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Atopic Dermatitis and Comorbidities: Added Value of Comprehensive Dermatoepidemiology

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Atopic dermatitis is common and in its severe form is devastating. This chronic inflammatory dermatosis is part of the atopic syndrome, which includes asthma, food allergies, and hay fever and is known to be associated with mental health disorders. In line with psoriasis, several recent observational studies using national survey and linkage data have suggested a link between atopic dermatitis and cardiovascular disease. The atopic dermatitis field can benefit from the past experiences in psoriasis research and should not follow the same path, but, rather, aim for a more comprehensive approach from the beginning. A recent German consortium studying links between atopic dermatitis and cardiovascular disease first screened a large claims database, followed by analyses of more deeply phenotyped (birth) cohorts with longitudinal data. In addition, genetic and metabolic analyses assessing the predisposition of patients with atopic dermatitis for cardiovascular disease were performed. Overall, the association between atopic dermatitis and cardiovascular disease was at most modest, but in more refined cohorts the cardiovascular risk profile and genetic architecture was comparable. A more integrated approach could create clarity about the clinical relevance of cardiovascular disease in individuals with atopic dermatitis sooner, avoid speculation that affects patient care, and save scientific resources.

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Classical sequential dermatoepidemiology

In skin research, the field of comorbidities research started with psoriasis, and it has now expanded to other inflammatory dermatoses, including atopic dermatitis (AD). In the 1990s, the observed comorbidities for psoriasis were attributed to smoking and to alcohol consumption as reported in a Finnish registry study (Poikolainen et al., 1999). There was also concern that treatment exposure increased the risk for comorbidities, such as (skin) cancer in psoralen plus UVA-treated patients (Stern and Lange, 1988). In 2002, it was demonstrated in a single center cohort that patients with rheumatoid arthritis receiving methotrexate experienced significantly fewer

cardiovascular deaths compared with similar patients not using this drug (Choi et al., 2002). The psoriasis comorbidity story became a “trending” topic after Gelfand et al. (2006) demonstrated that patients were at an increased risk for cardiovascular disease (CVD), especially younger and more severely affected individuals, based on analyses of the British Clinical Primary Care Research Database. Subsequently, hundreds of observational studies of varying quality and of which included a “me-too” approach have investigated the complex association between psoriasis and CVD, with the majority yielding positive results. A recent two-stage clinical epidemiology study complemented by positron

emission tomography data and serological biomarkers, suggesting that psoriasis is associated with subclinical CVD (Joshi et al., 2016). However, several recent well-designed, high-quality studies reported none to modest effects, thereby questioning causality in the link between psoriasis and CVD (Dowlathshahi et al., 2013; Koch et al., 2015; Parisi et al., 2015; Stern and Huibregtse, 2011). More than 10 years after the first evidence was published, good interventional studies are still lacking, making it challenging to interpret the clinical relevance of psoriasis as an independent CVD risk factor (Nijsten and Wakkee, 2009; Ogdie et al., 2015; Stern, 2010).

My clinical impression is that patients with AD are often younger, slimmer, and more anxious compared with patients with psoriasis. In addition to their allergic conditions such as asthma, food allergies, and hay fever, several studies have demonstrated that patients with AD are more likely to develop mental health disorders compared with control subjects (Egeberg et al., 2016; Schmitt et al., 2009). It took a surprisingly long time before the first studies on AD and CVD were published, and the recent reports seem to “coincidentally” occur with the introduction of biologic therapies for AD, but otherwise the scientific approach copies that of psoriasis. The best available studies are from 2014 onward, and they are based on national survey, claims, and linkage studies (Brunner et al., 2017). Analyses of the US National Health and Nutrition Examination Survey (i.e., question based diagnosis) suggested that patients with AD had a more adverse CVD risk profile (i.e., more smoking, alcohol consumption, and obesity combined with less physical activity) (Silverberg and Greenland, 2015), in line with the initial psoriasis studies (Poikolainen et al., 1999; Stern and Lange, 1988), and they were at higher odds of having cardiac conditions (Silverberg, 2015). In a recent national Danish linkage study, patients with AD also had an increased CVD risk profile compared with the general population, but after adjusting for several confounders not an elevated myocardial infarction risk in those with mild or severe disease (Egeberg et al., 2016).

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Clinical Implications

- Atopic dermatitis is not associated with most cardiovascular risk factors, myocardial infarction, or stroke.
- Atopic dermatitis has integrated lessons about comorbidities learned for psoriasis.
- Comprehensive clinical research saves resources and avoids waste.

Like the psoriasis community, but much sooner, the international eczema council reviewed the comorbidity evidence and concluded that there was a need for longitudinal and interventional studies to assess AD and its comorbidities (Brunner et al., 2017).

Comprehensive dermatoepidemiology

In contrast to observational research, laboratory-based studies often present results of more than one experiment, assessing the same hypothesis from different vantage points. Ideally, the experiments are complementary, explaining and validating each, thereby obtaining more reliable results and better insight into the underlying mechanisms. In observational research, there is a tendency to use one data source sequentially and one study design per paper, with intrinsic advantages and limitations, as illustrated in the first two paragraphs and in Figure 1. At the statistical level, several explanatory and confirmatory analyses are performed in such studies to deepen insight into the studied association. Different inferential statistical models are commonly used, sensitivity

analyses are often performed to understand the impact of applied assumptions better, or, more dangerously, subgroup analyses are employed to study the effect in different subsets taken from the initial dataset. In recent decades, genetic epidemiology has brought to conventional epidemiology the need for (inter)national collaborations and for replicating findings in different study populations and/or for including functional experiments to increase the reliability of the observed associations. However, this comprehensive approach of exploring datasets and validating findings within one project has not yet been adopted for more conventional epidemiological studies.

