INVESTIGATIVE REPORT

Psoriasis – The Life Course Approach

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Over the last decades, Life Course Research (LCR), predominantly the domain of sociology, has been increasingly applied in health research, as Life Course Epidemiology (LCE). The latter is concerned with disease patterns over time, accumulation of exposures over time, critical time periods and patterns of risk. We argue that concepts from LCR and LCE could be widely applied in dermatology, in general, and, more precisely, in the study of chronic inflammatory skin diseases, e.g. atopic eczema and psoriasis. The life course approach can generally be applied in two different ways. It may be used in the more traditional manner, in which the disease and its patterns over time are examined as the outcome variable. Conversely, it can examine life course as the outcome variable, which is dependent on the disease course, the treatments administered, and other physical or psychosocial environmental exposures. In dermatology, this second application of the LCR concepts is both promising and relevant because of the notable impact of chronic skin diseases on the patients' quality of life. In particular, we argue how LCR may be conducive to a better understanding of the concept of 'Cumulative Life Course Impairment', which is increasingly gaining acceptance. This approach helps identifying not only individuals at risk and particularly vulnerable patients but also critical periods for optimising interventions in order to avoid life course impairment. It also may facilitate more appropriate treatment decisions in clinical practice. *Key words: cumulative life course impairment; dermatology; life course; life course epidemiology; psoriasis.*

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Through individual constellations of predisposition and exposure the life-time risk of any given disease varies in the population. Similarly, the development of a disease affects the subsequent life of the patients, thereby influencing future risk. For many reasons, studies of these interactions in the medical field are often not long-term, and while such studies provide much important information, it is likely that as longer and more comprehensive view of the interactions between predisposition, behaviour and exposure may add significant depth to our understanding of the development and impact of diseases on the population as a whole.

Life Course Research (LCR), initially a sociological research area of the biopsychosocial interactions and events over lifetimes (or even over generations) has more recently become a topic of research within the behavioural and biological sciences (1). A life course approach in health care research and epidemiology is present in early studies (e.g. Dubos et al. [2]) focussing on factors in infancy, such as poor growth and adverse developmental conditions, which increase the risk of chronic disease in adulthood (3). The evidence that exposures influence health outcomes, beyond simple and direct biological correlations, is growing, but require further studies. For instance, while the adverse consequences of tobacco are well established, the complex mechanisms linking psoriasis, unemployment, psychosocial consequences and metabolic syndrome remain to date an important research focus in dermatology. Similar correlations constitute a great matter of interest for almost all fields in clinical medicine: the life course approach addresses a variety of potential processes where biological, social and psychological exposures that take place at different stages of life can influence risk of disease, disease pattern and disease course over time.

LCR is often performed using Life Course Epidemiology (LCE) which typically deals with concepts such as chronic disease patterns over time, consequences of accumulation of exposures over time, critical time periods, and patterns of risk (4).

Whereas the life course approach has been extensively implemented in some fields of medicine, e.g. diabetes, obesity and cardiovascular disease (CVD) (5–7), it has been applied only sporadically and non-systematically in other areas, e.g. in oral disease (8) and back pain (9). Although of particular interest and relevance to chronic disease the use of the life course

approach has been very limited in dermatology and it remains relatively uncommon in chronic skin diseases, such as psoriasis and atopic dermatitis (10–20). Issues like early exposures to triggers (e.g. streptococcal infections in childhood psoriasis [12]) or protective factors (e.g. varicella zoster virus infections in atopic eczema [13]) have occasionally been addressed; other models may yield interesting results if appropriately applied. For example, cumulative socioeconomic disadvantages and cumulative adversities have recently proven to be related to dyslipidaemia (14): it appears hence reasonable to investigate whether some cumulative biopsychosocial factors may result in psoriasis.

Also, life course methodology presents as a natural approach if one is interested in the life course as the outcome variable and one looks at the disease, its treatment and its course as the input parameters. Consistent with this, the cumulative burden of psoriasis as well as of other skin diseases, and its associated physical and psychological co-morbidities, over a patient's life, has been the subject of several publications exploring the concept of Cumulative Life Course Impairment (CLCI) (15–20).

