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Review article

Expanding conceptual frameworks: Life course risk modelling for mental disorders

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ABSTRACT

Psychiatric epidemiology has made significant contributions to the identification of risk factors for mental disorders. Available evidence underscores the complexity of the interactions between risk and disease and highlights conceptual and methodological challenges particularly in examining risk and disease relations beyond the level of simple associations. We propose that a life course approach in the study of risk factors for mental disorders, combined with fast developing analytical statistical tools, is the most promising avenue towards shifting the focus of the field from associations to generating and testing aetiological hypotheses. This review presents the basic tenants of life course risk modelling, highlighting key examples in the available literature that demonstrate the potential of this approach to advance our understanding of the trajectories from risk to disease and discusses priorities for future research.

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1. Introduction

Psychiatric epidemiology and especially analytical epidemiological studies have made great advances in identifying multiple risk factors for mental disorders, particularly for schizophrenia, mood disorders and anxiety disorders. Across diagnostic categories key risk factors include low socioeconomic status (SES) (Danese et al., 2009), familial psychopathology (Lichtenstein et al., 2009), stressful life events (SLEs) (Kendler et al., 1999), low IQ (Koenen et al., 2009), family dysfunction (Bouma et al., 2008) and cannabis use (Degenhardt et al., 2007). Although informative, these reports are commonly limited to simple associations between a risk exposure and a later adverse mental health outcome while the timing and exact mechanism of this transition remain largely unstudied. Here we advocate a life course approach in the study of risk factors for mental disorders as this has the potential to advance our understanding of the trajectories from risk to disease.

Within the current cohort designs, life course formulations have the potential to shed light on the mechanisms as well as the timing of exposures underlying the development of psychopathology, especially when combined with the appropriate analytical statistical tools. The objectives of this article are threefold: (a) to complement recent reviews on early risk factors and genetic variants for common mental disorders, e.g. schizophrenia (Brown and Derkits, 2009), by highlighting the additional value of the life course approach; (b) to present the basic concepts of life course

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risk modelling; and (c) to highlight key examples for its usefulness for psychiatry and public health. The examples presented provide evidence on how the life course approach can serve as the starting point in addressing questions about mechanisms mediating between risk and disease outcome on a more fundamental level. Finally, we make specific suggestions as to how life course modelling can be more fully integrated into psychiatric epidemiological research. Such information is crucial in moving the field from an associative focus to generating and testing aetiological hypotheses.

2. Life course approaches in epidemiology

The life course approach was mostly developed within the field of cardiovascular medicine from which we draw key examples to illustrate its two basic tenants, namely critical periods and accumulated risk (Lynch and Smith, 2005).

2.1. Critical periods

Life course models recognise that the timing of exposure plays an important role in determining the risk for disease. In this context life course models focus on critical or sensitive periods. The critical period model assumes that there are stages in human development during which the influence of external agents may have crucial effects that cannot be altered by subsequent events and precipitate disease in later life. Conversely, the influence of the same agents during any other developmental stage will be minimal or absent. Implicit in the critical period model is the notion that the influence of external agents, when it occurs during this particular stage, alters the function or structure of biological tissues or systems through processes of "biological programming" so that the effect of the exposure becomes "embodied" (Kuh et al., 2003). In contrast, sensitive periods are stages in development when the influence of external agents may have the strongest effect on disease risk that could be however modified by subsequent experiences or exposures (Kuh et al., 2003). At this particular junction, the distinction between critical and sensitive periods is often blurred as the basic biological effects of exposures that could result in altered "biological programming" which are poorly understood. For simplicity and parsimony we will refer to all models focusing on the timing of exposures as critical period models.

The best evidence for the critical period concept derives from the foetal origin hypothesis in cardiovascular medicine. It proposes that adversity very early in pregnancy, and especially poor maternal nutrition, leads to impaired growth and biological programming of the foetus, thus increasing the risk of cardiovascular disease later in life (Barker, 1995; Barker and Clark, 1997; Barker and Osmond, 1986; Eriksson et al., 2001; Painter et al., 2006). The incidence of Coronary Artery Disease (CAD) is increased following exposure to famine in the first trimester of gestation but not if exposure to famine occurs in mid- or late-gestation (Painter et al., 2006).

