

LETTER TO THE EDITOR

Increasing food allergies in Chile, a developing country post-epidemiological transition

To the Editor,

The clinical spectrum of food allergy (FA) is broad and includes immediate hypersensitivity reactions, typically IgE-mediated reactions, such as food-induced urticaria and food-induced anaphylaxis (FIA), and delayed or non-IgE-mediated reactions such as allergic proctocolitis and food protein-induced enterocolitis syndrome. IgE-mediated FA affects up to 2.5% of the adult population and 6%-8% of children.¹ Most of the epidemiological studies reporting an increase in IgE-mediated FA have been done in developed countries using proxies of FA incidence such as FIA hospitalizations and epinephrine autoinjector sales.² Although the literature on temporal trends of non-IgE-mediated FA is scarce, in developed countries its prevalence may have increased in parallel to the increase in IgE-mediated FA.³ To date, FA temporal trends have not been studied in developing countries.

Chile is a developing country that has undergone rapid demographic and epidemiological transitions over few decades. In recent years, it has greatly reduced infant mortality and infectious diseases such as tuberculosis and measles, giving rise to chronic non-communicable diseases.⁴ Thus, according to the epidemiological transition theory, which explains the surge of chronic diseases by an increased life span resulting from improved health care and disease prevention, Chile is considered in a post-transition stage.⁵

To describe the temporal trends of FIA and allergic colitis, as proxies of IgE- and non-IgE-mediated FA, in Chile during 2001-2018, we performed a retrospective review of national hospital discharge databases from the Chilean Ministry of Health and insurance claims. To identify FIA, we used the ICD-10 code T78.0 (anaphylactic reaction due to food), and for allergic colitis, we used the code K52.2 (allergic and dietetic gastroenteritis and colitis). To avoid the erroneous inclusion of other diseases miscoded as non-IgE-mediated FA in older age-groups, analyses of K52.2-coded hospitalizations were restricted to infants (Method S1).

During the 2001-2017 period, 353 hospitalizations due to FIA were registered. Fifty-five percent were female. Median age was 31 ± 21.2 years (range 0-85 years), and 33.1% of hospitalizations affected children. A higher number of patients had private insurance (61% vs 35% public insurance, $P < .005$). The overall 2001-2017 FIA hospitalization rate was 1.2 (95% CI 1.1-1.4) per 1 000 000

inhabitants. FIA hospitalization rates significantly increased from 0.8 (95% CI 0.4-1.3) in 2001 to 3.0 in 2017 (95% CI 2.3-3.9) ($\beta = 3.0$, 95% CI 1.9-4.2, $P < .005$) (Figure 1A). This increase affected both pediatric and adult patients ($\beta = 1.1$, 95% CI 0.6-1.5, $P < .005$ and $\beta = 1.9$, 95% CI 1.1-2.8, $P < .005$, respectively). Although an increase in FIA hospitalizations was seen in patients with private and public insurance ($\beta = 0.5$, 95% CI 0.3-0.6, $P < .005$ and $\beta = 0.05$, 95% CI 0.02-0.1, $P < .05$, respectively), this was more pronounced in privately insured population ($P < .005$) (Figure 1B). Between 2003 and 2018, 127 sick leave claims due to FIA were submitted to the private health insurance system. In parallel with rising hospitalizations, the number of yearly sick leave claims due to FIA increased significantly during the 2003-2018 period ($\beta = 1.3$, 95% CI 0.04 to 2.6, $P < .05$) (Figure 1C).

Regarding allergic colitis in infants, between 2001 and 2017, 248 hospitalizations were registered; 45% were female. There were no differences in the number of hospitalizations between patients with public and private insurance (48% vs 46%, $P = .5$). The global hospitalization rate due to allergic colitis was 5.9 (95% CI 5.2-6.7) per 100 000 infants. Hospitalization rates significantly increased between 2001 and 2017, from 1.6 (95% CI 0.5-3.8) in 2001 to 7.3 in 2017 (95% CI 4.4-11.5) ($\beta = 1.3$, 95% CI 0.8-1.9, $P < .005$) (Figure 2A). Subgroup analysis by insurance type showed that hospitalization rates increased significantly among those with private insurance ($\beta = 0.95$, 95% CI 0.7-1.2, $P < .005$), but not among public insurance population ($\beta = 0.26$, 95% CI -0.3 to 0.5, $P = .07$); however, temporal trends between groups were not significantly different ($P = .09$) (Figure 2B). Between 2003 and 2018, 9043 maternal medical leave claims for allergic colitis in infants were submitted to the Chilean private health insurance system, revealing a striking increase during this period ($\beta = 157$, 95% CI 88 to 227, $P < .005$) (Figure 2C).

