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Methods

Life-course epidemiology: concepts and theoretical models and its relevance to chronic oral conditions

B. Nicolau[1,2], W. M. Thomson[3], J. G. Steele[4] and P. J. Allison[2]

[1]Unité d'épidémiologie et biostatistique, INRS - Institut Armand-Frappier, Laval, QC, Canada, [2]Division of Public Health, Faculty of Dentistry, McGill University, Montreal, QC, Canada, [3]Department of Oral Sciences, School of Dentistry, The University of Otago, Dunedin, New Zealand, [4]School of Dental Science, School of Dental Sciences, University of Newcastle upon Tyne, UK

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Abstract: Etiological models that predominantly emphasize current adult life styles, such as smoking, diet and lack of exercise have recently been seriously challenged by a growing body of evidence that disturbed early growth and development, childhood infection, poor nutrition, and social and psychosocial disadvantage across the life-course affect chronic disease risk, including chronic oral disease. This relatively new area of research is called life-course epidemiology. The life-course framework for investigating the aetiology and natural history of chronic disease proposes that advantages and disadvantages are accumulated throughout life generating differentials in health along the life-course, but most importantly later in life. Furthermore, its dynamic framework brings together the effects of intrinsic factors (individual resources) with extrinsic factors (environmental factors). The aim of this paper is to give an overview of this new epidemiological approach and to discuss how the life-course framework has been applied to chronic oral conditions.

Key words: dental caries; early life; life-course; periodontal disease; review

Dr Belinda Nicolau, Unité d'épidémiologie et biostatistique, INRS-Institut Armand-Frappier, 531 boul. des Prairies, Laval - QC, Canada - H7V 1B7
e-mail: belinda.nicolau@iaf.inrs.ca

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The development of science has always been influenced by chronological eras, distinguished by their dominant paradigms, analytical methods and preventive practices. Susser and Susser (1, 2) outline the history of modern epidemiology in the 19th and 20th centuries; a history defined by three main chronological eras. First, the sanitary era, which dominated most of the 19th century, focused on environmental sources of 'foul emanations', in which the analytic approach was to demonstrate the clustering of mortality and morbidity, with sanitation at the centre of those efforts. Towards the end of the 19th century, the advent of the germ theory opened a new era of infectious disease epidemiology. The analytic approach of isolation and culture of infectious agents was combined with a practice comprised of vaccines, quarantine and antibiotics. In the years after World War II, infectious disease epidemiology gave way to chronic disease epidemiology. This era searched for multiple antecedent factors at the individual level. The guiding concept uses a 'black box' metaphor, that is, many risk factors are linked to outcomes without necessity for dominant factors. For example, postwar cohort studies identified both a number of bodily attributes (e.g. hypertension, raised cholesterol levels, etc.) and various personal behaviours (e.g. smoking, levels of exercises and diet) that predispose an individual to coronary heart disease (CHD). The focus here was in a single level of analysis and an aggregation of disconnected individuals. Preventive strategies related to modification of lifestyle were emphasized (1, 2).

Current developments in epidemiology propose the adoption of a wider and richer framework that considers but does not deny the importance of individual-level risk factors. It is suggested that the 'black box' paradigm should be replaced by the

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'Chinese boxes' paradigm (a Chinese box is a conjurer's nest of boxes, each containing a succession of smaller ones). Susser and Susser (1) use this metaphor to explain the 'eco-epidemiology era'. This paradigm entails the interplay between individuals (bodies), components of bodies and their relationships with the world (biological, physical, social and historical contexts) in which the individual lives (1, 2).

The 'eco-epidemiology' era has been evolving along four main analytic lines (4) (Table 1). Contemporary oral epidemiology has been inadvertently following these analytic approaches, using different conceptual models to explain oral health outcomes. This paper aims to give an overview of the theory and the related methodological issues of one of these emerging epidemiological domains, the life-course approach (fourth line). The paper will first focus on development of life-course epidemiology giving a historical overview of the theory and describing its theoretical models. We will then discuss how this theoretical framework has been used in dental research and may be used in future research. Finally, we will give an overview of the theoretical and methodological challenges posed by life-course studies.