The aim of the current article is to raise the profile of the life course approach in dermatology, and to evaluate how concepts and methods of LCE might improve our understanding of chronic skin diseases, with a particular focus on psoriasis. It is not within the scope of this paper to provide an extensive analysis of LCE; for a further understanding of this approach we direct readers to two excellent books on the subject (1, 3).

LIFE COURSE RESEARCH AND LIFE COURSE EPIDEMIOLOGY

The interest in life course approaches in medical research has grown steadily over the past two decades. Among academic publications that used "life course" as a key word in 2009, health-related publications were ranked second only to the traditional arena of sociology (21). Furthermore, a review published in 2009 on advances in LCR identified > 100 papers published since 2000 with explicit references to health and the life course (22).

In recent years, there has been increasing interest in studying epidemiological aspects of diseases over the life course, and LCE has become well established in medicine. LCE may be defined as "the study of long-term biological, behavioural, and psychological processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, earlier in adult life, or across generations" (3). It seeks to understand the causal links between exposures and outcomes, taking into consideration the duration and timing of such exposures in disease development, along with the social, psychological and behavioural dimensions of illness (3). Although LCE uses the research methodologies of traditional epidemiology, it is more than a collection of longitudinal data or the use of a particular study design. LCE is a theoretical model where hypotheses on the temporal ordering and interconnectedness of risk and exposure for health outcomes is examined using life course data (key features of LCE are presented in Table I). Chronic diseases by their very nature are particularly suitable for the life course approach, which has already greatly improved our understanding of mechanisms underlying CVD, and is now being applied to obesity, hypertension and diabetes (3).

In dermatology, epidemiological research from the life course perspective appeared at first to be scanty, at least until the first decade of this century, as suggested by a search (data on file) we performed in 2010 on the literature published from January 1995 to April 2010 cited in PubMed (Table II).

As from 2011, a whole volume (18) in the series "Current Problems in Dermatology", as well as several

Table I. *Key features of life course epidemiology (LCE) (1, 3, 4)*

Features of life course theory
The purpose of LCE is to create and test theoretical models that hypothesize pathways, which link exposures across the life course. They often include:
 • temporal ordering of exposures and their inter-relationships to later life health outcomes
 • consequences of accumulation of exposures over time
 • importance of critical time periods of exposure to risk, particularly key developmental phases
 • incorporation of gene-environment interplay
LCE attempts to integrate biological and social risk processes rather than draw false dichotomies between them; interests overlap with social epidemiology
Features of life course methodology
Research questions commonly:
 • have a developmental component concerned with identifying pathways that might involve precursor stages, mediating variables and chains of effect
 • involve a profile of health outcomes (over time or over a set of outcomes)
Study designs are often time-related: e.g., longitudinal studies that capture certain time windows or significant features of the life course
As with traditional epidemiology, LCE uses a variety of study designs and data sources
 • e.g., longitudinal studies, ecological studies, natural experiments, migration studies, genetic studies, birth cohort studies, historical cohort studies
Techniques for the analysis of time varying exposure and estimating causal relationships may move beyond those available in traditional epidemiology
Several analytical techniques or problems may be similar to traditional epidemiology, but are particularly relevant to LCE:
 • e.g., analytical problems associated with modelling repeat observations, hierarchical data, latent exposures, or multiple interactive or small effects
 • e.g., problems of missing data, omitted exposures, and measurement error associated with longitudinal studies
 • e.g., use of multi-level models, latent growth models, graphical chain models

Table II. *Main publications in dermatology with the life course perspective published within the first decade of the century[s]*

