Title: Development and validation of an algorithm to accurately identify atopic eczema patients in primary care electronic health records from the UK

Short title: Validation of atopic eczema in electronic health records

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Abbreviations used: Positive Predictive Value (PPV), CI (Confidence interval), The Health Improvement Network (THIN)

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ABSTRACT

Electronic health records hold great promise for clinical and epidemiologic research. Undertaking atopic eczema (AE) research using such data is challenging due to its episodic and heterogeneous nature. We sought to develop and validate a diagnostic algorithm that identifies AE cases based on codes used for electronic records used in the UK Health Improvement Network (THIN). We found that at least one of 5 diagnosis codes plus two treatment codes for any skin-directed therapy were likely to accurately identify patients with AE. To validate this algorithm, a questionnaire was sent to the physicians of 200 randomly selected children and adults. The primary outcome, the positive predictive value (PPV) for a physician-confirmed diagnosis of AE, was 86% (95%CI 80-91%). Additional criteria increased the PPV up to 95% but would miss up to 89% of individuals with physician-confirmed AE. The first and last entered diagnosis codes for individuals showed good agreement with the physician-confirmed age at onset and last disease activity; the mean difference was 0.8 years (95% CI -0.3,1.9) and -1.3 years respectively (95%CI -2.5, -0.1). A combination of diagnostic and prescription codes can be used to reliably estimate the diagnosis and duration of AE from the THIN primary care electronic health records in the UK.

INTRODUCTION

Atopic eczema (AE, synonymous with atopic dermatitis and commonly referred to as eczema) is one of the 50 most burdensome diseases worldwide (Vos et al., 2012, Weidinger and Novak, 2016). Therefore there is great interest in understanding its causes, natural history and potential associations with comorbid conditions. Yet most studies rely on highly selected specialty clinic populations, cross-sectional studies, or self-reported data, and are prone to bias and limited generalizability (Asher et al., 1995), (Deckert et al., 2014). Representative population-level data with validated diagnoses and longitudinal follow up are needed.

Electronic health data from primary care practices in the UK present an opportunity to directly address many of the unanswered questions about long-term outcomes in AE in particular. They are representative of the general population, include relatively long term follow up of both children and adults, and are appropriate for the study of AE since 97% of patients are managed by general practitioners in the UK (Emerson et al., 1998, Schofield JK, 2009). However, these data were created for administrative and clinical purposes, not designed specifically for research, and it is therefore critically important that the validity of AE diagnoses in these data sources is understood (Manuel et al., 2010). Because AE is a heterogeneous and episodic condition with non-specific terminology, there exists high potential for misclassification of diagnosis and duration of disease. There is no single diagnostic test for AE and it can be challenging to diagnose in population-based studies due to its variability in morphology, distribution and periodicity. The diagnosis relies on clinical judgment based on a combination of history and physical examination. Previous studies using UK primary care data to identify patients with AE report wide variations in prevalence from 0-38% based on the coding algorithm used (Anandan et al., 2009, Carey et al., 2003, McKeever et al., 2001, McKeever et al., 2002, 2004, Punekar and Sheikh, 2009, Simpson et al., 2002, Simpson et al., 2009). Moreover, there is some evidence that chronic diseases, such as AE, may be more poorly recorded over time in UK general practice data, as general practitioners are not required to enter codes on each occasion for chronic conditions (Jordan et al., 2004, Khan et al., 2010).

This study aimed to enhance identification of patients with AE within electronic health records. The objectives were to develop and validate a diagnostic algorithm for AE that identifies cases based on codes, and secondarily, to examine the agreement between physician report and codes for AE disease onset, duration and severity.

RESULTS

Algorithm development

A list of potential AE diagnosis and treatment codes were developed by employing a keyword search and examining affiliated codes (Supplemental Table 1), and the five most common and specific codes for AE were chosen to identify those likely to have AE: m111.00 atopic dermatitis/eczema, m1120.0 infantile eczema, m113.00 flexural eczema, m11400 allergic/intrinsic eczema, m12z100 eczema NOS. When we examined the frequency of medical codes among individual patients, we found that including 32 codes likely to be related to AE rather than only the 5 most common codes only slightly increased the number of individuals identified, but including up to 74 possible AE codes nearly doubled the number of individuals

identified (Table 1). The distribution of some codes varied between children and adults; for example, m1120.0/infantile eczema was more commonly used in children.

