Life course epidemiology and public health

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Life course epidemiology aims to study the effect of exposures on health outcomes across the life course from a social, behavioural, and biological perspective. In this Review, we describe how life course epidemiology changes the way the causes of chronic diseases are understood, with the example of hypertension, breast cancer, and dementia, and how it guides prevention strategies. Life course epidemiology uses complex methods for the analysis of longitudinal, ideally population-based, observational data and takes advantage of new approaches for causal inference. It informs primordial prevention, the prevention of exposure to risk factors, from an eco-social and life course perspective in which health and disease are conceived as the results of complex interactions between biological endowment, health behaviours, social networks, family influences, and socioeconomic conditions across the life course. More broadly, life course epidemiology guides population-based and high-risk prevention strategies for chronic diseases from the prenatal period to old age, contributing to evidence-based and data-informed public health actions. In this Review, we assess the contribution of life course epidemiology to public health and reflect on current and future challenges for this field and its integration into policy making.

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Introduction

Life course epidemiology aims to study the effect of exposures across the life course (notably early in life) on health, looking as far back as exposures during gestation or in previous generations.[1,2] It draws on expertise from multiple scientific disciplines, ie, epidemiology, sociology, psychology, biomedical sciences, and other fields related to population health sciences. In the biomedical sciences, Barker's hypothesis of fetal programming[3] was crucial for the early development of life course epidemiology, stating that fetal nutrition can contribute to the risk of adult chronic diseases, such as diabetes or hypertension. In the social sciences, alongside social epidemiology, interest in long-term socio-environmental exposures was notably introduced by Elder in his study of Californian birth cohorts to understand the social and health impacts of the Great Depression.[4] The term life course epidemiology was coined in the 1990s to define a field of study interested in early-life and later-life determinants of chronic diseases.[5]

Since then, life course epidemiology has contributed substantially to the study of chronic diseases and has gained popularity across epidemiology and public health. Barker's fetal programming hypothesis has grown into the developmental origins of health and disease approach in medical research, which places emphasis on prenatal environmental exposures as determinants of later-life health.[6] This approach expands the classic epidemiological and biomedical perspective of the crucial role of risk factors during midlife as the causes of chronic diseases in later life to exposure to risk factors at other ages or other life stages.[7] Life course research has been made possible through the availability of prospective and retrospective birth cohort studies and other large, population-based, longitudinal studies (within and across generations) that collect a wide range of individual, biological, social, and environmental data over decades of life. Beyond the analysis of longitudinal data, life course epidemiology is a field in its own right with unique theories, methodologies, and public health implications.[1,5]

Although life course epidemiology is established in scientific research, its application to public health policy making is less advanced. Possible reasons are the high context specificity of some findings, the complexity of the mechanisms involved, and the challenge of establishing causality across the life course. Nevertheless, policy making already benefits from life course epidemiological concepts and findings, notably in the form of primordial prevention, the prevention of exposure to risk factors.[8,9] Reviewing how life course epidemiology helps design prevention strategies for chronic diseases, how it changes the way the cause of chronic diseases is understood, and how it informs population-based, high-risk, and vulnerable population preventive strategies is therefore important and timely.

From life course models to policy making

Life course models

Life course research is based on a set of five basic principles defined by Elder and Shanahan.[10] These are: lifespan development (human development and ageing are lifelong processes not restricted to specific life stages); agency (people have the capability to take actions and make choices that shape their lives within the constraints of environmental, social, and historical contexts); time and place (every individual life course is embedded within and influenced by its specific historical time and place); timing (the same events and behaviours can have different effects depending on when they happen in the life course); and linked lives (people do not experience life alone but influence each other through shared interdependent relationships).