Studies with Life Events, Life Course as input variable and Disease Course as output variable	Ref	Studies with Disease course as the input variable and Life Events, Life Course as the observed outcome	Ref
Sun exposure in infancy and youth as a risk factor for melanoma and other skin cancers	Kennedy et al. (23)	Life course experience of Taiwanese women with leprosy	Shieh et al. (26)
Physical size at birth as a predicting factor for atopy in adulthood	Xu et al. (24)	Questionnaire-based study on the life course of children with atopic dermatitis, showing that patients with severe disease had difficulty in achieving developmental milestones compared with patients with moderate disease	Brenninkmeijer et al. (10)
Chronic trauma over the mother's life course linked to increased IgE levels in infants at birth."	Sternthal et al. (25)	Atopic dermatitis linked to increased sick leave and early retirements	Holm et al. (32)
Protective effect of varicella zoster virus infection against atopic eczema	Silverberg et al. (13)	Impact of childhood vitiligo on adult life	Linthorst Homan et al. (11)
Hygiene hypothesis for aetiology of atopic eczema	Björkstén (27)	Cumulative impairment of psoriasis and its associated co-morbidities and its social stigmatization over patients' life course	Kimball et al. (15)

[a]Although each of the publication in the second column incorporates the concept of disease impact throughout the life course, the fundamental concepts in LCE (such as patterns of risk over time, accumulation of risk, timing of risk and mediating/modifying factors) are neither explicitly nor systematically applied.

papers published in dermatological journals have addressed the issue of cumulative life course impairment, or, more generally, of the life course perspective in dermatology, thus witnessing the growing interest of this perspective for our branch of medicine. In particular, an interesting new approach within the life course perspective is the study of how chronic disease may have an impact on "major life changing decisions" (MLCD), which in turn influences the life course (28–31).

More formally, applying a theoretical framework using the life course approach may help to gain better insight into the impact of chronic skin diseases over the course of a patient's life and may be also conducive to developing more accurate prediction models. Several of the main concepts of LCR are likely to be helpful in this respect (Table III) (for a detailed discussion, see Pickles et al. [4]).

APPLYING LIFE COURSE APPROACH IN DERMATOLOGY – A CLOSER LOOK AT PSORIASIS

Applying life course methodology in psoriasis

Given the nature of psoriasis – i.e. a chronically relapsing condition with multifactorial aetiology – the life course approach offers a framework by which to improve our understanding of the disease, both in terms of its pathogenesis (when the disease and its course are seen as an outcome) and in terms of its outcomes (when psoriasis is viewed as an exposure and impaired life course is seen as the outcome). To our knowledge, few authors have explored the biopsychosocial impact of psoriasis over the life course. In the already mentioned article on CLCI, the authors hypothesised that in psoriasis the cumulative effect of the significant physical and psychological burden affecting all facets of a

Table III. *Main concepts of Life Course Research (LCR). (For a detailed discussion, see Pickles et al. [4]).*

Patterns of risk over time – trajectories, transitions and turning points
Biological, behavioural and psychosocial pathways interact over the course of an individual's lifetime. Trajectories a long-term view of any one such pathway (e.g., employment status). Over time, the status of an individual within any trajectory undergoes short-term changes or transitions (e.g., promotion at work), which may progress an individual along the same trajectory. In addition, the status of an individual may undergo a marked change or turning point (e.g., loss of employment, death of a close relative), which significantly alters a person's life, placing them on a new trajectory.
Accumulation of risk
Risks gradually accumulate over the course of an individual's life (3). With an increase in the number, duration and severity of exposures, cumulative damage occurs. Risks emerging at different times may exert independent effects, clustered effects, or additive effects, where one exposure leads to the next in a chain of risk, e.g. childhood obesity as a risk factor for psoriasis (33). Also see, for instance, the model of allostatic load as a risk factor for metabolic syndrome (34).
Timing of risk
Time is a fundamental concept in LCE, which states that the effect exerted by exposures on a health outcome is dependent on the timing of the exposure. An exposure may result in an altered outcome (e.g., disease or life impairment) only during a specific time period – a critical period of development – and may not be significantly modified by later life experience (critical period model). For example, varicella zoster virus infections occurring in the critical period of age 0–10 years are possibly a protective factor against atopic eczema (13). Alternatively, an exposure may always exert an increased risk but may have a stronger effect during sensitive periods: sun exposure may be for instance more conducive to skin cancer in the sensitive period until adolescence (23).
Mediating and modifying factors
Risks or protective factors may either mediate or modify the association between the exposure and the outcome. Mediating factors chronologically follow the exposure and lie on the same causal pathway, whereas modifying factors interact across different levels of exposure. In dermatology, modifying factors, for example, may include gender acting on the risk factor of smoking in patients with palmoplantar pustulosis (35) or a strong sense of coherence improving the response of psoriasis patients to therapy (36).