We report the first population-based nationwide epidemiologic study to describe temporal trends of FIA and allergic colitis, as proxies of IgE-mediated and non-IgE-mediated FA, in a developing country. We observed that hospitalization rates and insurance claims due to FIA and allergic colitis have consistently increased during the past eighteen years in Chile, a period considered to be post-epidemiological transition. However, they continue to be lower than rates reported in developed countries like Australia.^{3,6}

The epidemiology of IgE-mediated FA has often been described using surrogate markers such as FIA hospitalization

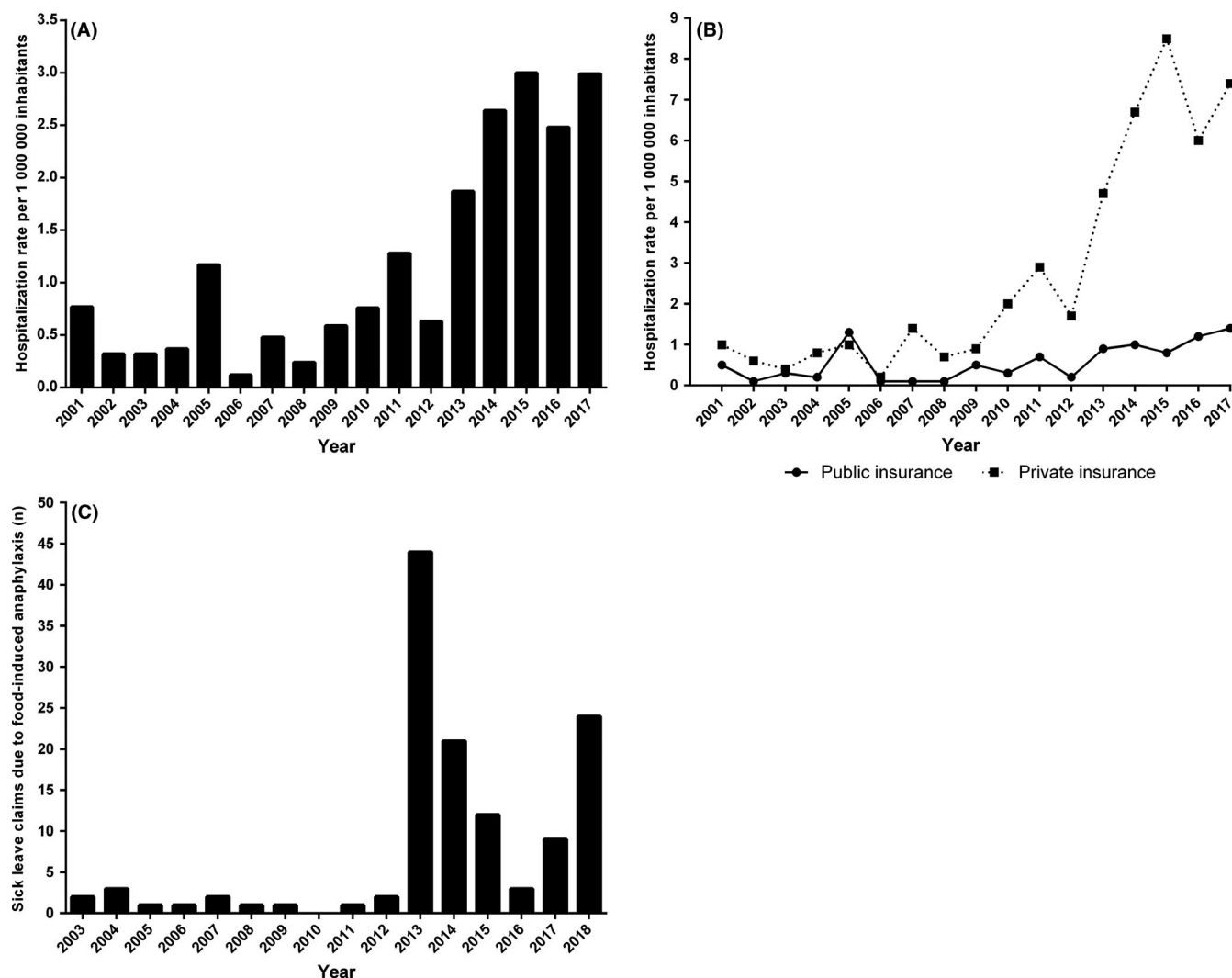


FIGURE 1 Temporal trends for food-induced anaphylaxis in Chile. A, Total food-induced anaphylaxis hospitalization rates, 2001-2017. B, Food-induced anaphylaxis hospitalization rates by insurance type, 2001-2017. C, Total number of sick leave claims due to food-induced anaphylaxis, 2003-2018

