health and disease across the life course. The organization is by study design and describes major features of each design approach, key instances of each design, and potential challenges and limitations associated with each design. To limit the scope of this chapter, we take as an example the study of substance use and substance use disorder diagnosis as an instance of a complex health condition warranting investigation from a life course perspective. Study designs included are (i) cohort studies (general prospective cohort studies, perinatal/birth cohorts, twin studies, and high-risk cohort studies); (ii) case–control studies, including nested case–control studies within larger cohorts; (iii) cross-sectional studies; (iv) quasi-experimental designs; and (v) randomized controlled trials (RCTs). Although certain design strategies, namely, cohort studies, lend themselves more readily to the life course approach, we have chosen to describe other study designs that can also be used to further our understanding of health, disorder, and disease from the life course perspective. The chapter concludes with general considerations for designing life course studies, as well as recommendations for future directions of the field.

One frequent topic in life course epidemiology is the initiation, progression, and trajectories following substance use. Given the emphasis in the LCHD principles of the role of synchrony in the timing of developmental processes at multiple levels, ranging from the molecular through the historical (evolutionary), a life course approach has been useful in assessing the timing of substance use onset, the broader contexts that contribute to early use patterns, the progression from use to abuse or dependence, and the identification of intergenerational and early life experiences on substance use patterns (Magnusson 1996; Jablonka and Lamb 2005). One particular research question that has been examined extensively is the relationship between traumatic experience and the development of a substance use disorder. Over the past century, this question has been examined using a variety of different study designs in an effort to more thoroughly probe the potential causal link between trauma and the aetiology of substance use disorder. As the chapter progresses, we use this topic to illustrate the ways in which various threats to the validity of a claim for causality manifest under different study designs. For the purposes of a clear illustration, we focus on diagnosed substance use disorder as our outcome.

2 Major Design Options

In the epidemiological literature, studies are typically grouped into observational and experimental studies (Ahern and Leslie 2014; Pickles et al. 2007).

2.1 Observational

The majority of life course studies are observational studies (Pickles et al. 2007). As compared with experimental studies, in which exposures are randomly assigned to study participants, in observational designs, the investigator observes and records data on a group of people, with no active manipulation of exposure conditions, generating information on the relationships between exposure and disease as they naturally unfold. Whereas the causal inferences that can be derived from observational studies are typically not as strong as those in experimental studies, observational studies are free from the ethical dilemmas associated with allocating exposure in experimental designs. Observational studies typically take two forms, cohort studies or case–control studies; each form has a number of variations.

2.1.1 Cohort Studies

In epidemiology, a prospective cohort study[1] is one in which participants are enrolled before the outcome of interest has occurred and are then followed for a period of time. This is one of the preferred design options for studying substance use disorders across the life course because it allows for direct measurement of both exposures and outcomes as they occur, providing strong evidence for temporality of exposure–outcome relationships. These designs are also useful for illustrating the importance of the LCHD principle regarding the importance of the timing and social structure of exposure to environmental events, both normative and non-normative (Baltes et al. 2006). There remain, however, many important design considerations, challenges, and limitations in the design and conduct of such studies.

In a cohort study, participants are often selected to be representative of a larger population of interest—defining the relevant population of interest is central to designing a maximally informative cohort study. In some instances, the population may be defined by the set of key exposures of interest—e.g. a pregnancy, school-age, or midlife cohort. In others, the most informative population may be those at elevated risk of developing disease, e.g. family history of disorder and certain environmental exposures. If an investigator has multiple outcomes of interest, it can be difficult to identify specific subpopulations at risk of disease, in which case a more general population may be most appropriate.

Data are collected to provide information on the outcomes that are the focus for the study; the implications for this are particularly important in a prospective study because, as the cohort ages, an investigator may wish that additional data had been collected on another exposure or disease (Susser et al. 2000). Additionally, decisions related to study design and data collection are made relative to the science of the field when the study is initiated. This phenomenon is referred to as the scientific period effect (Susser et al. 2000; Wadsworth et al. 2003). Illustrating and reflecting how health development research is embedded in historically defined scientific periods, it has become a truism that many of the greatest discoveries of long-term prospective cohort studies were not anticipated at the time of initiation and that certain data (such as genetic material) that become relevant at a later scientific time may have been overlooked at the onset of earlier projects.

Another key consideration in designing a prospective cohort study is minimizing study dropout and loss to follow-up. Given the long periods of follow-up often involved in prospective cohort studies, it is especially important to consider procedures to minimize study dropout during the

[1]Epidemiology has traditionally made a distinction between prospective cohort studies and retrospective cohort studies, also called historic *cohort* studies, in which the primary outcomes of interest have occurred prior to the initiation of the study, but longitudinal data on both exposures and outcomes exist. Distinctions between prospective, retrospective, and even 'ambispective' cohort studies have become less prominent in more recent epidemiology texts.

planning phase. A number of strategies have been used to minimize study attrition: collection of detailed contact information, sending reminders of follow-up interviews, building rapport, and sharing study findings with participants in the form of newsletters or bulletins (Wadsworth et al. 2003; Stratford et al. 1999).

Challenges and Limitations of Cohort Studies

Cohort studies have contributed greatly to our understanding of the prevalence and distribution of substance use disorders, the course of disorders across time, and information related to utilization of substance use treatment services. They have also been useful in illustrating a number of the challenges and limitations associated with carrying out a long-term prospective cohort study. Considerable human and fiscal resources are needed to enrol, track, and retain participants and to carry out meaningful follow-up for such a long span of time. These challenges are especially prominent in life course studies on substance abuse, due to the time and effort needed to accurately assess outcomes and the multiple potential contributing risk and protective factors that operate at varied levels of influence (from molecular to societal) on the initiation and progression of substance abuse. In addition, as in all observational studies, the designers of cohort studies must anticipate concerns about both imprecisely measured and unmeasured confounding which can undermine the utility of such efforts. Faced with limited resources, investigators must balance the breadth, depth, and size of such cohorts: breadth in terms of the range of contributing conditions and potential confounders assessed, depth regarding the length and intensity of assessment, and size in terms of the number of participants enrolled. Informative cohort studies have ranged from hundreds to hundreds of thousands of participants with commensurate trade-offs between statistical power, on the one hand, and richness of data regarding the multiple complex developmental trajectories that may eventually manifest as disorder, on the other.