These principles have contributed to the development of theoretical causal models that explain how exposures across the life course cause health outcomes in later life.[10] These models are simplistic by design to highlight potential causal mechanisms underlying the associations between exposures and health across the life course.[11,12] In the life course epidemiology of chronic diseases, four models are frequently used: the sensitive period model;

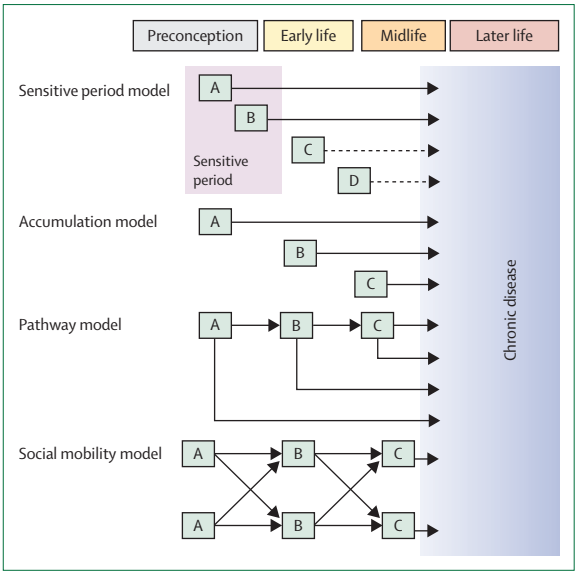

Figure 1: **Life course models for the causes of chronic diseases**
A, B, C, and D are exposure at different times during the life course. Arrows show causal effects; dotted arrows signify weaker causal effects.[11]

the accumulation model; the pathway model; and the social mobility model (figure 1).[11,13]

The sensitive period model focuses on the differential effect of an exposure depending on its timing. It posits that there are some periods across the life course, commonly in early life, during which an exposure has a stronger effect on health than if it were to happen outside of those periods. Gestation is a sensitive period for multiple exposures.[1] For instance, prenatal exposure to maternal starvation during the Dutch famine (1944–45) was associated with increased risk of later-life coronary heart disease, obstructive airways disease, and decreased glucose tolerance, depending on whether maternal starvation happened in early, mid, or late gestation, respectively.[14] Life transitions are also typical sensitive periods, such as the transition to motherhood, which is a major biosocial event.[15] Generally, there is the possibility of recovering from the effect of an exposure during a sensitive period. In contrast, an exposure during a critical period is considered to have a more permanent effect. For instance, lead exposure during early childhood, a critical period for brain development, can result in permanent cognitive impairments that persist into adulthood.[16] Identifying potential sensitive and critical periods for disease risk factors across the life course aids in the optimal timing of preventive interventions.

The accumulation model focuses on the accumulation and duration of exposures rather than their timing. It states that the accumulation of exposures across the life course determines later disease risk. This effect can be caused by an accumulation of different risk factors or by exposure to the same risk factor over an extended period. For instance, an accumulation across the life course of socioeconomic disadvantage,[17] low birthweight,[18] physical inactivity, and high salt intake during childhood and adolescence,[19] can result in hypertension in midlife.[20] The relationship takes the form of a dose–response association that incrementally builds towards a disease state. Accumulation of risks can be linear or exponential. Following this model, preventive interventions aim to stop the accumulation of risk before the disease threshold is attained.

The pathway model focuses on the sequential link between multiple exposures. It is also known as the chain-of-risk model since it states that each exposure to a risk factor increases the likelihood of being exposed to another risk factor.[21]

Finally, the social mobility model focuses on the direction of change of an exposure and is used almost exclusively for the study of the effects of socioeconomic exposures. According to this model, social exposures are states that individuals can transition in and out of: individuals can move between different social classes or income levels, and the direction of this change—upward, downward, or non-mobile—determines their later disease risk.[22,23] In a Swedish study, the direction of change between occupational classes between ages 25 years and 55 years was associated with myocardial infarction risk.[24] Specifically, moving from a non-manual to a manual occupation in later life—ie, downward mobility—was associated with an increased risk of myocardial infarction compared with no change in occupation class. Potential interventions could build upon this knowledge by promoting policies that favour upward social mobility in the population. One shortcoming of the social mobility model is the challenge of disentangling the effects of the final exposure, per se, from the effects of the trajectory leading up to this last exposure.[25]

These four models acknowledge the fundamental social causes of disease that contextualise individual-level determinants of health. Individual risk factors should be contextualised by "attempting to understand how people come to be exposed" or come to be put at the "risk of risks" to design more effective preventive interventions.[26] Furthermore, social factors such as socioeconomic status can be considered fundamental causes of diseases, since they determine people's access to health-protective resources, such as knowledge, money, power, prestige, and beneficial social connections.[26] If social conditions truly put people at risk of risks, life course-informed policies aiming to decrease health inequalities should target social causes in addition to more proximal causes. The vulnerable population preventive strategy is built partly on this concept.[26,27]