patient's life may prevent some patients from achieving a 'full life potential' when coping strategies and other factors (i.e. social support networks) are not sufficient to prevent this impairment (18). Applying the life course approach to CLCI in psoriasis differs from traditional approaches in that life course impairment becomes the outcome and psoriasis is one of the exposures. Although this may appear a substantial difference, on closer examination it is clear that, independent of the outcome that we wish to observe, we are always looking at a system of factors (biopsychosocial parameters) that mutually influence each other over life-time.

The accumulation of risk model may be applied to chronic inflammatory conditions, where "wear and tear" adds up over time to negatively affect health (8), a mechanism explained by the concept of allostatic load in biology (37). This model certainly fits CLCI in psoriasis, which postulates that it is the cumulative effect of exposures (i.e. psoriasis, stigma, physical co-morbidities and psychological co-morbidities) that occur at different points over a person's life that add up to impair life potential. The concepts of critical and sensitive periods also apply, as it is reasonable to postulate that an early onset of psoriasis during adolescence (a critical period) and early adulthood (a sensitive period), when patients are consolidating their personality, establishing social contacts, initiating higher education and planning career paths, will have a greater impact on life course than later onset of psoriasis. Likewise, exposure to co-morbidities such as psoriatic arthritis during the sensitive period of early adulthood may result in lower income (e.g. through the need to change career or take early retirement), leading to other exposures, such as anxiety, social impairment, depression, poor compliance and worsening of the symptoms, all of which interact in a cumulative manner to produce CLCI. These exposures will be modifiable and risks can be reduced (*i*) via psychosocial interventions, such as patient education to improve coping behaviour and quality of life (QoL) (38), support networks to facilitate social contacts and coping with the disease, or potentially early therapeutic intervention respectively

(*ii*) by the patient, for instance by using effective coping strategies and by seeking social support, and, or (*iii*) by biomedical interventions. Modifying a model from Dunn (9), the elements that potentially influence life course over time through the onset of psoriasis are represented in Fig. 1, although the exact risk factors for CLCI and their relative contribution to impairment have yet to be established. Nonetheless, the interaction of risks over time can be observed on an individual patient level and have been described by Warren et al. (17); Fig. 2 demonstrates these interactions of risk factors in a single patient.

In LCR, the concept of cumulative advantage or disadvantage is used to describe patterns of diverging cohort trajectories. Formalised mathematically, the central idea is that in social systems under certain conditions, the 'advantage' of an individual (or group) over another 'naturally' grows over time. This concept can be more formally defined as a systemic tendency (hence resulting from the interaction of a complex of elements) for inter-individual divergence in a given characteristic (e.g., money, health or status) with the passage of time (39–41). If disadvantage has a 'natural' or 'intrinsic' (systemic) tendency to accumulate, lifetime exposures are likely to lead to divergence in life outcome (or cumulative disadvantage). This concept is consistent with the potential for diverging life trajectories in patients with chronic diseases, such as psoriasis, compared with those without the disease.