Finite resources demand additional trade-offs between cohort enrolment and retention. Successful cohort studies not only need a rich array of data regarding potential risk factors and outcomes, but meaningful inference also requires a high level of retention and protection against threats to validity resulting from attrition and resulting selection bias. While some attrition is inevitable, considerable creative effort and investment in subject retention is necessary to ensure that costly cohort studies yield data of maximal scientific utility. While this applies for cohort studies in general, the close relationship between many disorders and social engagement (such as participation in a prospective cohort study) poses a particularly serious challenge for life course studies. The extent to which attrition is also associated with risk conditions of interest may irrevocably reduce the potential of cohort studies to generate unbiased estimates of interest.

Despite these challenges, however, cohort studies will remain at the forefront of design options to advance the understanding of health development. The strength of a cohort in the LCHD context is primarily the ability to investigate prospectively the synergistic influences of multiple conditions (e.g. genetic, biological, behavioural, social, environmental)—both risk and protective—over time, compare influences at different phases of development, identify potentially sensitive developmental periods, and characterize longitudinal health trajectories as they unfold. They are clearly the method of choice to examine the impact of potentially adverse or risk conditions, which could not be manipulated through a randomized design, due to ethical considerations.

Major Prospective Cohort Studies of Substance Use Disorder

There are several important and well-known general prospective cohort studies examining substance use disorders across the life course. Due to space limitations, we summarize the considerations and decisions made for two of these study designs: Woodlawn Study (2017) and Monitoring the Future Study (2016). These studies serve as excellent examples of the unique type of question that can be answered, as well as the challenges that arise in conducting a prospective cohort study for

life course health development. Both studies employed a multi-wave prospective cohort design, and the Monitoring the Future study was designed to enroll a nationally representative sample of the American young adult population. The Woodlawn Study, funded by the National Institute on Drug Abuse (NIDA) and initiated in 1966, recruited a high-risk community of African-American first graders from the same disadvantaged inner city community in Chicago to examine risk factors for substance use disorder. These first graders were followed for a total of four waves: first grade, adolescence, young adulthood, and midlife. This study collected data over the life course—from childhood through adulthood—and initiated data collection prior to the onset of drug use. This design approach allows investigators to compare the onset of substance use disorder and substance use trajectories among children who had similar early roots but disparate pathways to adulthood in terms of family relationships, school, work, peer relationships, religion, and community involvement—a very useful design for a life course health development approach (The Woodlawn Project: A Life Course Study 2017).

Monitoring the Future (MTF) project, also funded by NIDA, began in 1975 using a multistage, stratified random sampling framework to enroll a cohort of participants that were representative of American high school students; each year about 16,000 students in approximately 133 public and private high schools nationwide participate. Though many use this dataset as panel data, or annual cohorts of nationally representative data, there is potential to use MTF as a prospective cohort study. Beginning with the class of 1976, a randomly selected sample from each senior class has been followed up biannually after high school on a continuing basis. Twelve years past high school, participants receive their last young adult questionnaire and then follow-up procedures change to 5-year intervals to cover middle adulthood. This study design allows for investigators to examine (1) changes in particular years such as secular trends or 'period effects', (2) developmental changes that show up consistently for all cohort groups or 'age effects', (3) consistent differences among class cohorts through the life cycle or 'cohort effects', and (4) changes linked to different types of environments or role transitions (Rothman et al. 2008). Both of these cohorts span multiple decades and multiple life stages, providing detailed information on trends in substance use disorder over the life course.

Cohort Example: Trauma and Substance Use Disorder Across the Life Course

Using data from 5 years of follow-up, Chilcoat and Breslau examined the relationship between experiencing a traumatic event and the risk for drug abuse or dependence (Chilcoat and Breslau 1998). They found that participants who had a traumatic event had more than a fourfold increase in risk of drug abuse or dependence compared with those with no history of a traumatic event, after controlling for a number of potential confounders. This study exemplifies the value of prospective cohort studies to advance causal inference in the absence of experimentation: it clearly establishes temporality of exposure (traumatic event) and outcome (drug abuse or dependence), it uses a valid measure to identify diagnoses of drug abuse or dependence (DSM-III-R diagnoses), and it takes into account a number of important factors that could potentially confound the true association between trauma and drug abuse or dependence. However, despite the study's many strengths, because it is an observational study, there remain a number of potential threats to validity. Typically, selection bias is one of the greatest threats to the validity of an observational study. In this case, however, study participants were randomly selected from the membership list of a 400,000 member health maintenance organization in Southeast Michigan. Given all participants were likely from the same region, conclusions may not be generalizable to those in different parts of the

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country. Thus, conclusions should be replicated elsewhere. Information bias is reduced in this example, as diagnoses of drug abuse or dependence were generated independent of knowledge of experiencing trauma. Finally, there remains the potential that there is residual and unmeasured confounding. It would be impossible to measure every potential confounder that occurs over the 5 years that the study spans, and, further, the study was not designed solely to address this particular research question. In any study with such a wide scope and with multiple years of follow-up, there is always the possibility that an important potential confounder was overlooked or was not adequately measured. Prospective cohort studies can span decades, which is very useful for a life course approach, but this comes with additional challenge.