Life-course epidemiology: overview

Life-course epidemiology is defined as 'the study of long-term effects on chronic disease risk of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life' (3). It seeks to understand causal links between exposures and outcomes taking into consideration the importance of time (duration) and timing in the disease development (3). Chronic diseases, including chronic oral disease, by their own nature, develop over a relatively long period of time, that is, there are time lags between exposure, disease initiation and clinical recognition. This suggests that exposures in the beginning of life play a role in initiating disease processes before the disease manifests as overt pathology. Also, the fact that many risk factors have their own natural history further underlines the importance of time in studying the development of chronic disease (3). For example, the development of oral hygiene habits may be sensitive to the socioeconomic environment in which people live during their childhood.

The specific period in the life stage when an exposure occurs, known as the timing effect, may be also important in understanding its later effects on the aetiology of chronic disease (3). For example, there is growing evidence for an association between human papilloma virus (HPV) and the development of oral cancer (5). The role of HPV infection, which is acquired through sexual behaviour, may be time dependent. Studies have shown that starting sexual activity at a younger age increases the effect of HPV infection on the risk of developing cervical cancer (6).

From the above discussion, it is clear that the life-course approach to studying chronic disease aetiology is not merely a collection of longitudinal data or the use of a particular study design or analytical method. Rather, the unique feature of this approach is a theoretical framework which assumes and tests a temporal ordering of exposure variables and their interrelationship with a specific outcome (3).

The development of a life-course approach in epidemiology

The failure of the lifestyle model to provide a comprehensive and convincing explanation of social and geographic variations in chronic disease led some researchers to investigate the possible influence of early life factors in the subsequent development of chronic diseases (3). The possible

Table 1. Eco-epidemiology main analytical lines adapted from Susser (4)

First line	Considers multiple levels of causation as determinants of illness or health in populations. It concurrently investigates risk factors operating at a variety of hierarchical levels, from the macro (societal), individual (behaviour) and micro (molecular) levels
Second line	The interplay between genetic and environmental factors (very similar to the first line)
Third line	A multidisciplinary and transdisciplinary approach incorporating the various medical subspecialties
Fourth line	The trajectory of health and illness over the lifetime (3). It aims to elucidate biological, behavioural and psychosocial processes that operate along an individual's life-course, or across generations, to influence the development of disease (3): life-course epidemiology

importance of early life was raised by studies showing geographic correlations between past child mortality rates and current adult mortality rates (7). Forsdahl (3) first demonstrated these correlations with his analysis of the association between poor living standards in childhood and a high mortality risk from CHD in middle age. Other studies have replicated and built on Forsdahl's findings (8). Barker, in particular, has played a central role in raising the profile of early life factors as critical determinants of adult disease risk (3). His work has focused attention on the association between poor foetal or infant body size and greater risk of CHD, stroke, diabetes and respiratory disease in later life (9). According to Barker's foetal origins hypothesis, events or circumstances *in utero* or in infancy 'program' the individual's risk before other risk factors are encountered later in life. Specific causal factors act on particular organs or body systems at critical periods of their growth and development, altering their structure and function and restricting their developmental potential in a way that makes it difficult for the body to make up the deficit or repair the damage later (9). For example, in the case of CHD it was hypothesized that foetal and maternal undernutrition during middle and late gestation leads to disproportionate foetal growth and raises the risk of CHD by programming blood pressure, cholesterol metabolism and blood coagulation (9).

From a social epidemiological perspective, the results of the ecological analysis showing an association between infant mortality and high mortality rates several years later was interpreted in a different way. The explanation was that infant mortality was a surrogate measure of childhood socioeconomic status (SES) (3). The fact that the associations reported in some of these studies substantially decrease after adjusting for current adult SES raised the hypothesis that they were due to continuity in living conditions and social circumstances over the life-course (3). Indeed, a number of studies have investigated the association between markers of childhood SES and health outcomes, including oral health (10–13). In all but a few, the findings have shown that childhood SES further increases the risk of disease independently of adult risk factors and adult SES, suggesting that socially patterned exposures in childhood influence adult health and chronic disease.