2.2. Accumulation of risk

The accumulation of risk model suggests that exposures or insults act in a cumulative fashion to gradually increase the risk of disease or mortality. This hypothesis postulates that cumulative differential life time exposure is the main explanation for observed individual differences in disease risk (Kuh et al., 2003). Numerous studies have examined the risk accumulation hypothesis in relation to medical outcomes, health inequalities and social, physical and cognitive functioning (Power et al., 1996; Lynch et al., 1997; Smith et al., 1997; Hart et al., 1998; Power et al., 1999; Holland et al., 2000; Wamala et al., 2001). There are two main variations to the risk accumulation hypothesis relating to whether there is prolonged exposure to a single risk factor or an interaction between multiple factors either in an additive (risk clustering) or in a sequential fashion (chains of risk) (Kuh et al., 2003).

A typical example for the prolonged exposure model was provided by Smith et al. (1997). They employed a prospective observational study design with a 21 year follow-up focusing on mortality. They examined the risk of lower SES at three time points, in childhood based on father's occupation and in early and late adulthood respectively based on own first and more established occupation. They found a cumulative effect of lower SES acting over the lifetime; people who reported belonging to the low SES group at a single measurement point had a relative death rate of 1.29 (95% CI 1.08–1.56) which increased further to 1.71 (95% CI 1.46–2.01) for those reporting belonging to the low SES group at all three measurement points. Similarly, Wamala et al. (2001) report that, in women, early and late socioeconomic advantage are respectively associated with a 2.48 (95% CI 0.90–6.83) and a 3.22 (95% CI 1.02–10.53) increase in the risk for Coronary Heart Disease (CHD). However, women with both early and late exposure had an even greater risk of 4.22 (95% CI 1.4–12.1).

We now focus on how risk factors may interact to increase risk. Different risk factors may cluster together and may act cumulatively to increase risk. For example, Luchsinger et al. (2005) demonstrated by following 1138 individuals for 5.5 years that diabetes, hypertension, heart disease, and smoking were all associated with a higher risk of Alzheimer's disease. In a subsample of people with high risk for Alzheimer's disease ($N=246$) the risk conferred by the risk factors individually ranged from 1.4 to 3.6 (adjusted for age and gender). The hazards ratios of the interactions between these factors varied greatly and were highest for the interaction of diabetes and smoking which reached 13.7 (95% CI 1.8–101.7).

Alternatively, risk factors may be linked forming chains of risk or insults whereby each exposure may lead to further adverse exposures or experiences. Each link in the chain may have an independent effect on disease risk or else disease onset may be predicated only by the final link (trigger effect; Kuh et al., 2003). Dong et al. (2004) provide a detailed example of this model in relationship to ischaemic heart disease. They mapped the pathway from childhood adversities (including abuse, neglect and household dysfunction) to increased reactivity to stress leading to increased risk for negative affective states. Negative affective states (depression or anger) are now known to cause haemodynamic, haemostatic, immunologic and other endocrine changes leading to alterations in the platelet function and increased risk of coronary ischaemia.

3. Life course approaches within the psychiatric epidemiological research

Within psychiatric epidemiology, cohort designs have the greatest potential to shed light on causal mechanisms by which exposure to risk can lead to the development of mental disorders. They provide a framework for overcoming recall biases and allow the consideration of exposures and outcomes in a temporal context. Moreover, they provide data amenable to life course analyses and are therefore the ideal ground for generating and testing aetiological models for mental health. The most prominent birth cohorts include the Dunedin Multidisciplinary Health and Development Study (DMHDS) (Silva, 1990), the British 1946 Birth Cohort (BBC) (Wadsworth, 1987), the National Child Development Study (NCDS) (Power and Elliott, 2006), the 1970 British Cohort Study (BCS) (Ferry et al., 2003), the Northern Finland 1966