2.1.2 Perinatal and Birth Cohorts

In addition to the general design features of a prospective cohort study, in a birth or perinatal cohort, there are additional challenges involved with recruiting and enrolling participants at or before birth. Parents are the primary target for recruitment, and, depending on the length of follow-up, parents may serve as the primary respondent even though the cohort of interest comprises the offspring generation. In a perinatal cohort study, the emphasis is on factors that occur in the months immediately prior to and following birth. Therefore, studies of this design typically will recruit and enroll parents (usually mothers) who are pregnant or planning to become pregnant in the near future. Data are typically collected on the mother and child throughout the pregnancy, at birth, and for a defined length of time following birth. In a birth cohort, investigators typically design a sampling scheme to target births that occur in a specific geographic region within a specified period of time. For both perinatal and birth cohorts, the length of follow-up is determined by the research questions being posed and the resources available for the study.

Issues related to data collection are another unique concern for perinatal and birth cohorts. While parents may serve as the primary respondent during the child's infancy and toddler years, it is possible to collect data directly on very young children. Special consideration, however, must be given to the length and appropriateness of data collection procedures, training of interviewers, and study consent and assent procedures to ensure adequate protection of human subjects.

Over the years, birth and perinatal cohorts have proved an invaluable source of information in the study of life course health development. Benefiting from the general strengths of cohort studies (e.g. exposure data unbiased by later health status, ability to distinguish cause from effect and temporal sequences), cohorts started at or before birth have the added value of assessing risk, protective variables, and developmental course at the earliest stages of human development. This study design enables investigators to examine the impact of the foetal, infant, and early childhood experience on health development across the life course. We now describe two influential perinatal and birth cohorts, again limiting our scope to studies that have generated substance use disorder diagnoses.

Major Birth Cohort Studies of Substance Use Disorder

There are several important birth cohorts that allow for the study of life course health development and assess substance use disorders. Some of these we describe in detail: the Collaborative Perinatal Project (CPP), New England Family Study (NEFS), and Dunedin Multidisciplinary Health and Development Study (DMHDS).

The CPP was initiated more than 50 years ago to investigate prospectively the prenatal and familial antecedents of paediatric, neurological, and psychological disorders of childhood. The CPP is, in fact, not a birth cohort but rather a prenatal cohort. Across the United States, 12 university-affiliated medical centres participated, including two in New England (in Boston and Providence). More than 50,000 pregnancies were

enrolled between 2 January 1959 and 31 December 1965 (16,557 in the NEFS sites) (Broman 1984; Broman et al. 1985). The study followed up 88% of survivors at 1 year, 75% at 4 years, and 79% at 7 years.

Data from examinations and interviews were recorded by trained staff at each site beginning at the time of registration for prenatal care, using standardized protocols, forms, manuals, and codes. At the first prenatal visit, a complete reproductive and gynaecological history, recent and past medical history, socio-economic interview, and family history were recorded. Prenatal clinic visits were scheduled monthly during the first 7 months of pregnancy, every 2 weeks during the 8th month, and every week thereafter. Blood samples were collected for serology and for storage of frozen sera. After admission for delivery, trained observers recorded the events of labour and delivery, and the obstetrician completed labour and delivery protocols. Approximately 75% of subjects had cord blood samples drawn and stored. The neonate was observed in the delivery room, examined by a paediatrician at 24 h intervals in the newborn nursery, and received a neurological examination at 2 days. Study offspring received five subsequent assessments: at ages 4, 8, and 12 months and 4 and 7 years. At each follow-up examination, the mother was interviewed about the child's history, records of medical treatment were obtained if applicable, and physical measurements were taken. Paediatric–neurological examinations occurred at 4 and 12 months and at 7 years and psychological examinations at 8 months and at 4 and 7 years. Family and social history information was obtained from the mother at intake and at 7 years. Diagnostic summaries were prepared by study physicians following the 12-month and 7-year assessments.

Between 2001 and 2004, the New England Family Study was established to locate and interview a sample of the adult CPP offspring in Providence and Boston who lived beyond 7 years of age (15,721)—resulting in a multitude of birth cohort studies spanning more than 40 years. In recent years, this team has extended the follow-up and assessment of three-generation pedigrees in the NEFS, which is still ongoing (i.e. CPP mothers, their offspring who comprise the CPP cohort members, and the offspring of the CPP cohort members). These projects all seek to integrate family designs with early life risk conditions, capitalizing upon the large number of cohort members with multiple offspring. With the increased emphasis on family designs, the overall effort was renamed 'The New England Family Study' (NEFS) (Gilman et al. 2008).

A prominent birth cohort that measures substance use disorder and has taken a life course health development approach is the Dunedin Multidisciplinary Health and Development Study (DMHDS). Investigators enrolled children from 91% of consecutive births from 1 April 1972 through 13 March 1973 in Dunedin, New Zealand. Perinatal data were obtained at delivery, and follow-ups occurred at 3, 5, 7, 9, 11, 13, 15, 18, and 21 years of age. Future assessments are planned for ages 44 and 50 years. At each assessment, study members participated in physical tests, dental examinations, blood tests, and completed computer questionnaires and surveys. At the age 21 year assessment, 94% of cohort members remained in the study, showing no significant attrition effect—a remarkable feat in a longitudinal birth cohort of this nature. Investigators attribute this low attrition rate to aggressive retention measures such as flying participants who had moved away back to New Zealand and using interviewers in other locations such as Australia (Silva and Stanton 1997). Birth cohorts such as the CPP and the DMHDS are incredibly useful for life course health development research because they allow investigators to gain knowledge of developmental processes, as well as multilevel genetic and environmental risk factors.