Life-course epidemiology: theoretical models

Considering the variety and numbers of exposures over the life span and the importance of time (duration) and timing, the relationship between exposures and outcomes of interest is not straightforward (3). Kuh and Ben-Shlomo (3) developed a typology of models for life-course investigations to help the understanding of how exposure and its effects can be related to later health-related outcomes. An adapted graphic representation of these models is presented in Fig. 1. Scenario (a) shows an exposure in a critical period of development influences disease outcome much later in life; this is the *critical period model*. This model sees the time

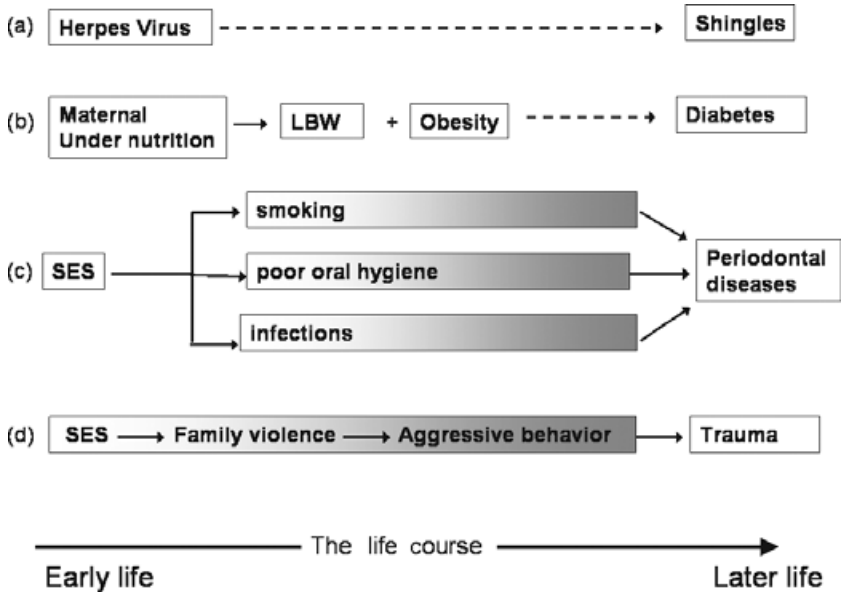

Fig. 1. Oral health examples of alternative mechanisms for the relationship between early-life exposure, other risk factors and disease outcomes later in life: (a) critical period, (b) critical period with effect modifier, (c) accumulation model with risk clustering: risk exposures cluster in socially patterned ways and (d) chain of risk model.

window of exposures as the key. The idea is that an exposure (i.e. herpes virus) during a specific period of growth or development physically alters some underlying structure or body system, resulting in permanent and irreversible damage or disease later in life (i.e. shingles). The 'biological programming hypothesis' (which is the underlying hypothesis of Barker's foetal origins of adult disease) is an example of the critical period model (3). Several markers of poor foetal and infant body size have been associated with risk of CHD, stroke, diabetes, respiratory disease and their associated risk factors (9).

In scenario (b), exposures in early life interact with exposures later in life, either enhancing or decreasing the risk of chronic disease; this model can be described as the *critical period with effect modifier*. It suggests that later factors modify a risk incurred earlier (3). For example, studies have shown that overweight adults who had the lowest birth weight have the highest risk of CHD and diabetes (14–15).

In contrast to the first two models, the *accumulation risk model* suggests that insults are accumulated incrementally through the life-course and initiate episodes of illness, with adverse environmental conditions and/or behaviours subsequently increasing the risk of chronic disease (3). This cumulative pathway mechanism proposes that 'wear-and-tear' adds up over time to affect health. The concept of allostatic load (16) has been used to explain this cumulative pathway mechanism. It is argued that, as the number, duration and severity of exposures increase, there is cumulative damage to biological systems (3). Of course, if there are numerous insults and some of them occur at critical periods, then the additive effects will be more marked.

According to Kuh and Ben-Shlomo (3), accumulation on biological systems may be caused by independent exposures; that is, the individual is exposed to a series of unconnected events at each stage of life and these exposures combine to raise disease risk later in life (3). However, it is argued that it is much more likely that exposures are clustered along the life-course (17) in what they called the *accumulation risk model with risk clustering* (3). For example, children raised in adverse social circumstances are more likely to be exposed to infection, to become a smoker and have poor oral hygiene habits which in turn may increase their risk of periodontal disease [pathway (c) in Fig. 1].

