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## **National and regional hospitalization rates for allergic disorders in the United States: a 17 year time-trend analysis**

**Short title:** Trends in US hospitalization rates for allergic disorders

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**Authors' contributions:** PK, NF, GH, AS and GS participated in the study design. PK conducted the data pre-processing and analysis. NF, GH, BIH, PW, AS and GS assisted in the statistical analyses and interpretation of the results. PK wrote the manuscript assisted by NF, GH, BIH, PW, AS and GS. All authors read and approved the final manuscript.

To the Editor:

Allergic disorders are common and responsible for considerable morbidity, impairment in quality of life, healthcare utilization and both direct and indirect healthcare costs<sup>1</sup>. For example, asthma in the U.S. affects an estimated of 26 million Americans, the medical expenditure is up to \$4423 greater for those with markers of uncontrolled asthma together with a greater healthcare utilization and decreased productivity<sup>2</sup>. High costs are also related to patients with anaphylaxis<sup>3</sup>, urticaria<sup>4</sup>, atopic eczema/dermatitis<sup>5</sup> and allergic rhinitis<sup>6</sup>.

Studies analyzing such national trends were performed for countries such as Poland<sup>7</sup>, UK<sup>8</sup> and Spain<sup>9</sup>. For example, in the UK Gupta et al.<sup>8</sup> analyzed trends in the prevalence, morbidity and mortality for allergic disorders, excluding asthma, based on hospital admission and mortality data. Studies on specific population subgroups showed variations in allergic disorder burden, e.g. different age groups, urban-rural division. Krzych-Fałta et al.<sup>7</sup> studied the prevalence of allergic conditions (seasonal allergic rhinitis and perennial

allergic rhinitis, asthma, atopic dermatitis) in metropolitan versus rural residents in Poland and found that the prevalence of the diseases was higher in the metropolitan areas than in rural areas, especially among adults.

Although now very common, there is a relative paucity of data on U.S. national trends in allergy epidemiology and outcomes, we therefore undertook an analysis of trends in hospitalizations from allergic disorders across the U.S.

We used the National Inpatient Sample for the period 1998-2014 to analyze a sample of 130 million hospital discharge records of all age groups from four U.S. census regions for the following allergic disorders: allergic conjunctivitis, allergic rhinitis, anaphylaxis, angioedema, asthma, atopic eczema/dermatitis, drug allergy, food allergy, urticaria and venom allergy. ICD 9 codes were used in all records to classify allergic disorders. At the same time this also represents a limitation of the study since in some cases coding reliability might be an issue when ICD 9 codes are used. After the application of population weights to the sample, we had a total of 622.6 million inpatient records (3.7 million annually). More detailed description of the study processes and definitions is provided as a supplement (Appendix 1 Methods) together with a summary table of hospitalization rates from these allergic disorders by demographic factors (Appendix 2 Table S1). Yearly age- and sex-standardized hospitalization rates and trends for primary and non-primary diagnoses, defined as up to 14 diagnoses following the primary diagnosis, over the 17-year period were calculated using segmented generalized linear regression (Figure 1).

In addition, we calculated rates for: different age groups (defined as children for patients aged <15 years; young adults for those aged 15–44 years; and older adults for those aged 45 years and over); statistical regions (U.S. regions West, Midwest, Northeast and South as defined by U. S. Census Bureau); and urban-rural division (Figure 2) adjusted with appropriate standardization rates.

Temporal trends over the study period were estimated using segmented (piecewise) regression models, each segment being estimated via generalized linear model with Poisson distribution and natural logarithm link function, as in similar study focusing on allergic diagnoses<sup>9</sup>. Complete description of the analytic approaches can be found in the supplementary material (Appendix 1 Methods). Trends were shown as either annual percent change (APC) if no break-points were present, calculated as slopes of the regression function or as average annual percent change (AAPC). In both cases, we presented the estimates together with their 95% confidence intervals.

Increases in hospitalization rates at national levels (Figure 1A) were observed for a primary diagnosis of anaphylaxis (APC 2.1%, CI: 0.1,4.2) and angioedema (APC 3.3%, CI: 1.8,4.8). In contrast, decreases were observed in drug allergy (APC -6%, CI: -9.4,-3.1), urticaria (APC -3.3%, CI: -6.3,-0.5) and asthma (AAPC

-1.8%, CI: -2.2,-1.4). Non-primary diagnoses showed some contrary trends, such as increases in asthma (AAPC 4.3%, CI: 4.1,4.5) and additional trends, such as increases in allergic rhinitis (AAPC 9.7%, CI: 8.8,10.6) and atopic eczema/dermatitis (APC 4.2%, CI: 3.6,4.6). Allergic conjunctivitis, food allergy, and venom allergy showed no change (Figure 1B).