Testing the value of these models has been made possible by the availability of large, population-based cohort studies in, for example, the UK (eg, the 1958 National Child Development Study and Lothian birth cohort studies), Finland (eg, the Northern Finnish Birth Cohort Study), and New Zealand (eg, the Christchurch

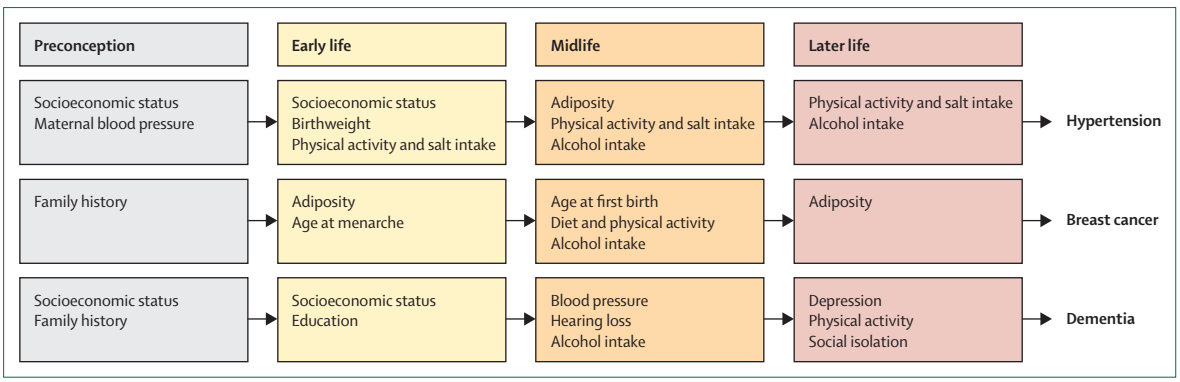

Figure 2: **Selected determinants of hypertension, breast cancer, and dementia risks across the life course**
Some determinants have an effect during a specific period of the life course and others during multiple periods.

Health and Development Study).[28] Birth cohorts typically consist of population-based samples of individuals born in a given period of time and followed up from birth or later in life over many years, if not across generations. The advancement of life course epidemiology has also been facilitated by biobanks linked to cohorts, aiming to assess the exposome of large samples of the population.[29] The strength of such large-scale cohorts lies in the collection of individual, biological, social, and environmental data over long periods of time, spanning decades of life. Together with the accumulation of these data came the development of advanced statistical methods for multicohort and big data research that make their analysis possible.[30]

Life course perspective on chronic diseases

A life course epidemiological approach can be applied to the study of any type of disease, but it has been especially useful in the understanding and prevention of chronic diseases. Life course epidemiology offers a framework for examining the cause of chronic disease across life stages with appropriate concepts and vocabulary (appendix pp 1–2) and, as a result, shapes disease definitions, health-related beliefs and fears, and preventive strategies.[31] In this section, we review how life course epidemiology has changed the way hypertension, breast cancer, and dementia are understood and its impact on their prevention (figure 2). These examples were chosen due to their high public health burden and suitability for a life course perspective.

Hypertension

Hypertension is a state of sustained elevated blood pressure and is a major modifiable risk factor for cardiovascular diseases—the leading cause of death worldwide.[20,32–34] The study of cardiovascular diseases lends itself particularly well to a life course approach since most cardiovascular diseases happen in later life and are typically understood as the outcomes of a lifetime exposure to causal risk factors, including smoking, dyslipidaemia, obesity, diabetes, and hypertension.[33,35] Although these risk factors were initially focused on during midlife, a growing number of studies have pointed at early life as a sensitive period for the development of these factors, establishing their effect on cardiovascular diseases in later life.[9]

Causes of hypertension can be identified across the entire life course, starting at conception and the first 1000 days of life.[36–38] Hypertension has been associated with fetal exposure to maternal smoking,[39] undernutrition while in utero,[3] low birthweight,[40] and increased salt intake in the first months of life.[19,41] In midlife and later life, elevated blood pressure is a major cause of cardiovascular diseases[42] and a large number of drug trials have shown that lowering blood pressure reduces the occurrence of these diseases (and related mortality)[33,43] and dementia.[44] Additionally, exposure to hypertensive risk factors is at its peak during midlife and later life, including high alcohol intake,[45] high salt intake,[46] and high BMI.[47]