The concept of a *chain of risk* where one adverse/beneficial exposure or experience tends to lead to another adverse/beneficial exposure is another version of the accumulation model [pathway (d) in Fig. 1]. This dynamic framework proposes an interaction between intrinsic factors such as individual social resources (also called behavioural capital, a psychological resource such as social competence, self-esteem, decision-making, problem-solving skills and coping strategies) and behaviour, and extrinsic factors such as material circumstances and sociocultural influences, such as the family (18). Although intrinsic risk processes are not excluded, this model emphasizes an extrinsic risk process, suggesting that external events affect an individual's chances of experiencing subsequent future events which, in turn, lead to a change in the risk of adult disease. For example, children raised in an adverse family environment are more likely to have lower self-esteem, worse problem-solving skills, have more aggressive behaviour and take more risks, which in turn make them more prone to experience trauma including head and dental trauma.

The life-course models proposed by Kuh and Ben-Shlomo (3) are an attempt to clarify the highly complex and dynamic life-course framework. They are not mutually exclusive and a combination or all models may operate together (3).

Life-course epidemiology: chronic oral conditions

Imagine that a group of health researchers wishes to explore the utility of the life-course epidemiological approach and are seeking a condition (or closely related group of conditions) to use as an exemplar in (say) a prospective cohort study. What are the characteristics of oral diseases that make them ideal conditions to study using the life-course approach? First, using a chronic condition (such as dental caries or periodontal disease) would make things simpler, in that, once the condition developed, it would be far more likely to be detected during an assessment. By contrast, an acute condition might have developed and resolved between assessments and it would be likely to go unnoted if the study participant failed to report it. Second, a condition which is cumulative would allow comparison of the degree of disease development among individuals so that, rather than all who develop the condition being enumerated together,

distinctions could be made among them with respect to the extent or severity of their disease. Third, the condition should be able to be validly and reliably measured, which requires that the evidence of disease experience (and therefore the diagnosis) be incontrovertible. Fourth, the condition should be at least moderately prevalent, so that the required sample size for the cohort is manageable. Fifth, the condition being studied should ideally be one which has public health importance, so that the study is justifiable, on both ethical and economic grounds.

It is clear that oral health is well suited to the life-course approach, because the common oral conditions (dental caries and adult periodontal disease, together with their clinical endpoint of tooth loss) meet these criteria. The discussion which follows examines the example of dental caries.

Critical or sensitive periods for development of dental caries

Much is known about the critical periods for the mineralization of teeth (19) and it is therefore somewhat surprising that equivocal findings have been reported from the studies which have addressed the association between markers of early development (such as birth weight) and an outcome such as dental caries experience in the primary dentition. A systematic review analysing the relationship between low birth weight (LBW) and subsequent dental caries in the primary dentition found no relationship, although it was based on a very limited number of studies (20).

More recent studies of the relationship between markers of early development and subsequent dental caries have found positive associations. A study of 818 South Australian adolescents found significant variation in the adjusted mean caries scores (DMFS) across tertiles of birth weight. The LBW groups were significantly associated with greater DMFS scores (21). Similarly, Brazilian adolescents who were LBW babies had high levels of dental caries at 13 years of age (22). Another study found an inverse association between height at 1 year of age and dental caries experiences at age of 6 years (23). A further example of how life-course factors can affect caries experience is found in a reported association between height at adolescence and caries experience, with taller adolescents having lower caries scores, on average (24). Owing to the cross-sectional nature of most of these studies, we cannot establish a causal relationship between early childhood development and dental caries experiences later in life. However, these life-course studies can generate some interesting hypotheses on the different pathways to explain these associations. For example, LBW – which is associated with poverty, maternal nutrition and habits during pregnancy (9, 25) – may affect tooth structure (26). Hypoplastic enamel is more readily colonised by mutans streptococci, organisms associated with dental caries (27, 28). LBW infants have poorer immune function (29, 30), which also may favour early colonization of the dentition by cariogenic organisms (20). In addition, malnourished children have a lower saliva secretion rate and saliva buffering capacity, lower calcium and protein secretion, and impaired immunological and agglutinating defence factors compared with well-nourished children (31, 32). These factors can all influence caries development.

