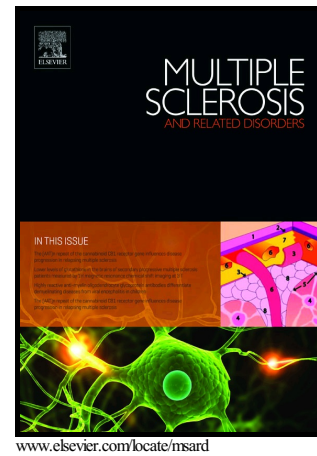


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Can falling infection rates in one country explain rising incidence of autoimmune and allergic diseases in other countries? Caution when (over) interpreting ecological data from disparate areas

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Myths are common in science.¹ Once assimilated into popular belief or medicine, they can be difficult to dispel, with consequences that may not be trivial. They have the potential to hold back some avenues of science,¹ inhibit publication of studies that refute ‘what is already known,’ and misdirect research or healthcare dollars.

Here, we refer to an interesting Article published in the NEJM, 2002², reviewing “The effect of infections on susceptibility to autoimmune and allergic diseases.” The article was intended to be hypothesis generating and has attracted over 2000 citations (Google Scholar 9-May-2017). However, specific aspects which were likely intended as interesting, thought-provoking ideas, are now commonly misrepresented as fact or common knowledge. We draw particular attention to Figure 1 of the review article which reports an “Inverse

relationship between the incidence of prototypical infectious diseases and the incidence of immune disorders” in two separate panels.² We do not intend to critique (or have issue with) other aspects of this interesting and influential review article. However, Figure 1 deserves further consideration as, even today, it regularly features as an established fact in keynote presentations at global venues by influential and well intending thought leaders based at leading research institutes (for examples, see^{3,4}). Whilst there may (or may not) be a relationship between infections and autoimmune/allergic diseases, what is presented in Figure 1 is the focus of this Viewpoint given the persuasiveness of the conclusions drawn.

The author applied ecological methodology to depict temporal changes in the incidence of different diseases and thus draw conclusions about links between them. For such comparisons to be valid there are a number of key requirements, including suitability of the data presented for the purpose of addressing the issue at hand. The two panels of Figure 1 are compared to make the hypothesised link between infections and autoimmune/allergic disease: Panel A shows decreasing “incidence” of infectious diseases, mainly in the USA; Panel B shows autoimmune and allergic diseases, all in non-USA countries. While the former are largely from population databases, the latter are based on findings from disparate single studies in different populations. Data on type 1 diabetes are from Finland,⁵ even though USA data were available over the graphed period.⁶ Further, the Finnish data relates only to children under 15 years of age, and as the original authors pointed out, the small sample size may give unreliable incidence estimates.⁵ At the same time, there was no increase in incidence of type 1 diabetes in a nearby country, Norway.⁷ The small sample size problem occurs again with the incidence estimates provided for multiple sclerosis. Here the data are from the small population in the northern part of Sardinia.⁸ The data on asthma are from

young male conscripts in Belgium – which makes them a rather different population and challenging to compare with the USA data on infectious diseases.

Other elements of Figure 1 create further challenges when drawing conclusions. The y-axes report incidence (%) of disease, with scales from 0-100 for infectious diseases, and 100 to 400 for autoimmune and allergic diseases. Although limited space may have prevented a detailed explanation, it appears likely this is not disease incidence, but the percentage change in incidence from the oldest data point. Further, for several of the cited studies incidence was not measured – the hepatitis A data are not incidence but seroprevalence;⁹ the asthma data are prevalence and it is not clear whether the plotted data are based on the prevalence of self-reported asthma or the proportion with airway hyper-responsiveness.¹⁰

Another challenge is locating the original data presented in the Figure from the cited papers. For example, the figure shows a steep increase in the incidence of multiple sclerosis (MS), beginning in 1950 – and this figure provides the baseline (comparator) incidence. However the cited study, from which the data are derived,⁸ reports findings only from 1968 onwards. A similar problem occurs with the data for hepatitis A, with Figure 1 showing “Incidence” data starting at around 1970, yet in the cited paper, data are available only from 1985.⁹ For Crohn’s disease, we are less clear which data from the cited review are used (noting that the authors listed under ‘references’ did not correspond to what we were able to find¹¹), or whether the line in Figure 1 represents some combination of data from disparate populations. Incidence of tuberculosis has been falling in the USA over the time period shown, but, as data from the World Bank¹² show, almost any incidence pattern is available, according to the country selected.