With the identification of risk factors across the life course comes the opportunity for targeted life stage-specific interventions, with the aim of directing the health–disease trajectory towards an optimal path (figure 3). An extensive and in-depth guide to possible interventions is listed in the *Lancet* Commission on hypertension's call to action[20] for a life course strategy to address the global burden of hypertension. To summarise, intervention strategies should be multifaceted and target prevention, diagnosis, and treatment at the population and individual levels depending on the absolute risk of cardiovascular diseases. Clinical approaches at the individual level, including drug treatments, should target subpopulations at high risk (ie, people with a high absolute risk of cardiovascular disease) typically in midlife and later life. At the population level, interventions can be tailored to the life course. At all life stages, primordial prevention can be achieved via reduced salt intake, increased physical activity, and improved dietary habits. Early in life and during adolescence, the focus should be on effective health education; screening for hypertension is not

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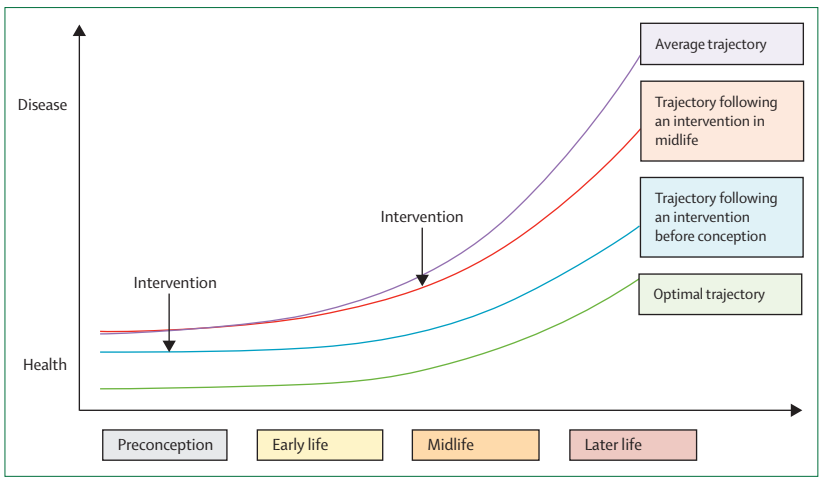

Figure 3: **Life course trajectories across the continuum of health and disease and how they are modified by interventions applied during different periods of life**
Depending on the timing and type of intervention, and the causal process at stake, the effect on the trajectory will be different. The arrows signify which trajectory the interventions apply to.

recommended during this period of life.[48] In midlife and later life, education should continue in the form of wide distributions of evidence-based knowledge and recommendations to promote cardiovascular health, and screening for hypertension and treatment programmes should be implemented.

Breast cancer

Breast cancer constitutes approximately 25% of all cancer diagnoses in women and roughly 16% of cancer deaths in women.[49] A classic life course perspective on breast cancer follows reproductive stages—ie, pre-menarche, menarche to first birth, pregnancy, and post-menopause.[50] The effect of breast cancer risk factors differs among these sensitive periods. For example, adiposity in early life, during premenarche, has been associated with lower risk of breast cancer,[51,52] whereas adiposity after menopause has been associated with higher risk.[53] Breast cancer can also be seen as the result of accumulated risk factors, particularly in relation to the timings of births and menarche. The Pike model postulates that the rate of breast tissue ageing, a risk factor for cancer development, slows down with each birth and after menopause, and is highest in the period between menarche and first birth.[50,54] Thus, depending on when a woman experiences menarche, and when and whether she gives birth once or multiple times could change her lifetime breast cancer risk. This relationship exemplifies how identifying risk factors for breast cancer is not enough—a life course perspective can add the context needed to design targeted prevention strategies.[55]

For the prevention of breast cancer, multiple windows for intervention exist along the life course. Much emphasis has been put on secondary prevention through screening for early disease detection in midlife. The US Preventive Services Task Force recommends mammography screenings for women aged 40–74 years.[56] The timings for screenings based on this traditional approach of early disease detection are informed by clinical trials.[56] Developments in the life course epidemiology of breast cancer offer new perspectives for primordial prevention strategies that are set earlier in life. Apart from genetic susceptibility and hormonal risk factors, large population-based studies have suggested that health behaviours (eg, alcohol intake, diet, and physical inactivity) could be modifiable risk factors for breast cancer and thus potential targets for preventive strategies.[50] Some studies suggest that environmental exposures (eg, dioxins, air pollution, and heavy metals) might also be involved.[57] Hence, rather than being limited to screening in midlife and later life, breast cancer prevention could start in early life within an eco-social preventive approach that targets both health behaviours and environmental risk factors at a population level.

