Life Course Epidemiology in Nutrition and Chronic Disease Research: A Timely Discussion

Niyati Parekh and Claire Zizza

Department of Nutrition, Food Studies and Public Health, Steinhardt School, New York University, New York, NY; Department of Population Health, Langone School of Medicine, New York University, New York, NY; and Department of Nutrition, Dietetics and Hospitality Management, Auburn University, Auburn, AL

ABSTRACT

Humans are exposed to a complex and changing combination of nutritional factors during the life course, necessitating their investigation over time to capture “critical periods of sensitivity.” A life course approach provides a framework to examine trajectories and long-term effects of nutritional and other risk factors, particularly the role of timing, accumulation, and temporal relationships of these exposures in relation to chronic disease development. Currently, most epidemiologic research does not sufficiently address this issue in relation to disease etiology. Although applying a life course approach would augment our knowledge about disease development, this approach presents major challenges in designing, conducting, and analyzing studies. A scientific symposium was held that reviewed emerging research and discussed methodological concerns in applying the life course approach. The research presented at this session focused on the role of timing, with the pre- and postnatal and pubertal periods as critical windows of exposure for chronic conditions. Methodological issues and complexities in analyzing and selecting datasets were highlighted. This symposium elucidated unique study designs and statistical strategies to demonstrate the strengths of this methodology, and served as a catalyst for new research in the area of nutrition and chronic disease epidemiology.

Introduction

Life course epidemiology is a methodology that includes studies of the biological, environmental, and psychosocial pathways that operate over an individual’s life span and across familial generations to influence health and describe the natural history of complex diseases. A life course approach provides a framework to examine trajectories and long-term effects of nutritional and other risk factors, particularly the role of timing, accumulation, and temporal relationships of these exposures in relation to chronic disease development. Lessons learned from birth and childhood cohorts are that fetal and early life shape the risk profile for the development of subsequent chronic diseases. A classic example of life course research comes from the Dutch famine of 1944, known as the Hunger Winter, that took place near the end of World War II, affecting approximately 4.5 million people. Individuals in utero during the famine, who thus experienced adverse fetal conditions and were subsequently exposed to plentiful food, were found to have increased rates of chronic diseases in adulthood.

Humans are exposed to a complex and changing combination of nutritional factors during the life course, necessitating their investigation over time to capture “critical periods of sensitivity.” Currently, most epidemiologic research does not sufficiently address this issue in relation to disease development. Animal and laboratory studies, an integral component of chronic disease research, have been used to address life course exposures; however, evidence from those studies is not directly interpretable for humans, because such studies are approximations of human mechanisms. For these reasons, our knowledge of chronic disease pathophysiology may be incomplete. In fact, the 2011 Institute of Medicine report “Breast Cancer and the Environment: A Life course Approach” emphasized the need to adopt this methodology. Applying a life course approach would augment our knowledge about disease development; however, this approach presents major challenges in designing, conducting, and analyzing studies.

To address the aforementioned gaps, a scientific symposium was held at Experimental Biology 2013 that reviewed emerging research and discussed methodological concerns.
in applying the life course approach. This session, organized by the Nutritional Epidemiology Research Interest Section, was chaired by Drs. Niyati Parekh and Claire Zizza. Experts in the field were brought together to showcase the present state of knowledge using examples from their own research in population studies. The research presented focused on the role of timing, with pre- and postnatal and pubertal periods as critical windows of exposure for chronic conditions. Methodological issues and challenges in analyzing and selecting datasets were highlighted.

**Summary of talks**

**Pre- and postnatal risk factors of childhood obesity: Dr. Matthew Gillman.**

According to the International Society for Developmental Origins of Health and Disease, perturbations during the perinatal period can lead to lifelong irreversible health consequences. The linkages between perinatal programming and subsequent adiposity and cardiometabolic consequences are well established in animal models and are now emerging in humans. Dr. Matthew Gillman described his findings from Project Viva, a cohort study of pregnant women and their offspring that investigates the impact of prenatal and perinatal factors on outcomes of pregnancy and childhood among the offspring. Childhood obesity and cardio-metabolic risk factors were outcomes of particular interest in addition to other outcomes, including asthma and allergies, cognition, and behavior. In Project Viva, school-age children had a 28% chance of being obese if their mothers smoked during pregnancy, had excessive gestational weight gain, breastfed for <1 y and the mothers’ infants slept daily for <12 h, whereas the probability was only 4% in the absence of these 4 risk factors. In a different analysis, higher perinatal leptin was associated with lower 3-γ adiposity, and higher leptin at age 3 y was associated with greater weight gain by age 7 y, suggesting a critical period of leptin sufficiency around the age 3 y of life. During infancy, early introduction of solid foods (before 4 mo vs. 4–5 mo) was associated with a 6-fold increase in obesity at age 3 y. The overall implications of this research are that multi-component pre- and postnatal interventions could prevent a substantial fraction of childhood obesity.

Based on the findings from this line of research, several interventions targeting gestational weight gain in obese and overweight pregnant women are now ongoing. The goals of these behavioral interventions in the US and abroad are to improve maternal and child outcomes by preventing excessive gestational weight gain.