The NEJM 2002 article presents an interesting and compelling story,² including a broader discussion of plausible underlying mechanisms and immune-mediated pathways providing support for Strachan's hygiene hypothesis.¹³ Comparisons of temporal patterns in population incidence of disease are, by necessity, of an ecological design. A valid comparison, however, requires that the changes are occurring in the same populations, at the same time. Confining comparisons to incidence rather than prevalence ensures a comparison of disease patterns that are not confounded by changes in care and/or treatment. Nevertheless, Figure 1 has become pervasive, cited and presented many times as a stand-alone-graphic in isolation of the wider original article,² and the concepts depicted seemingly accepted as common knowledge. The consequences may be significant. For example, we do not know what the incidence of MS is across the USA (the last study was conducted in 1975; source: US National MS Society). We assume it is increasing, as Figure 1 depicts. We seek environmental risk factors for MS that are driving this rapid increase, too rapid to be the result of genetic factors. Yet, researchers and funding bodies may not recognize that we do not have the evidence to support a general assumption of increasing incidence of MS – avoiding applications that seek to clarify the temporal patterns, and/or supporting funding that relies on the underlying assumption. We do not seek to review the worldwide evidence on MS incidence here – suffice to say that it appears to be increasing in some locations, and stable or even decreasing in others.¹⁴⁻¹⁸

We need the best possible evidence to drive our understanding of disease risk factors. We encourage the scientific community to challenge assumptions based on apparent evidence, critically evaluating the underlying data. It is easy to be misled, and to travel down fruitless pathways that take time and funds, trying to solve the origins of temporal and geographic patterns that may or may not exist.

Authorship / contributorship statement:

We all contributed to the writing of this article. HT and RL developed the original concept for this opinion piece. HT, RR and RL all contributed to the writing of this article. HT wrote the first draft with significant inputs from RR and RL.

Data sharing statement and Ethics:

not applicable; no additional data are available; ethical approval was not sought.

Disclosures:

The authors report no disclosures that are of direct relevance.

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Figure Source: from 'Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002; 347: 911-20'. ****Permission currently being sought to reprint****

References

1. Scudellari M. The science myths that will not die. *Nature* 2015;528:322-5.
2. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347:911-20.
3. Huttenhower C. Structure and Function of the Human Microbiome. In: Harvard University, Institute B, eds.: LabRoots (<http://labroots.com/webcast/id/565>); 2015.
4. Knight R. Breaking the Wall to Our Microbial Self. Falling Walls Conference Berlin, Germany. (<https://www.youtube.com/watch?v=R-QaEnO1bcY>).2016.
5. Tuomilehto J, Karvonen M, Pitkaniemi J, et al. Record-high incidence of Type I (insulin-dependent) diabetes mellitus in Finnish children. The Finnish Childhood Type I Diabetes Registry Group. *Diabetologia* 1999;42:655-60.
6. Krolewski A, Warram J, Rand L, Kahn R. Epidemiologic approach to the etiology of type 1 diabetes mellitus and its complications. *New England Journal of Medicine* 1987;317:1390-8.
7. Gale EA. The rise of childhood type 1 diabetes in the 20th century. *Diabetes* 2002;51:3353-61.
8. Pugliatti M, Sotgiu S, Solinas G, et al. Multiple sclerosis epidemiology in Sardinia: evidence for a true increasing risk. *Acta Neurol Scand* 2001;103:20-6.
9. Joussemet M, Depaquit J, Nicand E, et al. [Fall in the seroprevalence of hepatitis A in French youth]. *Gastroenterol Clin Biol* 1999;23:447-5.
10. Dubois P, Degraeve E, Vandenplas O. Asthma and airway hyperresponsiveness among Belgian conscripts, 1978-91. *Thorax* 1998;53:101-5.
11. Farrokhyar F, Swarbrick ET, Irvine EJ. A critical review of epidemiological studies in inflammatory bowel disease. *Scand J Gastroenterol* 2001;36:2-15.
12. World Bank. Incidence of tuberculosis. 2017. <http://data.worldbank.org/indicator/SH.TBS.INCD?locations=US-AU> (accessed 14 Jun 2017)

13. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259-60.
14. Kingwell E, Zhu F, Marrie RA, et al. High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (1991-2010). *J Neurol*. 2015; 262: 2352-63.
15. Marrie RA, Yu N, Blanchard J, Leung S and Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. *Neurology*. 2010; 74: 465-71.
16. Marrie RA, Fisk JD, Stadnyk KJ, et al. The incidence and prevalence of multiple sclerosis in Nova Scotia, Canada. *Can J Neurol Sci*. 2013; 40: 824-31.
17. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM and O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. *J Neurol Neurosurg Psychiatry*. 2014; 85: 76-84
18. Ribbons K, Lea R, Tiedeman C, Mackenzie L and Lechner-Scott J. Ongoing increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: A 50-year study. *Mult Scler*. 2016: 1352458516671819.

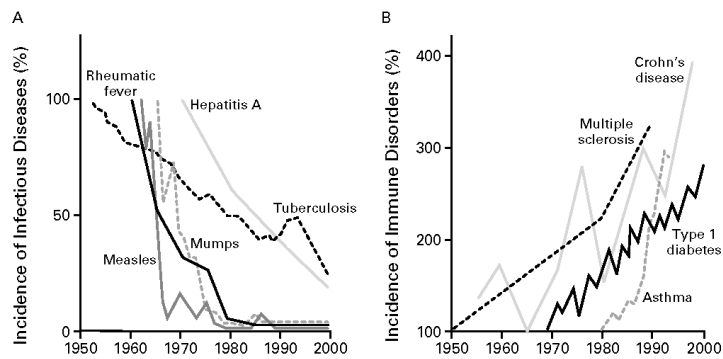


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

Source: from 'Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med.* 2002; 347: 911-20'. ****Permission currently being sought to reprint****