rates. A sustained increase in FIA has been observed in several developed countries during the past decades.^{6,7} However, temporal trends of IgE-mediated FA in the developing world have remained unexplored. To date, temporal trends in IgE-mediated FA in a developing country have only been reported by a single-center study from China increasing from 3.5% in 1999 to 7.7% in 2009.⁸ Our study shows a significant increase in FIA hospitalization rates, both in children and in adults between 2001 and 2017. This increase in FIA is significantly delayed when compared to developed countries, as both hospital admissions and insurance claims began to increase in Chile during 2008-2010 as opposed to countries such as Australia and the United States that had increasing incidence since the 1990s.² The increase in FIA hospitalizations is likely the consequence of multiple factors including progressive urbanization, vitamin D deficiency, increasing obesity, and the establishment of a westernized lifestyle throughout the country. Higher socioeconomic status has been associated with an increased risk of developing IgE-mediated FA.⁹ In line

with these data, our study shows that although FIA hospitalizations increased in patients with both public and private insurance, the change over time was significantly larger in privately insured patients.

In contrast to IgE-mediated FA epidemiology, there are limited data on temporal trends for non-IgE-mediated FA worldwide. Only one previous report documented rising hospitalizations due to allergic colitis in Australia and New Zealand.³ In agreement, our study shows significant increases in hospitalizations and insurance claims due to allergic colitis in Chilean infants. The factors involved in the rise of non-IgE-mediated FA have not been determined, and it is unknown if factors contributing to the increase in IgE-mediated FA might play a role in this type of allergy. In our population, socioeconomic status seems to have less influence on non-IgE-mediated FA, suggesting that different factors may contribute to its epidemiology.

Several limitations of this study must be considered, including possible miscoding and the lack of identifiable data in the databases that would allow diagnostic confirmation by medical record