Dementia

Worldwide, people live longer and are thus more exposed to age-related diseases such as dementia. Dementia is the loss of cognitive function typically attributable to vascular and neurodegenerative brain damage.[58] The occurrence of dementia in later life is affected by exposure to risk factors across the life course that diminish cognitive reserves—ie, an individual's ability to cope with brain damage.[59] Increasing and maintaining cognitive reserves throughout the life course could therefore prevent or delay the onset of dementia.[60]

In early life, education (as a form of mental activity) stands out as a target for intervention, since there is consistent evidence for education having a protective effect on later-life cognition,[61,62] for example through its association with healthier behaviours.[63,64] Nevertheless, mental activity might be beneficial across the entire life course and not only in the form of formal education. An individual participant data meta-analysis[65] found that people who perform cognitively challenging jobs have a lower risk of dementia, regardless of their education. Furthermore, there is evidence that the longer people are exposed to socioeconomic hardships, the lower their level of memory function and the higher their rate of later-life memory decline.[66] This evidence indicates that interventions are possible at every life stage, making dementia prevention a lifelong prospect that should combine widespread social and public health policies with individually tailored interventions at different life stages.[60,67]

A life course perspective for the prevention of dementia in early life, midlife, and later life has been adopted in policy and clinical guidelines. The 2020 report of the *Lancet* Commission on dementia prevention, intervention, and care, for example, identified 12 potentially modifiable risk

factors and incorporated these into a life course model of dementia prevention. These risk factors are, in early life: low educational attainment; in midlife: elevated blood pressure, hearing impairment, traumatic brain injury, high alcohol intake, and obesity; and in later life: depression, physical inactivity, diabetes, smoking, social isolation, and air pollution.[60] This model illustrates the value of intervening early and continuously throughout the life course.

Causality and the life course

Since the turn of the 21st century, developments in causal inference methods based on observational data have helped life course epidemiology move from a rich conceptual way of thinking towards a truly preventive strategy information tool. The three main data science tasks in epidemiology are description, prediction, and causality.[68] Description aims to describe the world as it is, prediction aims to predict how the world might be, and causality aims to estimate how an outcome would change if we were to intervene on an exposure. One major issue in epidemiology is the enduring confusion between association and causality when explicit causal inference is necessary to guide prevention.[7] This issue is especially true in life course, social, and environmental epidemiology in which evidence stems largely from observations and rarely from experiments such as randomised trials.[69–71]

Within observational studies, an increasingly adopted approach is based on the potential outcomes or counterfactual framework, with statistical models informed by expert knowledge encoded into graphical causal models and statistical estimation (notably via G methods).[72,73] This approach has advantages for life course epidemiology compared with traditional regression-based or adjustment-based methods, as these informed statistical models can better handle exposure-induced or time-varying measured confounding and reduce over-adjustment bias or mutual adjustment fallacies through appropriate covariate selection.[74,75] Other methods useful for life course research encompass causal evaluation of risk factors via instrumental variables (eg, genetic and non-genetic instruments) and policy evaluations via econometric methods (eg, difference-in-difference, regression discontinuity, and interrupted time series).[76–79]

For instance, the effect of BMI on all-cause mortality is a classic and highly complex question in life course research, which is plagued by confounding and reverse causation issues that are intractable by typical epidemiological methods.[80] Instrumental variables help overcome these limitations. In a large, population-based, intergenerational prospective study, when offspring BMI was used as an instrumental variable for paternal BMI, the estimated association between BMI and paternal cardiovascular disease mortality (hazard ratio [HR] per standard deviation of BMI 1·82, 95% CI 1·17–2·83) was stronger than that indicated by the directly observed association between individuals' own BMIs and their cardiovascular disease mortality (HR 1·45, 1·31–1·61).[80] Another example is how the life course mendelian randomisation technique can enlighten complex time-varying effects of age-dependent lifestyle factors on risk of chronic disease.[81]