Birth Cohort Example: Maternal Smoking and Alcohol Use Disorder Across the Life Course

Using the New England Family Study described above, second-generation individuals were followed from birth for more

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than 40 years. Investigators examined the relationship between maternal smoking during pregnancy and lifetime risk for alcohol use disorder (DSM-IV) among 1625 offspring (aged 34–44 years) of 1254 mothers (Nomura et al. 2011). Exposure information was collected from pregnant women at their first prenatal visit, and these questions were repeated at each subsequent prenatal visit up until the time of delivery. Given the robust birth cohort design and long follow-up period, analyses were able to account for maternal mental health during pregnancy, birth weight, neurological abnormality at age 1, childhood behavioural regulation at age 7 years, and academic functioning at age 7 years. Adjusting for these developmental factors and additional demographic variables, results indicated that those with mothers who smoked at least 20 cigarettes per day during pregnancy had a 30% increased risk of lifetime alcohol use disorder. Despite the study's many strengths, there are also limitations inherent to birth cohorts of this type. First, the sample of this particular birth cohort is not representative of a broader population, and therefore external validity is potentially limited. Also, given the long period of follow-up, obstetric care at birth was very different than the modern level of care. Specifically, the mortality rate for those born prematurely was much higher in the late 1960s—thus many children suffering from behavioural regulation problems and poor academic functioning may be offered more effective assistance had they been born today. Finally, as with all observational study designs and those with long follow-up periods, there remains the potential that there is residual and unmeasured confounding. It would be impossible to measure every potential confounder that occurs over the 40 years of that the study.

2.1.3 Twin Studies

Due to their unique genetic status, twins play a valuable role in life course health development research. Using twins as study participants helps investigators advance understanding of genetic and environmental risks, differentiate between genetic influences in different subgroups of people (e.g. males versus females, different age groups, people of different race/ethnicities), and better understand gene–environment interactions. Ultimately, twin studies allow researchers to estimate the proportion of variance in a trait attributable to genetic variation versus the proportion that is due to shared environment or unshared environment (Bundey 1991). Twins are usually recruited from registries, which now exist across the globe. Twin studies can be conducted across study design types, thought the most robust would be longitudinal—similar to a prospective cohort design (Boomsma et al. 2002).

There are several important considerations in twin studies. First, studying twins who grow up in a shared environment does not allow the researcher to consider the effects of both shared environment and gene–environment interaction simultaneously. Rather, this can be addressed by including additional non-twin siblings in the design. Second, results from twin studies cannot be directly generalized to a broader population as there may be genetic factors that lead specifically to a higher incidence of twinning. This raises potential threats to external validity (Bundey 1991). Traditionally, the general consensus was that twin studies represented an optimal study design to examine gene–environment interactions across the life course. Recent criticisms of twin studies and, more generally, 'variation-partitioning' methods employed by behavioural geneticists have emerged, calling into question the extent to which such studies can shed light onto nuanced developmental processes involved in life course development (Tabery 2014; Moore 2015). Tabery (2014) posits that the traditional twin methods offer an overly 'black-box' view of development and are better for general predictions regarding future health outcomes than for

nuanced 'mechanism elucidation' of the means by which such developmental processes unfold. This criticism may be unduly harsh as (1) with human populations, observation (rather than experimental manipulation) of gene–environment interactions is the only ethical option and (2) contemporary behavioural geneticists typically avoid simplistic black-box approaches, with hypotheses and analyses informed by other biological and developmental sciences. Recent developments in high-dimensional analysis of both genetic (e.g. GWAS) and environmental (EWAS) factors may help advance traditional approaches to understand the interactive influences of genetic and environmental influences on life course health development (Patel et al. 2010).

Major Twin Studies of Substance Use Disorder

There are many twin registries and twin studies around the world, most of which are in Europe. A few of these have been used to examine substance abuse, two of which we will highlight: the Danish Twin Registry and the Swedish Twin Registry. The Danish Twin Registry was established in the 1950s and is one of the oldest twin registries in the world. The registry now comprises information on almost all twins born in Denmark since 1870. It contains data from church books, the Central Office of Civil Registration, health behaviour and lifestyle variables, and clinical examinations for more than 88,000 twin pairs (Skytthe et al. 2011). Though substance use disorder is one of many outcomes assessed in the registry data, hundreds of other studies using this registry have examined ageing, age-related health, cardiovascular disease, and other rare diseases (Boomsma et al. 2002).

The Swedish Twin Registry contains three cohorts, each differing by ascertainment and extent of data collection. The first cohort was born between 1886 and 1925. Data for the first cohort was ascertained from all parishes across Sweden and contains information on demographics, risk behaviours, cardiovascular health, respiratory health, and environmental exposures. Information on the second cohort, born between 1926 and 1958, was ascertained using nationalized birth registrations and mailed questionnaires. Information covered similar domains as the first cohort and also collected an additional personality inventory. The third cohort, born between 1959 and 1990, was identified by birth registry and has been linked to the Medical Birth Registry. Researchers working with the Swedish Twin Registry have now begun an effort called Screening Across the Lifespan Twin (SALT) study in which investigators have identified subsamples of twins in the registry for more in-depth studies in which blood samples will be obtained; phenotyping and genotyping will be performed; detailed information on health behaviours, clinical diagnoses, and medications will be collected; and linkages will be made to medical records (Lichtenstein et al. 2002). Both of these registries, as well as twin cohorts generally, pose a unique opportunity to examine the multilevel and multidimensional genetic and environmental risks for health development across the life course.

Twin Cohort Example: Childhood Sexual Abuse and Substance Use Disorder

The research literature has consistently suggested a link between childhood sexual abuse and negative health outcomes, but there remain concerns for selection bias and confounding by family environment. To address this question while minimizing confounding by family environment, investigators derived a sample of 1159 female–female twin pairs and 832 male–male twin pairs from a young adult Australian volunteer twin panel. Structured psychiatric telephone interviews were conducted to assess childhood sexual abuse and adverse psychosocial outcomes including alcohol dependence (DSM-IV) and nicotine dependence (DSM-IV). Family background information was elicited including parental fighting, parental conflict, stepparent presence, neglect, and physical abuse. Results suggested that individuals with a history of childhood sexual abuse have increased risk

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of developing alcohol and nicotine dependence. Results also showed that childhood sexual abuse is associated with substantial risk that is not explained by other family background factors. There is, however, a potential for bias. Selection bias may have arisen due to the fact that parents aware of abuse may have been less likely to volunteer their twins for research. Regardless, using a twin study approach allowed researchers to dissect the direct and correlated family background effects of childhood sexual abuse (Nelson et al. 2002).

