Global associations of macronutrient supply and asthma disease burden

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To the Editor,

We read with interest the work by Shin et al. [1], investigating the global disease burden of allergic disorders. They showed that the age-standardized prevalence of asthma has decreased over time on a global level.

Following a similar theme, we curated asthma disease burden, macronutrient (protein, carbohydrate and fat) supply and gross domestic product (GDP) data around the globe (Supplementary Methods). Our analysis found that in parallel to changes in asthma disease burden, GDP per capita [2] has increased, and the global

nutritional landscape has also changed (Figure 1A-B). Both socioeconomic status and nutritional factors, are emerging critical confounders for asthma[1]. However, so far, most studies have neglected to consider their correlations and interactions, including among nutrients within diets (Figure 1C-E). They instead focused on individual parameters alone, like specific diets or foods [3]. Here, we adopted a recently published approach [2] to systematically interrogate the relationship between nutrient supply, a good proxy of food environment, socioeconomic status and asthma disease burden at a global scale over time. We focused on macronutrient supplies and their interactions, considering their important associations with many facets of health.

Various multi-response generalized additive mixed models (GAMMs) were used to analyze the effects on asthma disease burden from macronutrient supplies and GDP over time (Supplementary Methods). In all analyses, a model considering the interactions of macronutrient supply and GDP, and an additive effect of time was favoured (Supplementary Table 1, 3). This suggested combinatory effects of macronutrients on asthma and the impacts of socioeconomic changes.

The most recent year with all data available, 2018, is shown as a representative (Figure 1F-G, Supplementary Table 1-2). In brief, predicted association between asthma prevalence and macronutrient supplies were visualized using response surfaces on macronutrient supply plots. We focused on the fat (x -axis) and carbohydrate (y -axis) supplies while holding protein at 25%, 50% and 75% quantiles of global supply. Across the response surfaces, red indicated higher asthma disease burden, while blue indicated lower.

In our modelling, carbohydrate supply was most strongly associated with increases of asthma prevalence rates, while fat supply had the opposite effects (Figure 1F). This is reflected by the purple isocaloric line, along which the total energy from macronutrients remained constant but increasing fat:carbohydrate ratio decreased the allergy prevalence. Protein supply conferred less influences. Similar patterns were found for asthma incidences (Figure 1G, Supplementary Table 3-4) independent of gender (Supplementary Figure 1-2) and were not confounded by the total macronutrient energy supply, as changing total energy while holding fat:carbohydrate ratio constant (red radial in figures) minimally impacted asthma disease burden.

This represents the first study to link asthma to global food environment. Our results imply a driving role of carbohydrate supply for the asthma disease burden, after adjusting for the plausible interactions between macronutrients, total energy supply and socioeconomic status.

Interestingly, previous studies found that ketogenic diets, low in carbohydrates, might ameliorate established asthma [4], supporting our findings that ketogenic-like food environments are associated with lower asthma disease burden. Although further in-depth investigations are needed, diet quality might be an intriguing explanation for the positive association between carbohydrate supply and asthma. For example, high- and ultra-processed foods low in fibre have been found to be related to asthma development [3,5], while we have previously shown that dietary fibre exhibited a strong immune regulatory influence, protecting against asthma[6].

Hence, future studies in more depth are warranted to investigate the associations between macronutrient supply and asthma, including also other related socioeconomic and environmental factors. Such studies will be critical for guidance to future clinical research and practice and public health interventions.

Figure 1. Association of global macronutrient supply and asthma disease burden. A. Age-standardized asthma prevalence (blue) and incidence rate (red) of both sexes as functions of year. **B.**Global GDP per capita (in US dollars, black) and supplies of carbohydrate (green), protein (red) and fat (brown) as functions of year. **C-E.** Correlations among variables for global data from 1990-2018 (**C**) and for different countries in 1990 (**D**) and 2018 (**E**). Correlation coefficients are shown. **F-G.**Predicted effects of macronutrient supply on age-standardized asthma prevalence rate (**F**) and incidence rate (**G**) of both sexes (See Supplementary Information for statistics and interpretation).

Author contributions

Concept and design: Duan Ni, and Ralph Nanan

Acquisition, analysis and interpretation of data: Duan Ni, Alistair M. Senior, Ralph Nanan

Drafting of the manuscript: Duan Ni, and Ralph Nanan

Critical revision of the manuscript for important intellectual content: All authors

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Conflict of interest

Non reported.

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