Furthermore, advances in biobanks and omics have provided capacity for the joint measurement of thousands of biomarkers, such as proteins and metabolites, from a single stored sample. This increased availability of biomarkers has allowed for a better understanding of biological mechanisms across the life course, linking an exposure and a disease through the analysis of the mediating role of these biomarkers.[65,81]

Policy implications

To translate life course research into policies for chronic disease prevention, what determines health on a population level and how to intervene to improve it must both be made clear.[82] A relevant framework is the eco-social perspective that frames how health stems from interactions with the social environment.[83,84] In this perspective, the individual is embedded within multiple social circles, starting from the immediate family, and moving on to include peers, neighbourhoods, cities, and countries of residence. Each level has an influence on health at a personal level and therefore determines the patterns of chronic diseases at a population level.

When considering eco-social and life course perspectives together, different strategies for chronic disease prevention emerge that target different eco-social levels across the life course, and these preventive interventions can either work together or independently of each other. We give an example of prevention strategies for hypertension from an eco-social and life course perspective (figure 4).[20] In early life and in immediate social surroundings, policies targeting socioeconomic inequalities can create healthy family environments that allow children to engage in education and leisure activities, and to learn health-promoting behaviours early in life. Moving up a level, community-based projects can raise awareness of hypertension and grant universal access to screening and anti-hypertensive drugs in midlife and later life. On a city level, health-promoting urban spaces (eg, cycle lanes and walkable cities) can facilitate an active lifestyle in the entire population from childhood to old age. On a country level, legislators can protect the health of the population at all life stages via regulations, such as mandated salt limits in food production. Finally, at all ages and on a country-wide level, effective surveillance of hypertension and its risk factors are needed to ensure that prevention works.

Challenges

Research in life course epidemiology faces several challenges. Longitudinal cohorts are expensive and

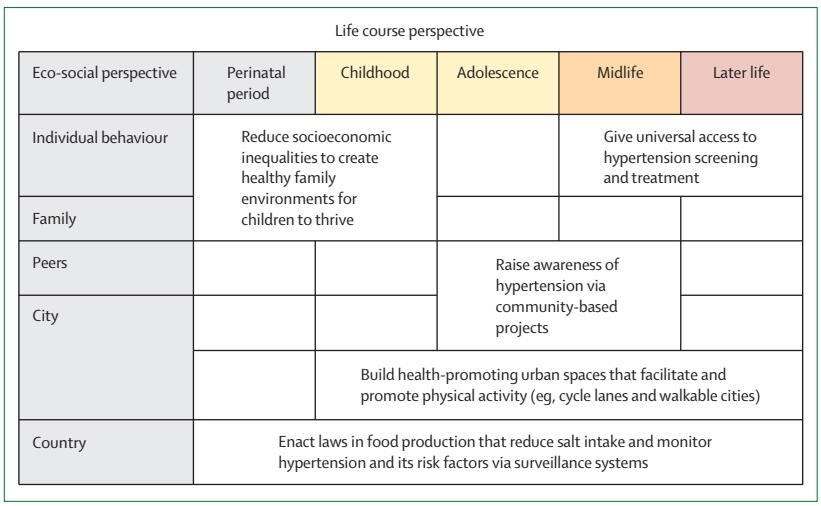

Figure 4: **Examples of hypertension prevention across eco-social and life course dimensions[83]**

Search strategy and selection criteria

The starting point of study selection for this Review was based on the expertise of all authors, who listed important life course epidemiological concepts that needed to be addressed. We identified key studies, reviews, or textbooks in our fields (appendix p 3), which were summarised and placed into context with the other papers included in this Review. We conducted a broad search on MEDLINE and Google Scholar to identify additional papers and reviews on the topic of life course epidemiology. We considered only full-text articles published in English; there were no limitations regarding article publication dates. We concentrated our Review on influential concepts within life course epidemiology from the past three decades, aware of the potential bias stemming from a subjective study selection. Furthermore, we particularly considered studies and reviews on the life course epidemiology of hypertension, breast cancer, and dementia. These diseases were selected due to their high public health burden and suitability for a life course perspective. References were chosen for their importance, ease of access, and usefulness to readers who might want further high-quality reading options in this field.

time-consuming to establish, and long periods of follow-up are needed before valuable data are available. These requirements, in turn, often result in life course research being questioned for its reproducibility and generalisability—can findings from a generation born 50 years ago be applied to the current generation?[85] Other study designs, such as case–control studies or trials, are limited when it comes to addressing life course epidemiological research questions.[86] Measurement of exposures across the life course is also a major source of bias. This results in life course research often having to rely on incomplete or poor-quality data.