2.1.4 High-Risk Cohort

The high-risk cohort study is a variation on the general cohort study described above, with the key distinction being that subjects are recruited because they have been selected on the basis of their exposure history. Often, subjects are identified as being at high risk for developing the outcome of interest based on particular behaviours and characteristics or manifestations of previous pathology in their parents.

Studies such as these allow researchers to better examine the natural history of disorders in relation to a particular high-risk population. One potential limitation of high-risk studies, however, is that their results, and, ultimately, the conclusions they draw, may only be applicable for high-risk populations. By contrast, high-risk studies do provide an efficient means of examining relatively rare disorders.

Major High-Risk Cohort of Substance Use Disorder

Though high-risk cohorts of substance use disorder tend to be smaller studies of very specific high-risk populations (e.g. injection-drug users, HIV-infected individuals, or the homeless), veterans have been identified as a high-risk group more likely than others to fall victim to substance abuse as a means of coping. Following the 1991 Gulf War, the US Congress and the Institute of Medicine recommended the US Department of Defense to conduct a high-risk cohort study of military personnel. This initiative was entitled the Millennium Cohort Study and is the largest prospective health study of military personnel including more than 200,000 participants. Data collection for the study began in 2001 with the 77,047 participants enrolled. Every 3 years additional participants are enrolled and an additional wave of data collection is conducted. The very first group recruited has completed five waves of data collection to date. Questionnaires at each wave assess general health, health behaviours, clinical diagnoses, physical symptoms, mental illness, health care utilization, and military life and experience. Many studies have already been conducted using this cohort and many focus on substance disorder and mental health (The Millenium Cohort Study 2010). This high-risk cohort allows researchers to better understand the risk associated with military service and seeing combat, but may not represent health development in the general population.

High-Risk Cohort Example: Posttraumatic Stress Disorder and Substance Abuse

An investigation into the relationship between posttraumatic stress disorder (PTSD) symptoms and substance abuse utilizing a high-risk cohort was conducted by Bremner et al. (1996). These investigators recruited Vietnam combat veterans with PTSD to study the effect of specific PTSD symptoms on substance abuse. Analyses examined the occurrence of substance abuse among veterans with respect to PTSD symptomology. The high-risk design ensured a large number of veterans with and without PTSD symptoms resulting in a powerful method to examine the influence of these symptoms on substance abuse. Analyses revealed a strong and consistent association between onset of PTSD symptoms and onset of substance abuse. Similarly, an increase of PTSD symptoms

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predicted onset of substance abuse. This study allowed researchers to better examine the natural history of substance abuse among Vietnam War veterans with PTSD. However, the conclusions they draw may only be applicable for this high-risk population.

2.1.5 Case–Control Studies

Unlike the study designs we have described up to this point in which participants are recruited into the study and followed over time to ascertain their outcome status, in a case–control study, participants are selected based on the presence or absence of a disorder, and exposure data are obtained after the outcome has been ascertained. Although case–control studies are not the strongest design option for conducting life course research, this particular study design has a number of benefits (Schlesselman and Schneiderman 1982). Because participants are selected after the outcome of interest has occurred, case–control studies are typically extremely cost-effective, especially in studying rare diseases. As compared with cohort studies, in which the investigator may need to follow a large number of participants for years to identify the outcome of interest, in a case–control study, the outcome has already occurred, and the investigator seeks to determine those exposures or conditions that may have contributed to this occurrence.

Challenges and Limitations of Case–Control Studies

In a case–control study, the primary threats to study validity lie in the selection of controls and in the ascertainment of exposure status. Because in a case–control study, the outcome has occurred prior to the investigator's assessment, there is a threat of recall bias (Schlesselman and Schneiderman 1982; Lee et al. 2007; Berney and Blane 1997). Exposures, by definition, occurred in the past, and those collected through participant self-report introduce the possibility of people inaccurately recalling their exposure history. Often, those who have developed the outcome of interest are more likely to examine their past exposures more carefully in an attempt to find an explanation for why they developed the disease. In a case such as this, where cases are systematically reporting exposure differently from controls, recall bias has been introduced into the study, and, because it systematically differs among exposed and unexposed, this bias may potentially skew study findings. The challenge lies in identifying a way to measure past exposures without introducing bias or inconsistencies in their assessment.

In the trauma and substance abuse literature, reports of childhood sexual abuse and physical punishment were shown to be unreliable. Specifically, unreliability arose because those who were subject to abuse often provided false-negative reports. This could cause estimates of abuse prevalence based on a single report to seriously underestimate the true prevalence; however, estimates of the relative risk of psychiatric problems conditional on abuse are robust to the effects of these reporting errors (Fergusson et al. 2000). It is very important when using a case–control design to optimize the reliability of exposure measurements to minimize or avoid the potential of recall bias being introduced into the study.

Another important limitation is the potential for selection bias. In a case–control study, identification of cases is fairly straightforward; it is the identification of controls, however, that presents a challenge (Schlesselman and Schneiderman 1982; Wacholder et al. 1992). Cases and controls must arise from the same study base; if controls were to have developed the outcome of interest, they must have been eligible to be identified as cases. Although this sounds relatively straightforward, in practice it can be quite difficult to ensure that the controls properly represent the study base from which cases have been drawn. This is an especially important point because, in order to estimate accurately the effect of exposure on the outcome, the controls are being used to estimate the exposure distribution in the study

population; therefore, a misrepresentative selection of controls could bias study results significantly (Lee et al. 2007).