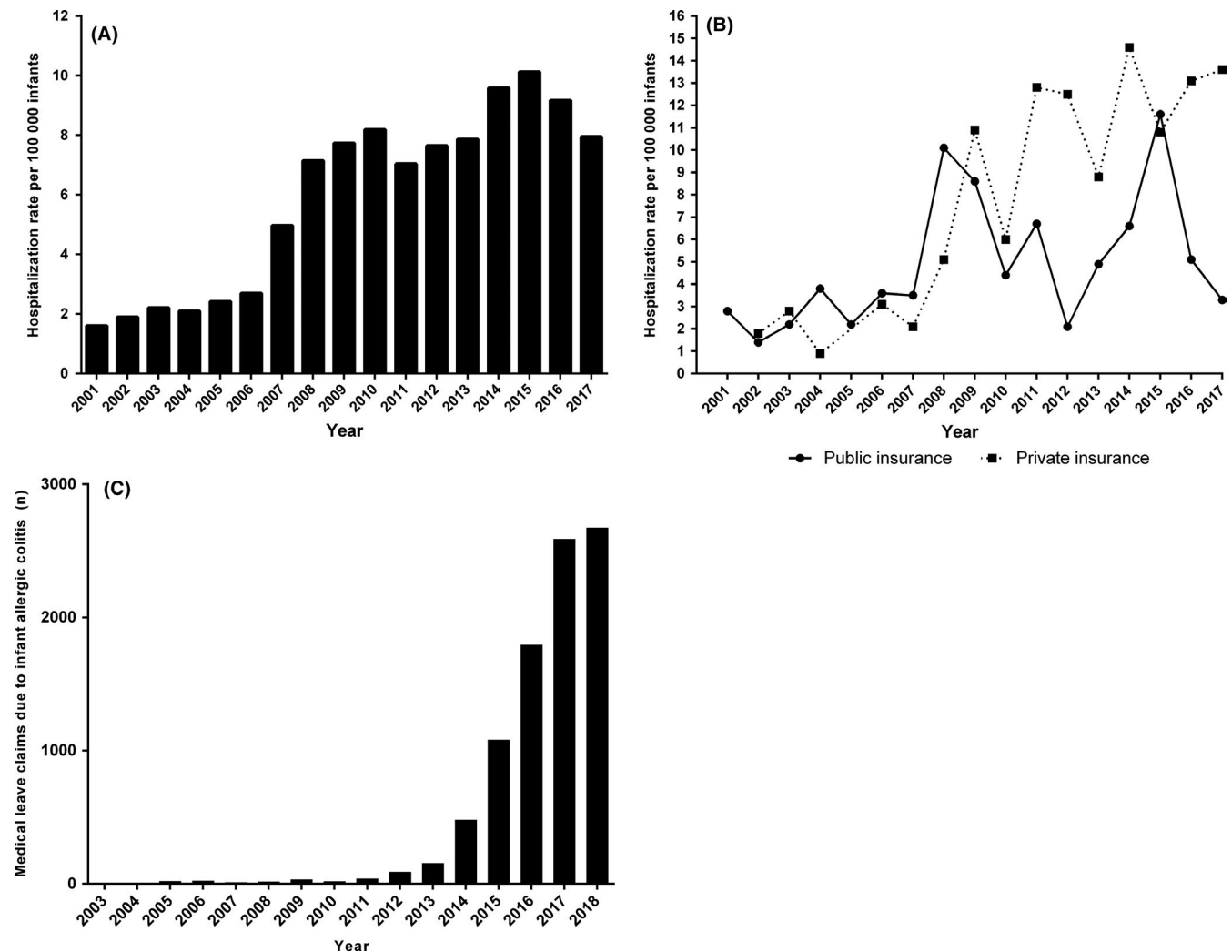


FIGURE 2 Temporal trends for allergic colitis hospitalizations in Chile. A, Total food-induced anaphylaxis hospitalization rates, 2001-2017. B, Allergic colitis hospitalization rates by insurance type, 2001-2017. C, Total number of medical leave claims per year due to allergic colitis in infants, 2003-2018

review or allergy testing. In addition, the de-identified hospitalization databases do not distinguish patients requiring multiple admissions. Previous studies have reported that recurrent anaphylaxis affecting the same patient is infrequent¹⁰ and, therefore, unlikely to explain hospitalization trends. Likewise, it is possible that children with a more severe phenotype of allergic colitis may require multiple hospitalizations; however, it is unlikely that the large increase in hospitalization rates would be explained by multiple admissions, especially considering that we limited analysis to infants.

In conclusion, the present study is the first to analyze population-based nationwide epidemiological data on temporal trends of FA, of both immediate and delayed hypersensitivity, in a developing country. Rising prevalence of FA in Chile may reflect significant changes in lifestyle in the Chilean population post-epidemiological transition due to increasing socioeconomic development and adoption of a westernized lifestyle in the country.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Methods:

We performed a retrospective review of national hospital discharge databases from the Chilean Ministry of Health to evaluate hospital admissions due to food-induced allergic reactions between January 2001 and December 2017. This database is a mandatory international classification of diseases (ICD-10) coded registry of all hospitalizations in Chile, both in the public and private healthcare system. It provides a main diagnostic code per hospitalization and a secondary code only for external causes or morbidity. The database does not provide identifiable information that would allow further chart review or allergy testing to confirm a food-induced reaction, thus, only codes indicating food-related causality were considered for analysis in this study. To identify hospital admissions due to IgE-mediated FA we used the ICD-10 code T78.0 (anaphylactic reaction due to food) in pediatric and adult populations. The code K52.2 (allergic and dietetic gastroenteritis and colitis) was used to identify non-IgE mediated FA hospitalizations. To avoid the erroneous inclusion of other diseases miscoded as non-IgE mediated FA in older age groups, analyses of K52.2-coded hospitalizations was restricted to infant population. For age group analyses, pediatric patients were defined as those younger than 18 years.

The current Chilean health system was established in the mid 1980s and options for insurance are “mixed”, consisting of 65-70% public insurance (low-middle socioeconomic status population) and 15-20% private insurance (high socioeconomic status population). Regardless of their insurance type, all workers in Chile have access to paid sick leave and all mothers of children under 1 year of age have access to paid medical leave due to a serious illness of their child. To further explore the temporal trends in food-induced allergic reactions we analyzed sick leave claims due to food-induced anaphylaxis and medical leave claims due to allergic and dietetic gastroenteritis and colitis affecting children under 1 year

of age during the 2003-2018 period. Claims databases were only available for the population with private insurance throughout the country. The insurance claims system is also coded by ICD-10, so the same codes used for hospitalizations were these analyses. No data was available for review prior to 2003.

The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines were followed in the conduct and reporting of this study.

The Ethics Committee of the School of Medicine of Pontificia Universidad Católica de Chile approved this study.

Statistical analysis

Hospitalization rates for food-induced anaphylaxis were calculated per 1,000,000 inhabitants, and hospitalization rates for allergic colitis were calculated per 100,000 infants. All rates are shown with 95% confidence intervals (95% CI). Lethality rates were calculated as deaths per 100 cases. Chi-square tests were used to compare rates. Two-way ANOVA was used to compare multiple rates. Simple linear regressions were used to evaluate temporal trends in hospitalizations due to food-induced anaphylaxis and allergic colitis, unstandardized b coefficients and 95% CI are reported for each regression. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics 21.0 (SPSS Inc, Chicago, IL, USA) and OpenEpi software version 2.3.1.