Another major challenge is that life course epidemiology often deals with weak effect sizes at an individual level.[87] As for all fields of epidemiology, weak effects can be difficult to distinguish from bias introduced by study design, measurement errors, analyses, and residual confounding.[88] The best ways to mitigate these issues are the same as for other epidemiological fields: use multiple approaches to verify results; strengthen statistical knowledge to prevent misuse of analyses; place importance on transparent and reproducible study protocols; and give researchers the right incentives to favour quality over quantity when publishing research.[88,89] However, even with adequate study designs and analyses, weak effect sizes across the life course complexify policy making in terms of deciding where, when, and how to intervene, especially within a consequentialist perspective.[90]

One important question is to what extent life course epidemiology informs population-level or individual-level preventive interventions. Epidemiology in general, and life course epidemiology in particular, is primarily focused on population-level or group-level effects, providing evidence for population-wide and high-risk preventive interventions. Even a small effect size at an individual level might have major impacts at a population level if a large share of the population is exposed to the determinant in question. This fact is a major argument for the population-based preventive strategy advocated by Rose,[82] which is built on the insight that both risk and health are a continuum distributed in the population, implying that targeting the whole population rather than only the people at high risk of a disease is better for reducing disease burden. Many exposures examined in life course studies are highly prevalent, and this prevalence is part of the reason why a life course perspective is increasingly adopted for optimising the timing of population-level preventive programmes.[91,92]

The life course approach is also increasingly mentioned in clinical guidelines[93] and family medicine,[94] but the potential benefit at this level should not be overestimated because it can lead to inefficient pseudo-high-risk preventive strategies.[95] Evidence from life course and social epidemiology also informs vulnerable population preventive strategies, promoting the mitigation of health inequities by tailoring preventive strategies towards vulnerable populations.[27]

Finally, the translation of life course epidemiological findings into preventive strategies is a balance between precision and simplicity. Policy makers could aim for precision, for example by acting early in life to reduce risk factor exposure during a sensitive period, but they might do so at the cost of simplicity (ie, by not acting at all ages to reduce overall risk exposure). For example, identifying smoking as a major risk for cardiovascular diseases in midlife does not mean that smoking prevention should not target other life periods. This translational challenge extends towards populations as well, for which the right balance between segmentation into subpopulations with targeted needs and wide population-based interventions needs to be found.[96] A further challenge with implementing a life course approach in policy is the difficulty of persuading both the public and policy makers to embrace preventive interventions whose benefits can take decades to appear.

Conclusions

Over the past three decades, research in life course epidemiology has flourished. The origins of many chronic diseases can now be traced back to early life, allowing for new intervention strategies that target specific times during the life course. With examples from research on hypertension, breast cancer, and dementia, we have described how the field has grown from the idea of fetal programming and findings from social epidemiology to a multidisciplinary research approach that informs public health policy making.

Life course epidemiology offers the evidence needed to design primordial prevention of chronic diseases. It has brought new understanding of the transitions between health and disease, which are now conceived more than ever as continuums, linking the life course exposome to biomarkers, diseases, disability, and death. This field refines Rose's population-based preventive strategy[82] by tailoring interventions to distinct life stages and, to a lesser extent, informs high-risk preventive strategies.

The future of the field is promising and will most likely be characterised by even stronger multidisciplinary collaborations, particularly by advances in causal inference and a broadening of research foci to capture disease trajectories and multimorbidity in addition to single diseases, facilitating a more comprehensive evaluation of morbidity associated with life course exposures.

Contributors

CW, CC, SC, and AC conceptualised this Review. CW wrote the first draft. All authors were involved in draft revisions and approving the final draft for submission. All authors approved the final manuscript and accept responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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