Given case–control studies are conducted, retrospectively, there are not commonly ongoing examples of case–control studies as there are with cohorts. Therefore, we present a specific example of a case–control study of substance use disorder, but will not highlight any major case–control studies as we did with cohorts.

Case–Control Example: Traumas and Alcohol Abuse and Dependence

Investigators selected cases from area intervention programmes, 132 adolescents with alcohol dependence (DSM-IV) and 51 with alcohol abuse (DSM-IV), and controls by random-digit dialling and advertisement in the broader community, 73 adolescents. Questions were asked concerning lifetime traumatic events such as physical abuse, sexual abuse, violent victimization, witnessing violence, and other miscellaneous traumas. Results found that traumatic events in every category had higher rates of occurrence in the alcohol dependence and abuse groups than in the control group. Some limitations remain in this study: we cannot assume causality, adolescents with disorder may not be representative of all adolescents with disorder, community controls may not be representative of adolescents in the general population, and there may be reporting error in trauma reports (Clark et al. 1997).

2.1.6 Nested Case–Control Designs

A nested case–control study is a variation of the traditional case–control study design. In this study design, cases of a disease that occur in a defined cohort are identified, and often, a specified number of matched controls are selected from among those in the cohort who have not developed the disease. This design is advantageous when the exposure of interest is difficult or expensive to obtain and when the outcome is rare. A nested case–control design is particularly efficient due to reductions in recruitment and data collection costs with relatively minor loss in statistical efficiency (Ernster 1994). Yet, challenges and limitations of this design remain and are similar to those of a traditional case–control design.

Nested Case–Control Example: Trauma and Substance Use Disorder

Cutajar et al. (2010) investigated the relationship between childhood sexual abuse and the occurrence of substance use disorder. In this study, researchers drew cases from a pre-existing cohort of child sexual abuse victims compiled by the Victorian Institute of Forensic Medicine in Australia. This approach is referred to as a nested case–control study design. Researchers identified 2759 sexually abused children from the cohort (verified via forensic medical records assessed between 1964 and 1995). The control group was drawn from a random sample of Victorian residents from the national electoral database. This yielded 2677 age- and gender-matched controls from the general population. Both case and control participants were linked with a public psychiatric database, the Victorian Psychiatric Case Register, between 12 and 43 years later. Control subjects were matched on gender and age groupings drawn from the general population through a random sample of the national electoral database. The use of archival data from childhood to identify victims of sexual abuse lends strength to this study as it minimizes the introduction of recall bias. Yet, there is the potential for selection bias insofar as the comparison group may not be representative of the population from which the cases arose; for instance, there may be something systematically different between those with a history of childhood

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sexual abuse and those in the general population. In a study such as this, where cases are identified from forensic medical records, it can be difficult to define clearly what constitutes the study base, i.e. what group of patients would have eventually been identified by forensic medical records had they experienced childhood sexual abuse. Results from this study suggest those with a history of childhood sexual abuse have almost six times the odds of substance abuse disorder compared to those with no sexual abuse history.

2.1.7 Cross-Sectional Studies

In life course research, cross-sectional studies provide information on both the prevalence of disease and associations between risk factors and disease but typically provide little definitive information to further understanding of causal relationships. In a typical cross-sectional study, participants are sampled and interviewed at a single time point (Gilman 2002). As compared to case–control studies described above, cross-sectional studies typically place less emphasis on reconstructing past exposure; rather they provide a snapshot of prevalence of disease and associations between exposure and disease in a given sample at a given time often limiting the inference we can make regarding the temporal sequence between exposure and disease. Another difference from case–control studies is the sampling framework. In case–control studies, a great deal of effort is placed on sampling an informative set of controls that are representative of the population that gave rise to the case. In cross-sectional studies, participants may include either a sample of convenience (based on their availability and willingness to participate) or they are often based on a representative sample of the general population (which allows for high generalizability). Cross-sectional studies, while not typically considered a strong design option for life course research, provide important insight into the prevalence of disorders in a population and can provide initial evidence as to potential associations that can be investigated further using a more stringent study design (Kraemer et al. 2000). Additionally, retrospective data can be collected from participants either using archival data or during the interview process in an attempt to reconstruct past exposure history.

Challenges and Limitations of Cross-Sectional Studies

Cross-sectional studies have a host of limitations. First, if the sample is a convenience sample, rather than representative of the population, threats to external validity exist. Second, non-response can result in bias of study measures. For example, despite trying to sample for a representative population, many individuals may not respond due to having severe negative health outcomes or being part of a high-risk, transient population; both of these examples would result in a loss of critical study information. Also, due to the cross-sectional nature of data collection, temporality of the exposure and outcome cannot be confirmed. Finally, cross-sectional designs are not suitable for studying rare diseases or diseases with short duration.

Major Cross-Sectional Studies of Substance Use Disorder

There are many publicly available, nationally representative cross-sectional surveys conducted in the United States. Of these, several include measures of substance use disorder. We will describe one of these: the National Survey on Drug Use and Health (NSDUH). The NSDUH provides national- and state-level data on substance use, disorder, and mental health in the United States. It is sponsored by the Substance Abuse and Mental Health Services Administration. The NSDUH is administrated annually to approximately 70,000 randomly selected individuals aged 12 years and older. The goals of NSDUH are to provide accurate prevalence estimates on the level and patterns of substance use and abuse, track trends in substance use, assess the consequences of substance use, and identify groups at high risk for substance disorder. Though this cross-sectional survey assesses

different individuals over time, it provides useful information on secular trends of and consistent risk factors for substance use disorder (National Survey on Drug Use and Health 2017).