The 'accumulation of risk' model and oral health

Recent research using the life-course framework has suggested that exposures to adverse environments along the life-course contribute additively to oral health problems. In a New Zealand birth cohort, oral hygiene habits, dental caries, tooth loss experience and periodontal disease at age 26 all showed a biological gradient according to childhood SES, with adult experience of any of those markers being lower among those of higher childhood SES. The adverse influence of low childhood SES persisted after controlling for childhood oral health and contemporaneous adult SES. Moreover, low adult SES was associated with poorer adult oral health after controlling for low childhood SES (10–11). A clear gradient was observed when analysing the effect of social mobility on adult oral health outcomes, with the highest disease levels observed among those who were born in low-SES households and remained low SES as adults, and the lowest levels were seen among those who began and finished up in high-SES strata. Intermediate disease levels were seen among those who were socially mobile: upward social mobility was associated with lower disease levels than downward mobility for almost all oral health indicators (11). Similarly, Brazilian children who remained low-SES throughout their childhood and adolescence were more likely to have high levels of oral diseases by the time they were 13 years old (13).

The dynamic framework provided by the life-course approach also suggests that the psychosocial environment in infancy and childhood

influences oral health later in life. For example, social problems in childhood were the most important predictors of gingival bleeding and traumatic dental injuries (TDI) among 13-year-old Brazilian adolescents (33, 34). The authors suggested that both social and material factors in those families were linked in a chain of events to the adolescents' subsequent oral health. In the same study, the best predictors for gingival bleeding by age 13 were family SES at two stages of the adolescent's life (birth and 13 years old), family structure, failing a school year(s) and levels of plaque. In discussing the potential pathways, the authors showed that adolescents who experienced adverse socioeconomic and psychosocial environments along the life-course were significantly more likely to be in lower grades at school for their age. Adolescents in low school grade levels were more likely to brush their teeth less than twice a day. Both low educational progress and adverse socioeconomic and psychosocial environments were significantly associated with low toothbrushing frequency. This, in turn, was associated with high levels of plaque, which was the strongest predictor for gingival bleeding (33).

Findings from the same study showed a noteworthy (but not unexpected) similarity between the model for gingival bleeding and TDI. Adolescents from a nonnuclear family, those who reported high levels of paternal punishment and those in lower school grades had higher rates of TDI. Poor family functioning was significantly associated with low grade at school for adolescents' age, which in turn was associated with TDI (34). Child abuse and neglect are associated with family difficulties such as a poor child-parent relationship, severe conflict between parents, broken homes and poverty (35). Abused and neglected adolescents tend to be more likely to have problem behaviours such as being aggressive, violent and having affective disorders (36) and therefore more TDI.

A life-course study investigating a cohort of 50 year olds followed from birth in the UK demonstrated the persistence of early life variables on oral health using tooth loss as the outcome, even at age 50 years of age (37). Although, by this stage in life, the majority of variance that could be accounted for was explained by factors acting in adult life, around a third was still accounted for by early life factors and even this is likely to have been an underestimate as some important early life variables were not available from the original (1947) dataset.

The dental examples discussed above suggest that the life-course approach is indeed a valid one to use in dental epidemiology. The processes of accumulating advantage or disadvantage through a range of biological events and social experiences over time result in social inequalities in dental caries, which are observable in adulthood. Other factors being equal, a child with good self-care practices is more likely to have good self-care as an adult. Similarly, a child who has grown up in an environment where routine dental visiting is the norm is more likely (than a child from a family in which problem-oriented dental visiting is the norm) to attend for regular dental check-ups as an adult. It is likely that those influences continue during adulthood as well: the continuation of sound self-care and professional care-seeking behaviours amounts to an ongoing, cumulative dental advantage for the former which is likely to be readily observable as better oral health at any stage of his or her adult life. If observed at any single point in time, those differences may be quite subtle, but it is important to bear in mind that their accumulation over the life-course results in much greater dissimilarity in exposure.

Life-course epidemiology: theoretical and methodological challenges

This paper has described concepts and models in life-course epidemiology and has discussed dental examples of studies examining possible factors acting along the life-course. Hypothetical biological or social pathways which lead to development of chronic oral conditions were discussed. The life-course framework can be implemented using different study designs to better understand the aetiology of chronic diseases including oral diseases. However, most of the studies that have used the life-course framework using oral health outcomes to date have been cross-sectional in nature. Cross-sectional studies may give a less accurate time sequence of exposure and outcome events, as well as being subject to recall bias. Therefore, they are prone to measurement errors as well as being limited in their ability to test accumulation models and interactions between early and later life exposures. Nevertheless, such studies are able to generate important hypotheses which can be confirmed by longitudinal studies.