Despite the chronicity of AE, any of the 5 most common diagnosis codes were rarely repeated in the database; overall, patients had a mean of 1.2 (standard deviation 0.5) codes during 5.6 years (standard deviation 8.0) of follow-up. Because AE is by definition a chronic condition, it was important to include more than one code in our algorithm, but requiring individuals to have two or more diagnosis codes would exclude >80% of the potential AE population. Therefore, the distribution of treatment codes was also examined. In the UK, medical record codes and treatment codes can be entered independently (i.e. a prescription code does not require an associated diagnostic code). Prescriptions, including emollient preparations, are available through the National Health Service, so we examined prescription codes for all potential relevant therapies including topical emollients, topical steroids, topical calcineurin inhibitors, topical anti-infective treatments, and systemic immunomodulatory medications (including methotrexate, azathioprine, mycophenolate, cyclosporine, or biologics) based on British National Formulary groupings, and phototherapy codes (British National Formulary, 2016; Supplemental Table 2). Since prescriptions are free of charge for children only, we stratified our analyses by age (i.e. children under 18 versus adults). We also specifically examined the use of topical steroids and topical calcineurin inhibitors (which are likely to be more specific for AE). To ensure we captured patients with chronic AE in our algorithm, we chose to include patients with at least one of the 5 medical codes frequently used for AE as listed above *and* at least 2 treatment codes for any AE-related therapy on separate dates (at any time point relative to the AE diagnosis, since symptoms may precede the actual diagnosis).

Physician Survey

To validate the algorithm for AE, we surveyed the physicians of a random sample of 100 children (< 18 years of age) and 100 adults (Figure 1). The response rate was 97% overall (96% for adults and 97% for children), and there was no significant difference in response rate by age or sex. The algorithm for identifying patients with AE performed well and there were no significant differences in codes between those with and without physician confirmed AE (Table 2). The positive predictive value (PPV) for a single diagnostic code and at least two treatment codes was 86% overall (95%CI 80-91%); and was higher among children (90%) than adults (82%), though this difference was not statistically significant (Pearson chi2=2.76, p=0.097).

When we examined whether the use of more stringent criteria would improve the prediction of physician-confirmed AE, we found that adding additional criteria to the algorithm had the potential to increase the PPV, but would result in smaller numbers of individuals being detected (Table 3). For example, requiring two AE codes would increase the PPV to 91%, but would only detect 83/163 or 51% of those with physician-confirmed AE. Similarly, requiring a dermatology consult code in addition to the AE and prescription codes would increase the PPV to 95%, but would only detect 18/163 or 11% of those with physician-confirmed AE. Requiring the prescriptions to be for medications more specific to AE (i.e. topical steroids or calcineurin inhibitors) did not significantly change the PPV.

The average age of onset and oldest age of disease activity requiring physician contact estimated using codes from the database were similar to what physicians reported (Table 4). The mean

estimated age at onset using the first diagnosis code or first treatment code were both slightly younger than the physician estimate (mean difference 0.8 years, 95%CI -0.3 to 1.9 and 0.4 years, 95% CI -0.8 to 1.7 years, respectively), and 76% of estimates were within one year of each other. The mean estimated age at last date of AE activity using the last diagnosis code or last treatment code were both older than the physician estimate (mean difference -1.3, 95%CI -2.5 to -0.1, and -3.9 years, 95%CI -5.3 to -2.4 years, respectively), and 79% of estimates within five years of each other. Bland Altman plots for all estimates are shown Supplemental Figure 4. When we stratified these estimates by age comparing children under age 18 to adults we found similar results (Supplemental Table 4).

In our sample, 48 patients were reported by the physician to have had symptoms in the year prior to their last visit; 27 (56%) of whom were assessed as having mild disease and 19 (40%) of who were assessed as having moderate disease based on the severity descriptions in the National Institute for Health and Care Excellence (NICE) guidelines. Patients with moderate disease had more treatment codes during that year than patients with mild disease (median 5 versus 2, p-value for two-sample Wilcoxon rank sum test =0.887). None were reported to have severe disease, limiting our ability to draw any conclusions about the validity of medical record codes to predict disease severity.