Additionally, when analyzing specific hospitalization rates (Figures 2, Appendix 3 Figure S1, and Appendix 4 Figure S2), we found that increases in hospitalization rates were observed for anaphylaxis, especially in children, for most regions, and angioedema, especially in adults and in urban hospitals. Decreases were observed in drug allergy, and angioedema, especially in adults, for most regions. Decreases in asthma hospitalization were consistent across all age groups, regions and in both urban and rural division. Non-primary diagnoses showed opposite trends with increases for asthma.

Our results also showed large differences between urban and rural hospitalization rates (Figure 2) related to seven out of 10 allergic disorders, where either significant increase in urban hospitals (anaphylaxis, angioedema) or decrease in rural hospitals (asthma, atopic eczema/dermatitis, drug allergy, urticaria, venom allergy) were observed.

In conclusion, recent national hospitalization data from 1998 to 2014 for allergic disorders revealed a complex picture with some conditions showing increased hospitalization rates across observed covariates (anaphylaxis and angioedema) whilst others have shown a decline (asthma, drug allergies, urticaria) or something in between. Of particular concern were the increased rates of anaphylaxis and angioedema in urban settings, where in some cases they at least doubled over the observed time period, whereas in more rural environments rates were stable or decreasing over the same time period. This trend analysis therefore provides an opportunity for policy deliberations on resource allocation for the management of allergic disorders in the U.S. and additional studies might clarify the implications of these trends.

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### Figure legends

**Figure 1. Trends in hospitalization rates for allergic disorder diagnoses.** Age- and sex-standardized hospitalization rates per million population of (A) primary and (B) non-primary allergic disorder diagnoses together with segmented regression models and the 95% confidence interval and APC or AAPC trend estimations.

**Figure 2. Urban-rural trends in hospitalization rates for allergic disorder diagnoses.** Age- and sex-standardized hospitalization rates per million population of (A) primary and (B) non-primary allergic disorder diagnoses with

respect to urban-rural division together with segmented regression models and the 95% confidence interval and APC or AAPC trend estimations.