Theoretical and methodological challenges and advantages

The life course approach can be implemented using different study designs to better understand the aetiology and course of chronic disease on the one hand, and the impact of chronic disease on life course on the other hand. Longitudinal designs with repeated data collection are the most appropriate for studying accumulation of risk and testing causal hypotheses (3). However, such designs are expensive, take time to yield data, and may suffer from attrition and missing data (3). Studies
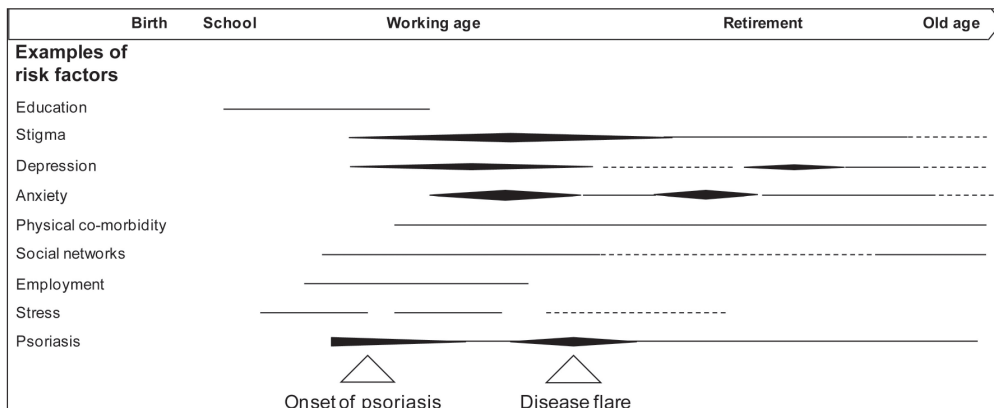

Fig. 1. Examples of risk factors for psoriasis over a lifetime. Some risk factors may be more important when they first occur, represented by a broader line at inception, which narrows over time. Other factors may build up and reduce during an 'episode', represented by broadening and narrowing of the lines. Some may be important only during certain developmental periods and not at other times, others may be less important in some periods (represented by dashed lines).
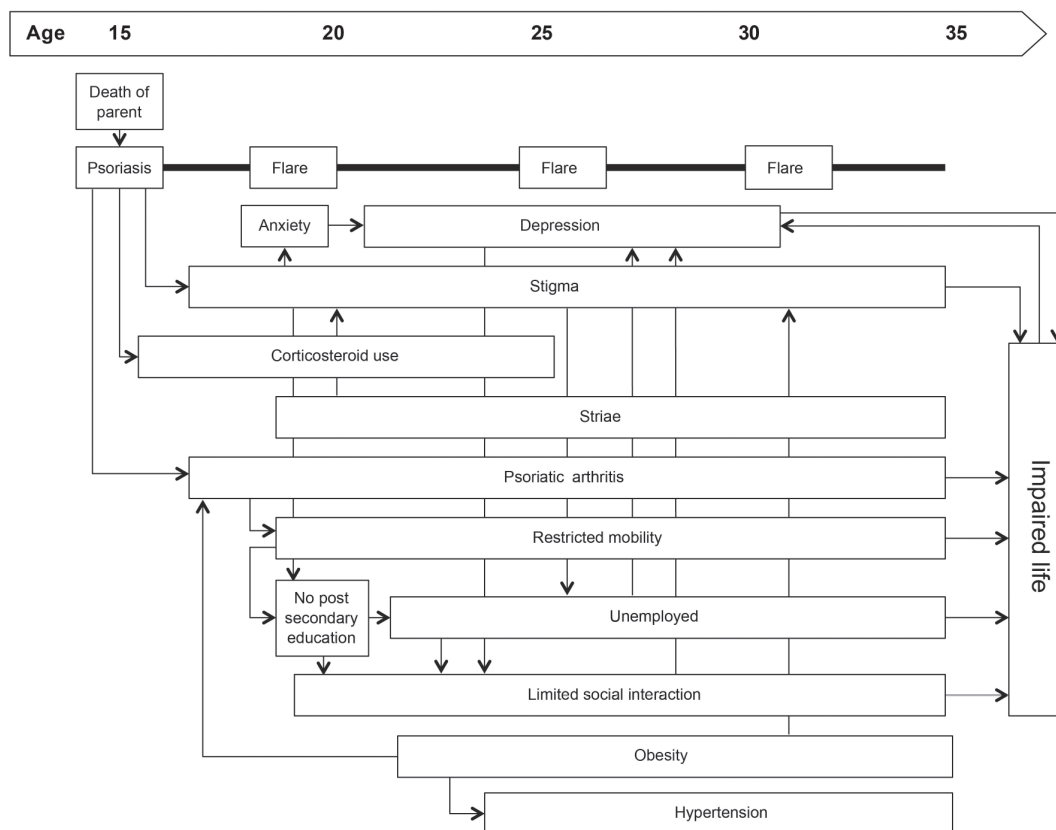
Fig. 2. An example of the interaction of risk factors in cumulative impairment in psoriasis from a single patient.

performed to date looking at the impact of psoriasis on physical, psychological, social and economic outcomes have been largely cross-sectional using point-in-time outcome measures (15). Such assessments are unlikely to adequately reflect the impact of psoriasis, and its co-morbidities and psychosocial disadvantages, over the life course of patients, and they do not allow any assessment of causal pathways[1].