**Pre- and postnatal risk factors of breast cancer: Dr. Jo Freudenheim.**

Dr. Jo Freudenheim discussed early-life nutritional exposures and breast cancer risk, examining patterns of DNA methylation as a potential underlying mechanism in breast tumor development. The findings from her current epidemiologic research within the Western New York Exposures and Breast Cancer (WEB) study and other studies suggest that higher birth weight is associated with increased risk of breast cancer. In addition, there are several studies, including the WEB study, which indicate that women who were breastfed as infants may be at lower risk of breast cancer. Growth patterns of girls in relation to breast cancer in later life were also discussed, specifically the impact of height. There is very consistent evidence to demonstrate that increased height, a proxy for a number of different exposures including history of infections, nutritional status, hormonal milieu, and genetics, is associated with increased risk of breast cancer. Furthermore, it has been hypothesized that early-life alterations in DNA methylation may lead to increased cancer risk later in life. Results from the WEB study suggest that lack of breastfeeding and low birth weight were also associated with altered DNA methylation of candidate genes. Such alterations may contribute to the pathway linking early-life exposures to adult cancer.

In summary, early-life exposures such as birth weight, an indicator of in utero nutritional exposure, hormones, and the mother’s genetic makeup may influence DNA methylation in breast tissue and impact breast carcinogenesis. Furthermore, breast milk may also affect risk. Although the mechanism is not known, breastfeeding might act in a number of ways, including by altering the gut flora and affecting DNA methylation. The implications are that pre- and postnatal risk factors may affect later breast cancer risk, presenting a critical window of sensitivity in early life for potential interventions and behavioral change.

**Puberty as a window of breast cancer susceptibility: the role of phytoestrogens and mycoestrogens: Dr. Elisa Bandera.**

Mounting evidence suggests that the peripubertal period is a critical period in a woman’s life, during which environmental exposures can play a critical role in her future breast cancer risk. Early menarche is a well-established risk factor for breast cancer later in life, but environmental and genetic triggers of menarche are poorly understood. Phytoestrogens and mycoestrogens have been shown to act as endocrine-disrupting chemicals in experimental studies and may influence the human maturation process. Both have been shown to exert mild estrogenic or antiestrogenic effects depending on the dose and the body’s hormonal environment. There is growing evidence from epidemiologic studies suggesting that intake of soy products (a major source of phytoestrogens) during adolescence may have a protective effect on subsequent breast cancer risk. The Jersey Girl Study recently examined urinary mycoestrogens in relation to growth and development in healthy girls aged 9–10 y. These compounds (in unbound form) were found in approximately 78% of the girls. Compared to girls with urine samples negative for mycoestrogens, girls with positive samples were of shorter stature and less likely to have started puberty. The findings from this study suggest a possible antiestrogenic effect in healthy girls, delaying the onset of breast development and growth. Further studies are clearly needed to clarify the role of these...
xenoestrogens, widely distributed in the food supply, in girls’ pubertal development, with important implications for their future breast cancer risk.

**Life course research tools and statistical methods: Dr. Kristen Bub.**

Employing a life course framework poses considerable challenges from data management to data analysis. Various statistical analysis techniques have been developed for analyzing trajectories and long-term effects of nutritional exposures on chronic disease risk. The statistical technique most suited for an analysis depends upon the research question being posed. For observational study designs, a research question of event timing is best addressed with hazard modeling, whereas a research question of accumulation and sequence of exposures is best examined with individual or latent growth modeling. Another type of analysis, structural equation modeling, may be more suited to studying complex relationships, especially when indicators of a variable are measured and not the actual variable. Selection bias or unobserved variables bias is inherent in any nonexperimental study. Statistical techniques such as regression discontinuity and propensity score analysis derived from the field of economics and can provide stronger causal estimates of the associations of interest.

**Life course research tools and existing cohorts: Dr. Nancy Potischman.**

A prominent challenge in applying a life course framework is the selection of a suitable dataset. The ideal dataset would be a large cohort with continuous reliable and valid data from pre-pregnancy through adulthood in offspring. Unfortunately, such datasets do not exist at this time; current cohorts generally have intermittent collection periods across the life course. Extant datasets that can be used for a life course approach include life-long cohorts with relatively small sample sizes for many adult outcomes. Cohorts with information from various time periods include birth, adolescent, and adult cohorts and case-control studies. A few more recent large birth cohorts, mostly from European countries, are best suited to evaluate methodological research and exposures in pregnancy and early outcomes in the offspring due to their short length of follow-up. Data from 5 countries have been pooled to form the Consortium on Health Oriented Research in Transitional Societies that will enable evaluation of life course questions across different populations with information from pregnancy to adulthood in the offspring. Common challenges with these datasets include loss to follow-up and changes in measurement techniques during the data collection period. Replicating life course work is also problematic, because there are a limited number of cohorts with similar time frames and exposure measurements. Important life course questions regarding critical time periods, cumulative dose, and potential interactions regarding dietary exposures have yet to be answered.

**Conclusion**

A life course approach in chronic disease epidemiology explicitly recognizes the importance of timing and accumulation of exposures in identifying links between risk factors and outcomes within an individual’s life span, across generations, and on population-level disease trends. Limited existing evidence that uses the life course approach supports the developmental origins of chronic diseases in early life. Studies suggest that invoking early behavioral changes holds promise for disease prevention and may interrupt inter-generational cycles of these diseases. This symposium elucidated unique study designs and statistical strategies to demonstrate the strengths of this methodology and served as a catalyst for new research in the area of nutrition and chronic disease epidemiology.

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