Typically, in observational research, exploration of an association begins with a retrospective case series or with a cross-sectional case-control study (population- or hospital-based) followed by cohort studies, with each succeeding study building on the results of previous studies, which bring us to the article under consideration. In this issue of the *Journal Investigative Dermatology*, a German consortium led by Stephan Weidinger studied the

risk of CVD in patients with AD in a comprehensive manner (Standl et al., 2017), as was done previously by the same group for psoriasis (Koch et al., 2015). In the first part of the current study, a claims database was used to “screen” whether an association existed between AD and CVD. The advantages of routine, previously collected data are that they are available in large quantities (AOK PLUS cohort included more than 1.2 million beneficiaries) and that they reflect daily practice, providing them with good external validity. The common issues in using routinely collected data are case and outcome definitions (e.g., how reliable is an ICD-10 code for AD? How is disease severity defined?), surveillance bias (i.e., the more you are evaluated by a doctor, the more likely you are to receive a diagnosis), and temporal relationships (i.e., incident vs. prevalent cases) (Nijsten and Wakkee, 2009). Another issue about previously collected data is residual confounding, because, besides age and gender, treatment and environmental and lifestyle characteristics are often not available or incomplete. Some routinely collected datasets such as the Clinical Primary Care Research Database have been modified to fit research purposes and do include information on more confounders, but even so, these datasets are often not designed to answer the posed research question. Altogether, routinely collected data are an excellent tool to generate hypotheses at an aggregated level, but not at the level of patients, nor for understanding disease etiology. In a cross-sectional

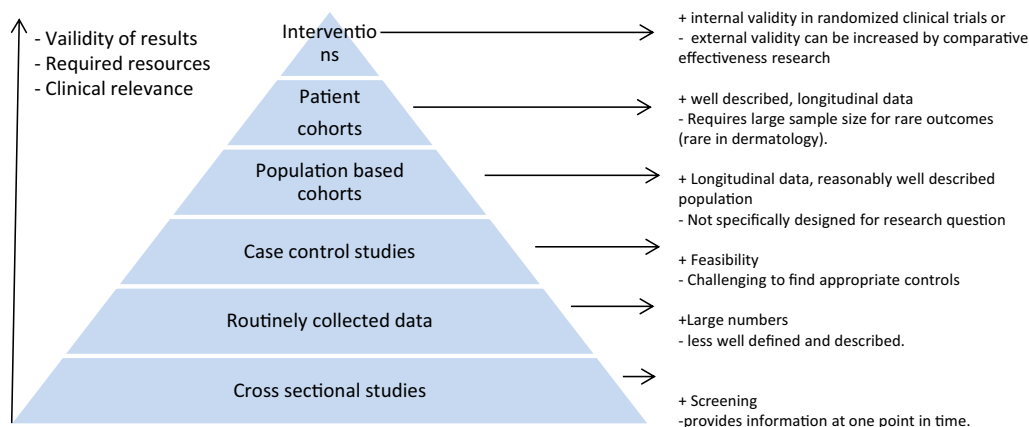


Figure 1. Classical sequential order of different observational study designs and their most important (dis)advantages.

analysis of the AOK PLUS cohort that only adjusted for age, gender, and socioeconomic status, having had an insurance claim with an ICD-10 code for AD was modestly, but significantly, associated with increased risk of hypertension, peripheral arterial disease, and angina pectoris (relative risks <1.3), but not with the clinically more relevant CVDs such as myocardial infarction and stroke. In longitudinal prospective analyses that accounted for AD preceding CVD, the relative risks remained significant but were weaker, as expected (relative risks <1.2). Without taking the possible differences between AD and control individuals into account, AD seems to predispose to some of the CVD components.

To test whether these adverse CVD risk profiles persisted in a more deeply phenotyped population, the authors subsequently investigated a sample of almost 3,000 individuals, with an average age above 50 years, in a population-based cohort (KORA F4), of whom 209 had been diagnosed with AD by a physician. After adjusting for age, gender, smoking, education, alcohol intake, physical activity, and medication use for hypertension, diabetes, and/or hyperlipidemia, none of the investigated CVD risk factors such as waist-hip ratio, blood pressure, or serological lipid levels were elevated in individuals with AD compared with those without AD. The same nonsignificant findings were observed in a sample of more than 2,200 adolescents from a birth cohort (GINIplus/LISAplus) in which AD was defined as "ever having been diagnosed with AD up to the age of 15 years." On the basis of these cohorts, patients with AD did not seem to be predisposed to developing CVD, after adjusting for multiple confounders.

Often, observational studies end by concluding that nonassessed factors such as genetic predisposition may explain the results. The German team went one step further and performed genetic and metabolomic analyses.

Based on the existing genome-wide association study literature, 126 common variants for coronary arterial disease were identified of which 118 were available in the AD genome-wide association study. KORA F4 and GINIplus/LISAplus were part of larger AD consortia, and in these consortia, none of the 118 variants remained significant after adjusting for multiple comparisons in a candidate gene approach analysis. The nominal significant variants in IL6R and ADAMTS7 pointed in opposite directions. In KORA F4, 151 metabolites in 2,878 participants were analyzed and no differences were observed between those with and those without AD. These results indicate no relevant overlap in the genetic architecture between CVDs and AD.

Conclusions

This study has set a new standard in dermatoepidemiological comorbidity studies by using different datasets, and study designs, assessing both the primary outcome and its risk factors, and by including genetic epidemiology as well. This scientific collaboration may have saved science a decade of investigation, and it emphasizes the need for comprehensive studies before suggesting that (new) treatments may prevent CVD comorbidities.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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