Chapter 16
Life Course Epidemiology

Toshiyuki Ojima and Katsunori Kondo

1 Definition of Life Course Epidemiology

Life course epidemiology is defined as "the study of long-term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood, and later adult life" [1, 2]. This term has been used widely since the first edition of the book by Kuh and Ben-Shlomo was published in 1997. A similar term is "life course approach," which was used by psychologists, sociologists, demographers, anthropologists, and biologists for many years before being adopted in the field of epidemiology [1]. In Japan, Kondo [3] has discussed the use of the life course approach for some time.

One famous historical study is the fetal origins hypothesis, which was published by Barker et al. in 1986 [4]. From an ecological study of 220 regions in England, they found that the standardized mortality ratio for ischemic heart disease and bronchitis in adults between 1968 and 1978 was high in regions with high infant mortality between 1921 and 1925. These findings led them to speculate that undernutrition during gestation or infancy could cause the development of disease in adulthood. Even earlier in 1951, the World Health Organization published a report [5] by

Toshiyuki Ojima is also the English translator for this chapter.

T. Ojima (✉)
Department of Community Health and Preventive Medicine, Faculty of Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan
e-mail: ojima@hama-med.ac.jp

K. Kondo
Professor of Social Epidemiology and Health Policy, Department of Social Preventive Medical Sciences, Center for Preventive Medical Sciences, Chiba University, Chiba, Japan

Head of Department of Gerontological Evaluation, Center for Gerontology and Social Science, National Center for Geriatrics and Gerontology, Obu City, Aichi, Japan

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Bowlby regarding the poor development of children after separation from their mother and placed in the care of an institution such as an orphanage (deprivation of maternal care). Although the term "life course" has only been used in recent years, the concept has existed for some time and relevant research has been conducted.

2 Significance and Recent Development

Life course epidemiology has recently gained increased attention, probably as a result of several factors. One is that the links between lifestyle habits during adulthood and subsequent lifestyle diseases have become well understood, so that understanding the factors preceding adulthood has become important for future research. Although it is still possible for people to change their lifestyle habits during adulthood, albeit with great effort, they cannot change the factors that impacted them during childhood or in utero, which are important social determinants of health. Life course epidemiology provides researchers with the capability to understand such factors. On that account, interventions in earlier life stages may be more cost effective than interventions in adult life to prevent noncommunicable diseases. Furthermore, life course epidemiology is gaining attention because it can bring researchers closer to understanding the causal associations and mechanisms of development of diseases. In other words, longitudinal studies from childhood would be useful to determine which factors are actual causes, confounding factors, or intermediate stages among various factors. Moreover, life course epidemiology can also be used to study biological factors jointly with socioeconomic factors.

Common study designs in life course epidemiology have included ecological studies and retrospective cohort studies. The results from prospective cohort studies that have tracked participants from birth are now starting to be published. Although we do not discuss the issue of study design in detail, we point out the analytical problems such as repeat observations, hierarchical data, latent exposures, and multiple interactive or small effects [1], as well as this emerging field with respect to factors such as developments in epidemiological research methodologies. Advances in computing capabilities that have made it easier to conduct complex statistical analyses, such as multilevel analysis (also called hierarchical linear modeling or latent growth modeling), have also driven the growth of life course epidemiology.

3 Basic Theories

Two types of conceptual model, as shown in Table 16.1, the critical period model and the accumulation of risk model, address why early life factors including in utero and childhood factors increase the risk for diseases during adulthood [6]. The critical period model postulates that certain periods in life have an important meaning. The simplest example of this model is that children whose mothers took thalidomide

Table 16.1 Life course conceptual models

Critical period model
• Does/does not become a risk factor in adulthood
• Becomes a modifying factor in adulthood
Accumulation of risk
• Caused by independent, noncorrelated factors
• Caused by correlated factors
–"Risk clustering"
–"Chains of risk" caused by additive effects or a trigger effect

during a certain period of gestation developed phocomelia; no such danger exists if the mother takes thalidomide at any other time. In this example, phocomelia develops because exposure occurs during the period of in utero growth, when the structure of the limbs develops. Recent studies have shown that the same phenomenon occurs with function, and it is now believed that the in utero environment has a profound effect on shaping the functions related to metabolism and hormones. However, unlike the effects on structure, the effects on function can be changed even during adulthood. At a more detailed level, even if genes themselves are determined at conception, gene expression (epigenetics) later in life can also affect function [7]. A similar concept is "biological programming." It should be noted that the term "sensitive period," which is a similar concept to the critical period, is often used without clear differentiation. Strictly speaking, the "critical period" denotes that the effects of exposure appear only when the exposure occurs during that period and do not occur during any other period. The term "sensitive period" is used if the effects are more likely to appear during that period but can still occur during other periods. A slightly more complex mechanism within the critical period model is the influence of effect modifiers (interactions). For example, it is now known that low birth weight increases the risk of ischemic heart disease during adulthood in individuals who develop obesity in childhood or adulthood, but not in those who do not develop obesity. In addition, a better understanding of the interactions between social and biological factors is anticipated.