Finally, we assessed whether physicians would be able to adequately respond to the UK Working Party criteria (originally designed for in-person assessment), enabling us to compare a set of well-validated criteria for use in large epidemiologic studies to our outcomes in routinely collected electronic health data. For each question, we gave physicians the option of choosing ‘don’t know’. The high number of uncertain responses resulted in poor ability to discriminate between those with and without AE (Supplemental Table 5). We found that only 52 (32%) of those with physician-confirmed AE in our sample met the criteria (an itchy skin condition plus at least 3 of history of flexural involvement, history of asthma/hay fever, history of generalized dry skin, onset of rash under age 2, and visible flexural dermatitis).

DISCUSSION

Interpretation of main findings

Patients with AE were accurately identified if they had at least one AE diagnostic code and at least two prescription codes for AE-related treatments in a large electronic medical record database representative of the general population in the UK. The positive predictive value, or probability that individuals identified by our algorithm truly have the disease as determined by their doctor, was 86%, which is similar to the PPV of coding algorithms for other chronic diseases in routinely collected data (Khanet al., 2010). The PPV was higher in children, but the algorithm still performed well to identify adults with AE.

This study indicates that the types, number, and frequency of codes used to identify AE patients in routinely collected data are important because small differences have the potential to cause substantial misclassification. After examining the distribution of all of codes potentially related to AE, we chose to use the 5 most common AE codes in addition to treatment codes for the primary algorithm. As shown in Table 1, expanding the definition from 5 to 32 codes (likely related to AE but rarely used) would have only increased the proportion of the population identified from 13 to 14%, so we opted for the more parsimonious algorithm. In contrast, using a single code to define AE, for example AD/Eczema (M111.00), would identify far fewer individuals (only 6% of the population). Although it was impractical and prohibitively costly to sample enough physicians to calculate the sensitivity, specificity and predictive value of each of these variations, we present the proportion of patients identified by each set of codes to illustrate the potential magnitude of misclassification. We were able to calculate *post-hoc* changes in the PPV caused by adding criteria to our algorithm. Inclusion of a second diagnosis code, allergy code, or consult code all increased the PPV, but would identify far fewer patients. The ideal balance between these factors depends on the research question. For example, an algorithm with a very high PPV that captures only a fraction of those with disease may be acceptable for a case-control study. On the other hand, the ideal algorithm for a prevalence study would aim to assess the total population burden accurately and may include more mild or marginal cases.

Because AE is a chronic condition, we explored the possibility of using codes from more than one time point to identify patients. In the UK, providers are not required to re-enter codes for chronic conditions, and only 36% of individuals had more than 1 AE diagnosis code. Treatment codes, which can be entered independently from diagnostic codes, were used more frequently, and were therefore included in the algorithm. When selecting the treatments, we opted for an inclusive approach and used all potential AE-related treatments, even emollients, as listed under British National Formulary categories. This approach may include treatments not specifically for AE, so we examined the performance of a more limited definition of treatments (only topical steroids or topical calcineurin inhibitors), and found it did not change the PPV but would identify 4-18% fewer patients (Table 3). Of note, 22% of individuals with one of the 5 most common medical codes never received any treatment codes. Our algorithm excluded these patients, some of whom may have had mild untreated disease.

Because we randomly selected individuals with AE diagnoses at any time point, only a fraction had disease activity during the year prior to their last visit, resulting in too few numbers to meaningfully assess the validity of codes relative to disease severity. Additional research is

necessary to validate whether codes can be used to ascertain severity and disease flares in routinely collected data.