Cross-Sectional Example: Trauma and Substance Use Disorder

Returning to our examination of the relationship between trauma and substance use disorder, Molnar, Buka, and Kessler conducted a cross-sectional study using a US national household probability sample of 8098 participants aged 15 to 54 years from the National Comorbidity Survey (Molnar et al. 2001). Given the size and relatively low cost of a single cross-sectional assessment, researchers were able to account for age, race, parental divorce, parental psychopathology, parental verbal and physical abuse, and parental substance use problems while examining the association between childhood sexual abuse and substance use disorder (DSM-III-R). Results found those with a history of childhood sexual assault had about a twofold odds of drug dependence and 1.7 times the odds of alcohol dependence compared to those with no history of childhood sexual assault. However, cross-sectional data do not allow for causal inferences to be made about the relationship between being assaulted and substance use disorder; given that all data are from one time point, there is no evidence as to the temporality of the exposure–outcome relationship. Further, information bias can arise depending on how data are collected. In the example above, timing and characteristics of childhood sexual assault and substance use disorder were self-reported, introducing the possibility of reporting bias and recall bias. Cross-sectional studies also have the potential for unmeasured confounding. Given that all data are collected from one time point, many other factors that could be influencing the association of interest are not captured by the one-time assessment.

2.2 Quasi-Experimental Designs

Unlike true experiments, where the investigator manipulates the exposures or conditions affecting research participants, quasi-experiments are characterized by investigator manipulation of observations (not treatments). Given the focus of this chapter, observations would typically be assessments of substance use disorder, implemented after the occurrence of major events of relevance to life course theory—such as natural disasters (e.g. Hurricane Katrina), acts of terrorism, and events resulting from policy changes and the like, such as marijuana legalization. Such quasi- or natural experiments largely differ from traditional observational studies in that participants are largely 'selected' into exposed or unexposed groups by an event that is substantially not within their own control.

2.2.1 Challenges and Limitations of Quasi-Experimental Studies

As natural experiments, these studies are often less subject to selection bias than typical observational studies. However, at the same time, attempts to study the consequences of such quasi-experiments may be hampered by the challenges of responding quickly to initiate an investigation soon after a natural occurrence of interest has taken place. Poorly implemented efforts may introduce problems related to both information bias (where respondents are typically not blind to the event of interest and may provide non-comparable information) and confounding, where the investigation may not be able to assess the full relevant set of potential confounding factors.

Quasi-Experimental Example: Trauma and Substance Use Disorder

Returning to our example on trauma and substance use disorder, Reijneveld et al. found themselves in a position to examine the impact of trauma in a natural experiment (Reijneveld et al. 2003). In 2001, a fire in a café in Volendam, Netherlands, wounded 250 adolescents and killed 14.

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Surprisingly, 15 months prior to the disaster, all students aged 12–15 years from a school in Volendam (of whom 31 had been in the café during the fire), and from two other schools, had been selected as controls for a study. Five months after the disaster, researchers obtained follow-up data from Volendam adolescents and controls from the other two schools. Contrary to previous study designs, which examined the impact of trauma on substance use, Reijneveld et al. were able to examine this relationship in a setting in which trauma, a potentially strong explanatory variable for substance use, was directly manipulated by forces outside the control of the researchers. The exposure (the disaster) was a horrific accident; yet, only adolescents living in Volendam were 'exposed'. Compared with an observational design, in which there are very many interrelated factors impacting an adolescent's likelihood of exposure to trauma, in this study, trauma was controlled by a force outside of the researchers' and participants' control (an 'exogenous' factor). It was not, however, randomly assigned; the exposure to the disaster was correlated with going to school in Volendam, raising potential concerns of remaining confounding. Therefore, any factors related to neighbourhood or town that differ between those exposed to the fire and those not exposed were not addressed. The authors observed that Volendam adolescents who were exposed to the disaster had almost fivefold the odds of excessive alcohol use compared to other adolescents, providing important new evidence supporting the causal relationship between trauma and excessive alcohol use among adolescents.

2.3 Experimental Designs

In experimental studies, such as randomized control trials (RCTs), participants are randomly assigned to receive exposure or not with the exposure being manipulated by study investigators. Given a large enough sample, the implications of this randomization and manipulation of exposure are related to the inferences that may be made about causality. When exposure is truly assigned at random to study participants, it is assumed that, on average, all known and unknown confounders are evenly distributed across the study arms and, therefore, that the two arms of the study are exchangeable. When these and other conditions are fulfilled (adequately large sample, effective randomization, reasonably representative sample, meaningful external validity/generalizability), RCTs provide a unique opportunity to generate evidence of the causal impact of exposures on subsequent health and development. As discussed below, conventionally the major limitations raised regarding experimental studies concerned feasibility and ethics. More recent contributions from the developmental and social sciences raise more fundamental questions regarding the utility of experimental approaches in the context of rich and multifactorial developmental processes such as those involved with life course health development (Lerner and Callina 2014; Sampson 2010).

2.3.1 Challenges and Limitations of Experimental Studies

In substance abuse epidemiology, investigators typically examine the impact of harmful exposures or 'risk factors' on substance use disorders; obviously, the random allocation of harmful exposures to study participants is not ethically permissible. To illustrate, researchers have long wanted to understand the impact of trauma on the development of substance use disorder; nevertheless it would be unethical to randomly assign participants to undergo a traumatic life event so that investigators could study their response. Further, logistic considerations and the high cost associated with the long-term follow-up of subjects further limit the use of RCTs in life course research. As a result, due to the ethical considerations combined with practical constraints, experimental studies (in particular of potentially harmful conditions) are not often used in psychiatric or substance use research. Randomized controlled trials pertaining to trauma and substance use disorders

are limited to those that assess the effectiveness of treatments or interventions such as cognitive behavioural therapy or sertraline administration (Cohen et al. 2007; Van Dam et al. 2012).