Another conceptual model is the accumulation of risk model. This model postulates that various factors gradually accumulate throughout life and cause diseases to develop in adulthood. This accumulation can arise from various independent factors that do not correlate with each other. For example, the factors of being involved in a car accident, incurring a job loss, and experiencing the death of a spouse may accumulate incidentally, leading to the onset of a disease. In another pattern called "risk clustering," various factors correlate with one another. For example, low birth weight, childhood undernutrition, secondhand smoke, and a low education level can overlap. Such factors likely arise from a common cause of low socioeconomic status (SES) during childhood. Another concept is "chains of risk," in which, for

example, job loss could bring about financial difficulties, causing marital discord or domestic violence, subsequently leading to divorce. It is important to understand the chain of risk because intervening in the chain at some point can prevent the situation from deteriorating.

In the broader picture of life course epidemiology, it is important to consider intergenerational effects. The environments of the grandparental generation, the parental generation, and the generation of children and their siblings intertwine at the country level, the community level, and the household level. When a person is living far from their grandparents, they share only a country-level environment. On the other hand, community-level and household-level environments directly affect parents and their children, as well as children and their siblings. If time is added as a variable, various effects such as cohort effects from childhood and period effects common to three generations can intertwine. Although it is complex, life course epidemiology is an important and interesting field of research.

4 Research Results

Studies in life course epidemiology have revealed various findings, which are briefly summarized in the literature [8, 9]. In particular, factors such as low birth weight and low SES during childhood increase the risk of coronary artery disease, cerebral hemorrhage, and chronic obstructive pulmonary disease. Conversely, the risk of breast cancer increases when birth weight and SES during childhood are high. Reviews also summarize various risk factors for type 2 diabetes such as the increased risks associated with abnormally high or low birth weight.

Infectious diseases are another important topic in life course epidemiology [10]. For example, it is well known that hepatitis C infection increases the risk of hepatoma later in life and that varicella zoster infection during childhood can cause herpes zoster during adulthood.

Several studies have also been conducted in Japan. In a cohort study of adults, Tamakoshi et al. [11] examined maternity health records and found that low birth weight increased a person's susceptibility to hypertension in adulthood. Sekine et al. [12] followed a birth cohort in Toyama Prefecture until the subject's first year of high school and analyzed relationships with lifestyles in their health check-up data at the age of 3 years as baseline data. They revealed that having a large number of undesirable lifestyle habits such as skipping breakfast, physical inactivity, and long hours of watching television is associated with an increased risk of developing obesity in later life [12]. Suzuki et al. [13] followed a group of children from before birth to 10 years of age as Project Koshu and found that boys whose mothers smoked during pregnancy had a higher body mass index, but the same association was not observed in girls.

The Japan Gerontological Evaluation Study (JAGES) have published several papers that revealed relationships between childhood events or SES and health status in older years. Matsuyama et al. [14] reported that adverse childhood experiences

(ACEs) were significantly associated with fewer remaining teeth after adjusting for covariates (odds ratio = 1.14). Amemiya et al. [15] revealed that ACEs showed significantly greater higher-level functional limitation (prevalence ratio = 1.46, adjusting for age, sex, and childhood disadvantage). Moreover, Tani et al. [16] showed that low childhood SES was positively associated with depression onset (risk ratio = 1.44). Yanagi et al. [17] reported that older people with low childhood SES were 1.36 times more likely to have poor fruit and vegetable intake (FVI) than those with high childhood SES. They suggested that a school lunch program could help improve FVI because the relationship was not observed among people aged 65–69 years who were fully exposed to such a program [17].

In Japan, a couple of national projects on life course epidemiology are ongoing. The Ministry of Health, Labour and Welfare has been conducting the Longitudinal Survey of Newborns in the Twenty-First Century since 2001 and since 2010 [18]. The Ministry of the Environment has conducted the Japan Environment and Children's Study since 2011, involving 100,000 mother–child pairs living throughout Japan [19].

5 Future Outlook

The research results from life course epidemiology have started to be used for development of health policy. Through its Recommendations for the Control of Lifestyle-Related Diseases from Before Birth through Childhood, which summarize research findings from Japan and abroad, the Science Council of Japan advocates the importance of awareness and education on the health problems that can arise in adolescent and young women who are underweight, among other issues [20].

Although targeting lifestyle habits during adulthood plays a specific role in preventing adult diseases, it is difficult to substantially reduce the incidence of such diseases with that approach alone; it is important to target childhood influences, intergenerational influences, physiological factors, and socioeconomic factors. Progress in life course epidemiology research should help to build a more detailed understanding of such factors and make it possible to target them effectively.

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