Comparability to other studies

Three other studies attempted to validate routinely collected data for identifying individuals with AE. Two examined the use of medications alone and found they had poor discriminatory power to identify patients with AE in the Netherlands and Sweden (Mulder et al., 2016, Ortqvist et al., 2013). The distribution of treatment codes in our data, as shown in Table 1, also suggested that the were not likely to selectively identify patients with AD, which is why we designed our algorithm to incorporate both diagnosis and treatment codes as described above. The third compared ICD-9 codes from a tertiary care population in the US with Hanifin & Rajka and UK Working Party (UKWP) criteria found in the medical record and found poor overlap (Hsu et al., 2016), possibly due to the lack of standardized recording of specific diagnostic features in the medical record. We assessed whether it was possible to compare our results to the UK Working Party diagnostic criteria, which have been used for epidemiological studies in multiple international settings, but were developed for in-person assessment (Brenninkmeijer et al., 2008, Williams et al., 1994). Because physicians responded, "don't know" to so many of the UK Working Party questions in our survey, we were unable to make meaningful comparisons. We hypothesize the high rates of uncertainty were because there was not enough data in the medical record to enable physicians to answer all of the required questions, and therefore caution against using these as a gold standard from medical record review when they were not systematically assessed. It is also possible that those deemed to have AE by their physician simply would not fulfill the criteria if they had been ascertained fully, and further specially designed studies are needed to test this notion.

Strengths and weaknesses

Strengths of our study include the use of diagnosis and treatment codes, stratified sampling among children and adults, a large representative database with longitudinal follow up, and physician-confirmation of disease as the gold standard. We sampled general practice physicians rather than dermatologists because 97% of patients with AE are managed by general practitioners in the UK, and sampling specialists would have limited the generalizability of the results (Emersonet al., 1998, Schofield JK, 2009).

Ideally, patients would have been assessed in person to confirm their diagnoses. Because this was not possible through the Additional Information Services in THIN, we queried their physicians instead. The physicians were asked to assess the patient based on their recall and review of the medical record. This approach was chosen over a medical record review because it allowed for direct assessment as to whether the physician really believed the patient had AE (regardless of coding).

Our results are only directly generalizable to The Health Improvement Network, though the algorithm is likely to perform similarly in the other UK primary care databases which have substantial overlap (the Clinical Practice Research Datalink https://www.cprd.com/, and other UK primary care data sources including QResearch http://www.qresearch.org/). Validation studies are inherently context-specific, and the PPV of our algorithm may vary in settings where the prevalence of AE and data structure differ. For example, we found that adding a dermatology

consult code to our baseline algorithm increased the PPV to 90% (95%CI 74-100%, Table 3), however it only identified 11% of the patients with confirmed eczema because very few patients are referred to specialists in the UK. In the USA, where the proportion of patients who are referred to a specialist is higher (it is estimated 43% of pediatric AE visits were to generalists between 1997 and 2004, Horii et al., 2007), adding a dermatology consult code to the baseline algorithm is likely to identify a higher proportion of patients with confirmed AE. If our algorithm were used in settings where patients do not receive prescriptions for emollients or other topical preparations or anti-infective treatments, its performance may be more comparable to the first 2 alternative algorithms listed in Table 3 that are based on the use of topical steroids and calcineurin inhibitors alone. We emphasize the importance of carefully examining the distribution and types of codes before undertaking a study using electronic medical record data, and we present the distribution of categories of codes in Table 1 so that researchers can evaluate how applicable our results may be to their data.

Implications for future research

Validation studies that ensure patients are accurately identified are a high priority to enable the use of increasingly available and robust sources of routinely collected electronic health data (De Coster et al., 2006), but have not been widely employed in the AE literature to date. This study showed that AE patients can be accurately identified in the UK Health Improvement Network, and that changes in the number, type or frequency of codes used could result in large differences in the number of patients identified. Additional work is necessary to determine the PPV of our algorithm in other contexts. We highlight factors to consider when examining the frequency and distribution of diagnostic and treatment codes in any electronic medical record database, which are important for researchers to avoid misclassification bias. Efforts are underway to determine how AE patients have been identified in published studies using electronic health data (Dizon et al., 2016), and we encourage the research community to work towards developing standards for methodology and reporting to improve comparability of studies and advance our understanding of AE.

METHODS

Study design

Our study consisted of two parts: a longitudinal cohort study to develop a diagnostic algorithm, and a physician survey to validate it. We followed guidelines for reporting of validation studies and reporting of studies conducted using observational routinely collected health data (Benchimol et al., 2011, Benchimol et al., 2016).