The prospective cohort study is the ideal design with which to use the life-course framework,

particularly where information is gathered from birth to adulthood (the birth cohort study design). This type of study provides the most accurate time sequence of events and intra-individual change over time and is ideal for testing causal life-course hypotheses. However, as is well-recognized, this type of study can be prohibitively expensive and logistically difficult and can be impractical when applied to the study of diseases with a low incidence (such as oral cancer). The design has the disadvantage of taking a long time to yield findings (38). In addition, the data collected are pertinent to scientific hypotheses designed at the time of the cohort generation; these may not be relevant to the research questions addressed by contemporary hypotheses (38). The daunting challenge for the researchers involved is to collect data which have contemporary utility and relevance while also trying to anticipate future technical advances and developments as much as possible.

Historical cohort studies (which collect new data on populations where data collected earlier are available) and record linkage studies are alternative and efficient methods to test hypotheses about early-life exposures (3). However, they have usually been limited to data from one period (such as perinatal information). Although information on other periods of the life-course can be recalled, this is most likely subject to recall bias. However, these study designs do allow the identification of potential periods of etiological relevance which can be used to generate hypotheses. Unfortunately, life-course models (such as accumulation models) and effect modification (such as interactions between early and later life exposures) cannot be tested (3).

The case–control study is another design which has been proposed to test life-course hypotheses (39). This design is also limited because of the high risk of recall bias, although alternative interview techniques (such as the life grid) have been suggested as a way to improve recall in information collected retrospectively (38), questions remain regarding the validity of early life exposures reported in adulthood (38). However, the case–control design remains the only realistic approach for testing life-course hypotheses about the relatively uncommon conditions (such as oral cancer) for which the prospective cohort study design is impractical. Thus, its utility for life-course research should not be discounted and it is appropriate that research continues into improving the validity and reliability of retrospectively-obtained exposure data.

Analysis of large and complex datasets is the next challenge in studies using the life-course framework (3). Losses to follow-up are an inevitable feature of longitudinal cohort studies, leading to missing information which further complicates the data analysis. Although there are ways to deal with missing data (such as imputation methods), the methods are mostly limited, as the 'missing completely at random' assumption needs to be respected (40). An important advantage of the prospective cohort study design is that baseline data on those lost to follow-up is available and can be compared with that from the remaining cohort in order to allow evaluation of the degree to which panel attrition has affected the estimates. In addition, modelling the steps along the hypothesized life-course pathways is a challenge for data analysis. As previously discussed, the primary tenet of the life-course approach is a theoretical framework where a diagrammatically ordered class of variables across the life span is established. This means modelling repeated observation, hierarchical data, latent exposures and multiple and interactive or small effects (3). Structural equation modelling, path analysis and graphical models (where prior conceptual representations are required before statistical modelling) are some of the techniques being used in life-course analyses. Nevertheless the field remains a challenge, and much research is needed to determine the advantages and disadvantages of these analytical strategies over the traditional regression approaches used in longitudinal studies (18). A recent review (40) offers a good source of further information for readers interested in the statistical challenges of life-course epidemiology.

Conclusions

The genesis of life-course epidemiology may at first glance be seen as a replacement for the adult lifestyle model of chronic disease risk. However, the framework expands upon the adult lifestyle model to build a bridge where biological, psychological, and social models of disease causation are incorporated. Although it is intuitively logical, the framework is ambitious in its essence. It considers, in a time perspective, that the physical (individuals bodies and components of bodies) and environment are mutually constitutive; that is, that aspects of bodily form can influence trajectory in the same way as the environment becomes imprinted our bodies. Understanding the ways in which

environment becomes biological and the biological in turn becomes part of the environment is a key in understanding ill/health processes. However, as Kuh and Ben-Shlomo have said, 'the future value of a life-course approach will depend for its success on elucidating new mechanisms and disease pathways as well as its ability to explain social, geographical and temporal patterns of disease distribution' (41).

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