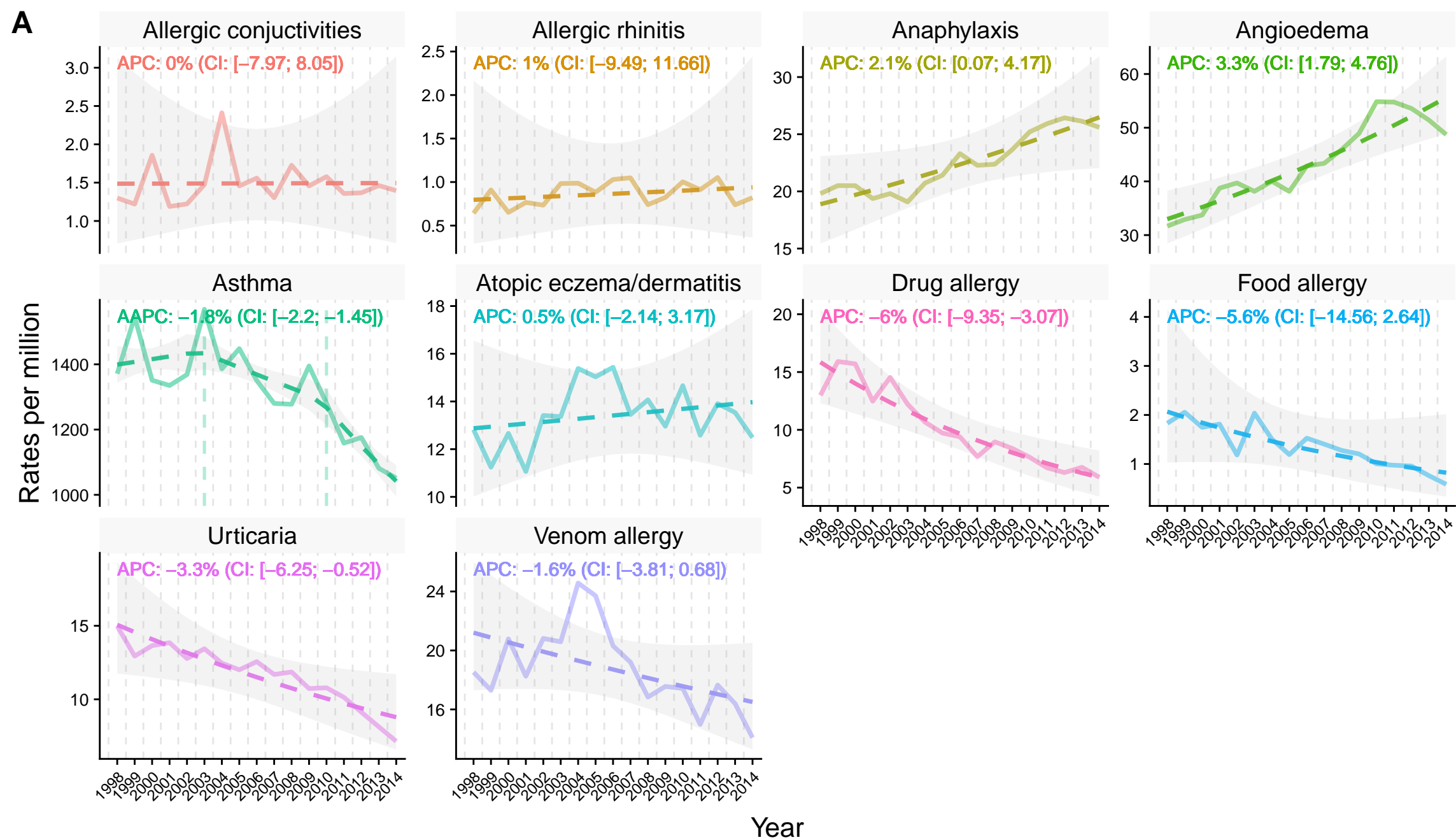
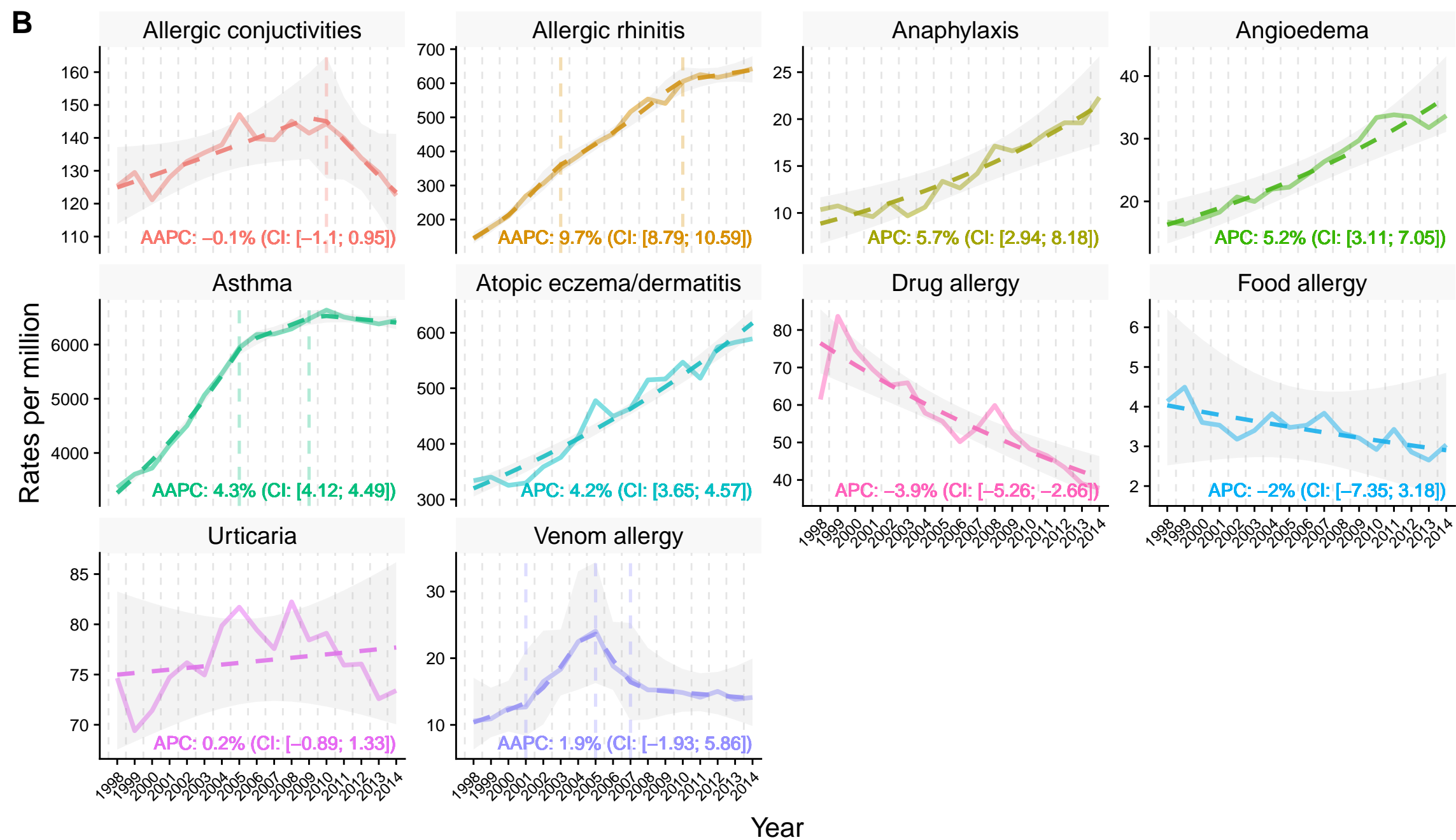
### **Supporting Information**