Historical cohort studies using data on psoriasis patients that have been previously collected in a given population (perhaps for another purpose) are more cost effective than longitudinal, prospective studies, and provide a potential opportunity to examine the effects of psoriasis over time. In cohort studies evaluating general health psoriasis has however been seldom, if

ever, recorded, thus limiting any value of large existing epidemiological databases for evaluating the effect of psoriasis over the life course (45–51).

Disease-specific registries, such as the PsoCare registry along with other similar registries (52), may provide suitable populations for retrospective case-control studies. Purpose-designed 'course-of-life' questionnaires for use in such studies in psoriasis patients need to be developed and validated (53–55). Fundamental methodological problems, however, remain, as the results of retrospective studies in large populations may be weakened by recall bias.

Mathematical modelling (56) and subsequent computer simulations, which have been extensively applied in demography, may provide another potential solution in LCR in chronic disabling diseases, including psoriasis. Such models can be macro models (describing subpopulations over time in a given country) (57), micro models (58, 59) (where the life course of each individual is modelled, for instance being represented as a series of predefined states, time being assumed as a discrete unit) or combined macro–micro models (60). In these models, the known risk factors determined in cross-sectional studies (e.g., reduced employment or increased divorce rates) serve as input variables; the models then output life courses of patients and of healthy controls, thus providing an additional method to assess the impact of chronic diseases on life course.

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[1]One notable exception within psoriasis research is an 11-year prospective study by Unaeze et al. (42), which indicated that the impact of psoriasis on HR-QoL decreased over time, suggesting that patients with psoriasis may adjust their internal standards and values to accommodate the realities of their condition. These findings give further support to a theoretical model developed by Sprangers & Schwartz (43), explaining how internal standards, values and conceptualisation of QoL of a patient can change over the course of a disease trajectory and, as a result, may maintain or even improve a patient's perception of QoL: retrospective assessment of QoL shows a similar pattern (44). These studies, however, primarily examine subjective perception of QoL rather than the objective outcomes of the cumulative effect of disease on patients' lives, such as economic or employment status, or social advancement.

versity Press, 2007.

Increasingly sophisticated models and/or more detailed data from questionnaires used in retrospective case-control studies have the potential to provide additional data on the cumulative impact of chronic disabling diseases over a patient's life. Given the prevalence of psoriasis and the heavy economic impact of the disease on public health expenditures (61, 62), applying life course approaches to understand the accumulation of disadvantage and interconnectivity of exposures in patients with psoriasis may prove relevant in public health planning and management of this disease. Such an approach might eventually allow the assessment of critical periods for more invasive therapies, not only aiming for the best possible clinical outcome, but also at avoiding life course impairment, which might prove irrevocable.

CONCLUSIONS

In contrast with the ever increasing use of the life course approach in many other fields of medicine, this methodology appears to have been rarely adopted in dermatology and, when applied, it was more to address specific research questions rather than in a systematic manner. Still, the life course approach applied in the field of chronic inflammatory skin diseases may provide important new insights into the nature of disease, both from the 'classical' point of view of identifying early risk factors for later disease development or risks (which, cumulating, may constitute triggering or aggravating factors), as well as from the 'new' point of view of looking at the disease as an exposure and the life course as the outcome. Whether these new insights will be achieved by examining available cohort data, administering specially developed course-of-life questionnaires or mathematical modelling of known risk factors remains to be seen. Addressing the need to better understand the impact of chronic skin disease over the life course may help identify more vulnerable patients and facilitate more appropriate treatment decisions or earlier referrals for improved patient care.

ACKNOWLEDGEMENTS

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