Participants/Data source

The Health Improvement Network (THIN) is a database comprising the electronic health records of people registered with participating general practices. THIN is broadly representative of the general UK population in terms of age, sex, ethnicity, and geography and is one of three major UK primary care databases (Shephard et al., 2011). We chose this data source because it is one of the world's largest sources of anonymized longitudinal data from primary care practices with over 85 million patient-years of follow up, and because we had institutional access and experience using the data (Margolis et al., 2007, Margolis et al., 2008, Ogdie et al., 2015, Seminara et al., 2011). Previous validation studies have shown that the recording is highly

accurate and nearly complete, and THIN has been used to study multiple chronic conditions. Participating practices are remunerated for recording data on clinical diagnoses, test results, prescriptions, and referral data via the Read/OXMIS (Oxford Medical Information System) coding framework, which is based on the International Classification of Diseases (ICD) coding system. The raw data are updated monthly and undergo extensive quality control and validity checks by a centralized research team before release. Practices may choose to participate in the Additional Information Services Program, which administers surveys to consenting physician practices. Approximately 60% of all THIN practices actively participated in this program when our survey was administered in October 2015.

Algorithm development

A list of potential AE diagnosis and treatment codes were developed by employing a keyword search and examining affiliated codes (Supplemental Table 1). The distribution of codes was examined, and in consultation with a panel of experts on AE epidemiology and use of routinely collected data (HCW, DM, LM, SML, KA) a parsimonious algorithm was developed to identify patients most likely to have AE.

Physician Survey

The survey was sent to the physicians of a random sample of 100 children (<18 years of age) and 100 adults with acceptable records who were alive and currently enrolled in practices participating in the Additional Information Services (Figure 1). The primary outcome was the positive predictive value (PPV), or probability that subjects identified by the algorithm truly have the disease, as this measure is the most relevant for avoiding misclassification bias in subsequent studies of AE (Choi, 1992). Assuming a physician response rate of 90% (based on prior studies using physician confirmation of chronic disease in routinely collected data (Khanet al., 2010, Seminaraet al., 2011)), a sample of 200 patients should have enabled us to obtain a 95% confidence interval of 0.85-0.94 around an *a priori* estimated PPV of 0.90. Given funding constraints we chose to sample only patients with codes suggestive of AE. Sampling additional subjects without AE codes would have enabled us to also calculate sensitivity and specificity of the algorithm.

A standardized letter was sent to each practice requesting completion of a 1-page survey (supplemental Figures 2-3), and physicians received monthly reminders for completion and compensation for their time. If the diagnosis of AE was confirmed, we then asked the physician to (1) provide a global assessment of average AE severity over the past 12 months, (2) confirm the age at AE onset, and (3) confirm whether the patient still has active AE or whether the patient's AE is in remission. Although many eczema-specific severity scales have been developed and validated for assessment of patient outcomes in clinical trials, few are designed to address long-term severity (Schmitt et al., 2007). Therefore, to asses severity, we used descriptions of mild, moderate, and severe disease from the UK National Institute for Health and Care Excellence (NICE) guidelines for management of eczema (NICE, 2007). Finally, to determine whether our results could be compared to another widely used definition of AE in large epidemiologic studies, the survey included the UK Working Party refinement of Hanifin and Rajka's diagnostic criteria questions (Brenninkmeijeret al., 2008, Williamset al., 1994).

AE is a clinical diagnosis, and biopsy and laboratory tests are non-specific, therefore we relied on the physician's confirmation of the diagnosis as the gold standard. This approach is consistent with other validation studies of chronic conditions in medical record databases in UK primary care databases (Ogdie et al., 2014, Seminaraet al., 2011, Soriano et al., 2001). Physicians were asked to fill out the survey based on their knowledge of the patient and review of his or her medical record.

Analysis

For the 200 patients whose physicians were surveyed, differences in codes between those with and without physician-confirmed AE were examined and the PPV of our algorithm for identifying AE patients was calculated. The PPVs of alternative algorithms with additional criteria for identifying patients with AE were also calculated. Next, the age of disease onset and "remission" reported in the physician survey were compared to dates calculated from the database using the first and last AE diagnosis and prescription codes. Agreement was assessed descriptively using Bland Altman plots (Bland and Altman, 1986). All analyses were stratified by age (i.e. children under 18 *vs* adults). Analyses were performed using Stata (Version 14, Stata Corporation, College Station, Tx).

Ethics

Approval was obtained from the Scientific Research Council of THIN and the University of Pennsylvania IRB.

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