Randomized Controlled Trial Experimental Example: PTSD and Substance Use Treatment

A recent RCT by Mills et al. aimed to determine whether an integrated treatment for PTSD and substance dependence can achieve greater reductions in PTSD and substance dependence symptom severity compared with usual treatment for substance dependence (Mills et al. 2012). In 2007–2009 in Sydney, Australia, 103 adults with diagnoses of PTSD and substance dependence were recruited from substance use treatment services, media advertisements, and practitioner referrals. Fifty-five participants were randomized to receive Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE) in addition to usual treatment for substance dependence, and 48 were randomized to receive the usual treatment only. Participants were reinterviewed at 6 weeks, 3 months, and 9 months. Results suggested the treatment group had significant reductions in PTSD symptom severity relative to the control group, yet there was no significant difference in prevalence or severity of substance dependence between treatment and control groups. Whereas this study does not perfectly map on to previous examples examining the relationship between trauma and substance use disorder, it does illustrate the strengths of the RCT for life course research. In this study, the randomization of adults diagnosed with PTSD and substance dependence created groups that appear to be exchangeable at baseline. Exchangeability of the groups allows us to make comparisons between the groups under the assumption that the groups are identical with the exception of the treatment. Further, we would expect that randomization would eliminate the potential for selection bias to occur in the allocation of treatment, thus preventing systematic differences between the two groups (i.e. all participants have equal probability of receiving treatment or control). RCTs can be incredibly informative for establishing causation between an exposure and an outcome, though many exposures would be unethical for an investigator to administer. However, in assessing the impact of treatments for disorders throughout the life course, RCTs would be the gold standard.

3 Discussion

We close by revisiting several of the central principles of the life course health development framework introduced at the beginning of this volume (see Halfon and Forrest 2017) and discussing opportunities to advance understanding of the causes and promotion of health development through the various research design alternatives covered in this chapter. The current chapter discusses traditional epidemiologic designs and offers examples of how these have been altered and extended to contribute to our nascent understanding of how health and disease develop across the life course. However, the concept of 'health development' goes beyond traditional and often static definitions of 'health', 'disease', and 'disorder'. Fully integrating the life course health development framework into study design selection requires new thinking and innovation from the epidemiology community. As outlined in Principle 1, health development—the focus of scientific inquiry in this field—is conceptualized as a dynamic process that 'combines both health and development…blends a temporal dimension into our conceptualization of human health… {with} time-dependent and transactional connotations' (p. 15). Designs that are faithful to

this view will require new perspectives, measures, and analytic methods. Developments in latent class trajectory modelling (Nagin 2016), behavioural trajectories, and their investigation in multilevel contexts (Cerda et al. 2008) are all contributing to this extension of traditional design approaches.

Principle 3 in the LCHD framework addresses the topic of complexity. Complexity refers to how health development is dependent upon complex reciprocal interactions between individuals and their physical, natural, and social environments. To appropriately study complexity, a broad array of individual and environmental factors must be measured. Epidemiologic methods allow for the assessment of interactions and multiple interactions in studies; however, the number of variables and variable interactions assessed is inversely related to the resulting level of statistical power and directly related to the number of type II or false-positive findings. Similarly, understanding that interactions play an important role in health development, researchers should examine bidirectional relationships between individual and environmental characteristics. Future studies examining interactions should be designed as longitudinal studies (to determine temporality/causality), and large sample sizes should be used to increase power to detect important interactions. New efforts to develop 'environment-wide association study' (EWAS) methods, to parallel genome-wide association studies (GWAS) and new developments in machine learning, may provide additional solutions to the problem of sample size and growing numbers of potential risk and protective factors (Patel et al. 2010). Also, given the complexity of the life course approach, it is unlikely that a single study will definitively advance LCHD theory. Rather, a compilation of studies from different populations (or the same population over time) at different stages in the life course and across different realms of development (e.g. physical, social, environmental, genetic, epigenetic, etc.) and contexts will be necessary for advances regarding health development throughout the life course.

Another fundamental element principle of the LCHD framework is timing. This principle refers to the concept that there are specific developmental stages throughout the life course (e.g. in utero, pubescence) in which the impact of certain exposures on an individual can be greater than during other periods, with the attendant implications of the importance of nurturing children when they are most sensitive to these influences. Reflecting the importance of the time dimension for health development, this principle further underscores the value of prospective cohort designs, not only as these involve the study of time, but also, in contrast to retrospective or cross-sectional designs, they permit more accurate prospective assessment of multiple risk and protective conditions as these occur. For example, the landmark Adverse Child Experiences Survey has documented the association between childhood adversity and a range of poor health outcomes, using adult retrospective reports of child experiences (Felitti et al. 1998). Refined understanding of the impact and timing of such early adverse experiences will, however, require prospective studies that are less subject to potential recall, detection, and selection biases (Widom et al. 2015). Interest in 'timing' does not necessarily always imply the need for longitudinal designs. Cross-sectional studies conducted during particularly sensitive stages of the life course could also be informative, and preferable to cross-sectional studies during other, less impactful periods. Also, in longitudinal cohorts, researchers may want to consider giving more weight to exposures during these sensitive periods. Collaboration across disciplines will help suggest certain stages in the life course that are likely to have particular relevance for long-term health development, for example, due to a propensity for epigenetic alterations or other forms of biologic sensitivity (Moffitt 2013).

In closing, life course approaches to advance understanding of the causes and prevention of disorders are rich in both potential and challenges. Relatively rare disorders and outcomes require large sample sizes; complex conditions require considerable effort and resources for accurate assessment and characterization; multiple contributing factors from the molecular to the

societal level require rich exposure assessments; and the complexity of the human condition introduces a range of potential confounding factors. Each of the study designs presented in this chapter has advanced our knowledge of how disorders originate, progress, may be treated, and may diminish over the life course. Yet they have been traditionally used to investigate relative static conditions, disorders, and disease states. Further work applying the principles of life course health development to study design, measurement, and analytic approaches are essential to help realize the goals and aspirations of the life course framework (Buka and Lipsitt 1994; Buka 2003).

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