Appendix 1: Methods

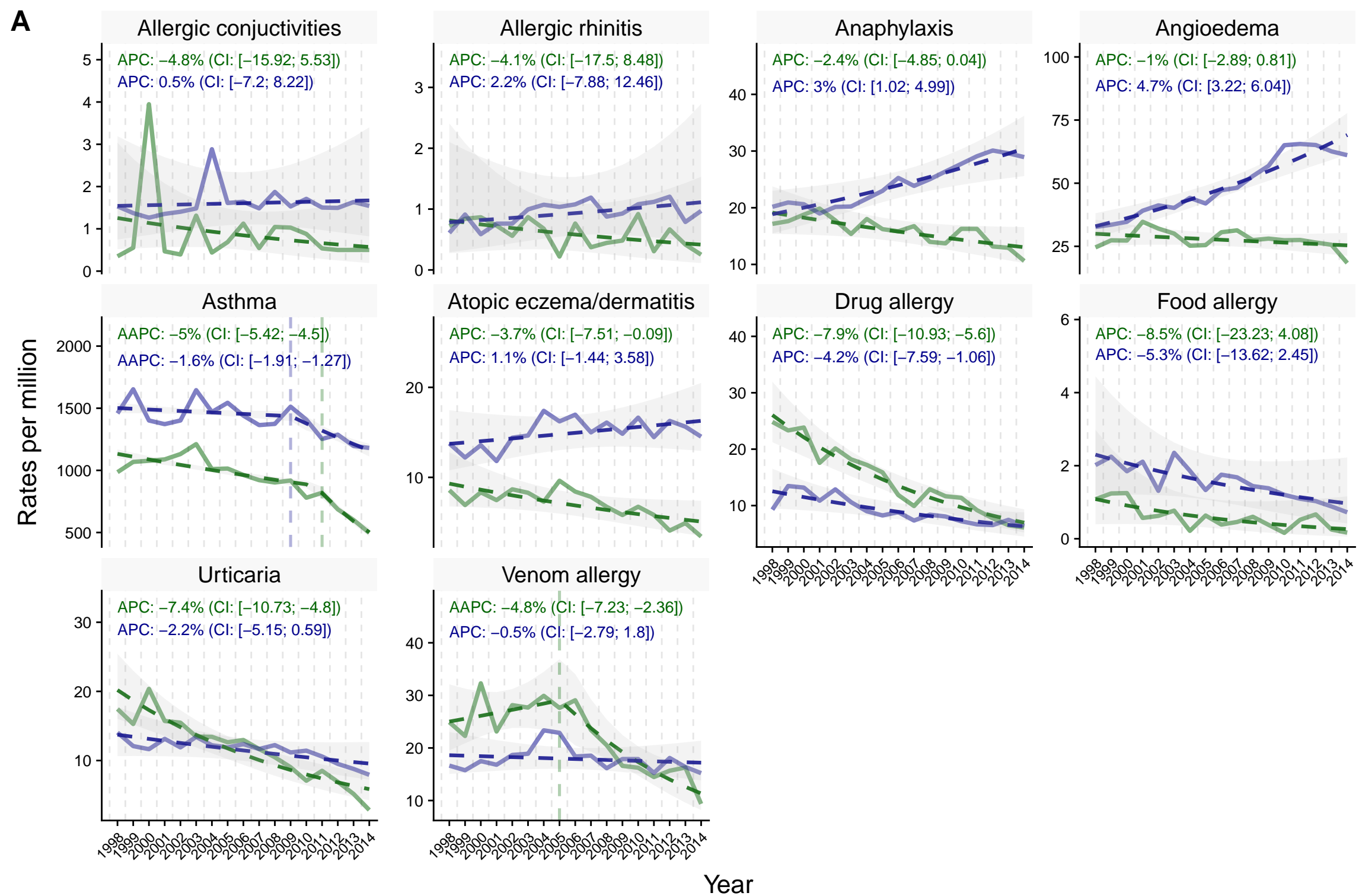
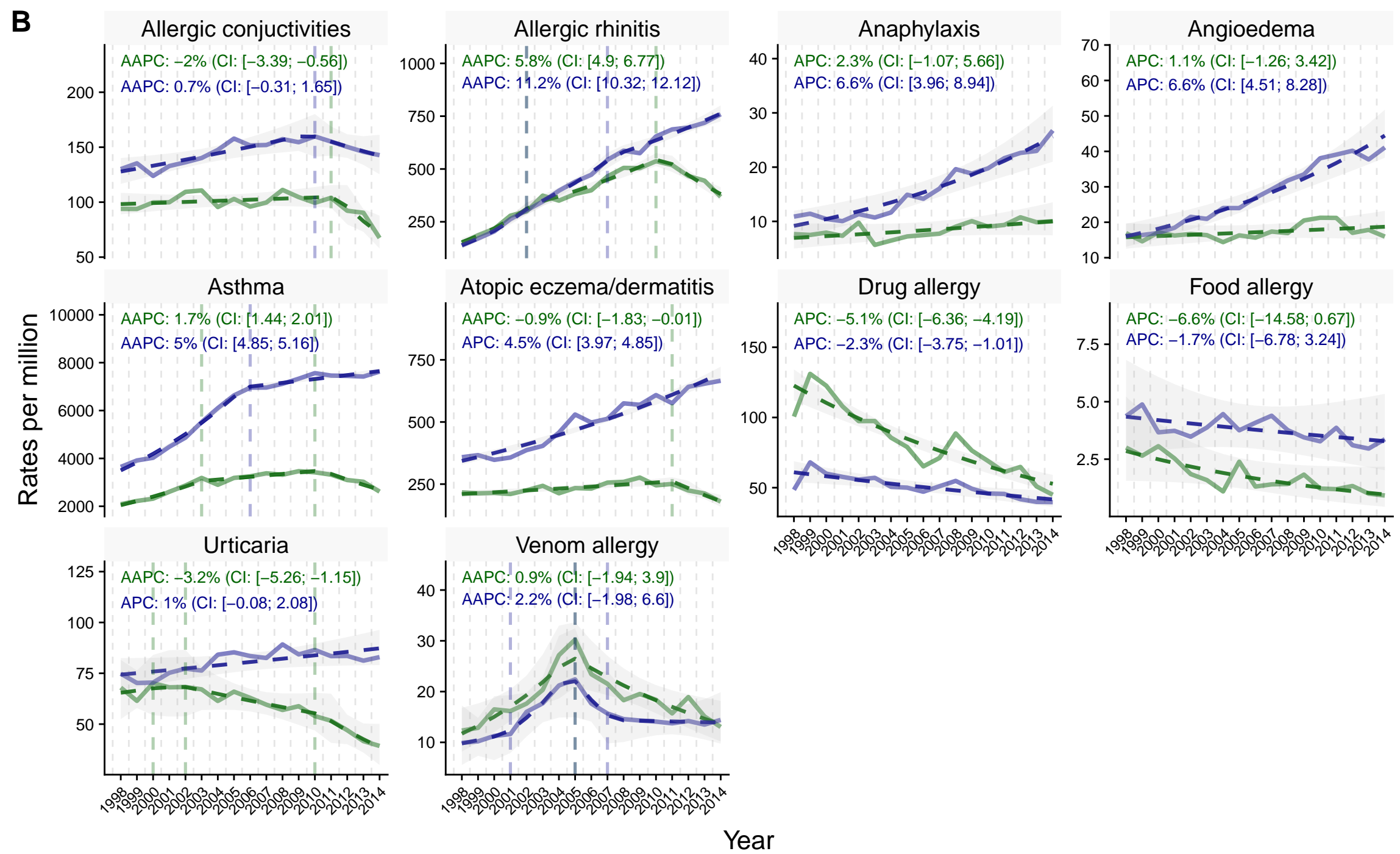
Appendix 2: Table S1 - Summary table of hospitalizations for allergic disorder

Appendix 3: Figure S1 - Age group trends in hospitalization rates for allergic disorder diagnoses

Appendix 4: Figure S2 - Regional trends in hospitalization rates for allergic disorder diagnoses

**A****B**



**A****B**

Area — Rural — Urban