

Is affluence a risk factor for bronchial asthma and type 1 diabetes?

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In the last decades, an increase in bronchial asthma and type 1 diabetes occurrence has been observed in affluent countries, and a positive association between the two disorders has been demonstrated at the population level. This association could be explained by common risk factors predisposing to both disorders. Altered environmental and lifestyle conditions, possibly related to socio-economic status, might account for the rising trend of the two disorders. To test this hypothesis, we calculated the correlation between the occurrence of type 1 diabetes and asthma, the gross national product (GNP) and the infant mortality rate, in several European and extra-European countries. GNP was positively correlated with the incidence of type 1 diabetes and with symptoms of asthma in European (r_{sp} : 0.53 and 0.69; $p = 0.001$ and $p < 0.0001$, respectively) and extra-European countries (r_{sp} : 0.44 and 0.46; $p = 0.04$ for both diseases). Infant mortality rate was inversely correlated with GNP and with the occurrences of the two diseases in Europe (r_{sp} : -0.66, $p < 0.0001$ for type 1 diabetes; r_{sp} : -0.51, $p = 0.01$ for asthma). In extra-European countries, a significant relationship was found between infant mortality and asthma (r_{sp} : -0.46; $p = 0.03$); a trend towards a negative correlation between infant mortality and type 1 diabetes was also found, although no statistical significance was reached (r_{sp} : -0.21; $p = 0.31$). This analysis indicates that type 1 diabetes and asthma are positively associated with the GNP at the population level. Similarly, countries with low infant mortality rates tend to have a higher incidence of these immune-mediated diseases. Although GNP reflects many societal and lifestyle differences, it is notable that a high socio-economic status implies a reduced or delayed exposure to infectious agents. The reduced pressure of infectious agents on the immune system throughout life might contribute to increase the susceptibility to bronchial asthma and type 1 diabetes.

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The hygiene hypothesis has been proposed to explain the rising trend of Th2-mediated diseases, such as asthma and allergies, in industrialized and affluent countries (1). According to this theory, changes in the exposure to infectious diseases and microbial products might be associated with the increased prevalence of allergic diseases observed in recent decades. It has been suggested that a limited exposure to bacterial and viral pathogens during early childhood results in an insufficient stimulation of T lymphocyte-1

(Th1)-cells, which in turn cannot counterbalance the expansion of Th2-cells and predisposes to allergy (2).

The increase in asthma and allergies in industrialized countries has been paralleled by an increase in the incidence of type 1 diabetes, a Th1-mediated autoimmune disease (3, 4). Moreover, there is a positive correlation between prevalence of asthma symptoms and incidence of type 1 diabetes at the population level (5). The association between occurrence of asthma and

type 1 diabetes at the population level could be explained by the presence of common risk factors predisposing to Th2- and Th1-mediated diseases (6).

To explore the hypothesis that the occurrence of asthma and type 1 diabetes is related inversely to the infectious burden of the population, we used basic indicators relating to the world health situation, such as the gross national product per capita (GNP) and infant mortality rate. Therefore, we calculated the correlation between the occurrence of these immunologic diseases and the economic status in several European and extra-European countries.

Materials and methods

Data on worldwide asthma prevalence were obtained from the International Study of Asthma and Allergies in Childhood (ISAAC), an epidemiological survey among children aged 13–14 yr conducted in 1994 and 1995, using written and video questionnaires about asthma symptoms (7). There is a close correlation between the ISAAC asthma prevalence data for teenagers (13- to 14-yr age group) and young children (6- to 7-yr age group). In the countries that studied both age groups in the ISAAC programme, the mean prevalence rate of current wheezing in the 6- to 7-yr age group was 105% of that recorded in the 13- to 14-yr age group.

The patterns in type 1 diabetes incidence among children aged 0–15 yr were derived from childhood diabetes registers obtained in Europe from 1989 to 1994 and outside Europe from 1990 to 1994 (3, 4). Age-standardized incidence rates were obtained by the direct method with a standard population consisting of equal numbers of children in each of the three subgroups defined by age group (0–4, 5–9, and 10–14 yr).

Data for asthma prevalence were available for 23 countries in Europe and 21 countries outside Europe. Data for type 1 diabetes incidence were available for 31 countries in Europe and 24 countries outside Europe.

The GNP per capita, expressed in US Dollars (USD), and data on infant mortality rate were available from The World Health Report 1995 by the World Health Organization (available at <http://www.who.int/entity/whr/en/>). The World Health Report 1995 presents an overview of the global health situation based on an assessment carried out in 1994 using 1993 data. The content of the report was determined essentially by the availability of information concerning key health and health-related indicators.

The Spearman correlation coefficients (r_{sp}) between the occurrences of the two diseases, the GNP and the infant mortality rates were calculated to measure the strength of association between pairs of variables, without specifying which variable is dependent or independent; a significant relationship between the variables was considered for pairs with p values below 0.05.

Results

Both European and extra-European countries showed a positive correlation between the occurrence of type 1 diabetes and asthma symptoms (r_{sp} : 0.53 and 0.54; $p = 0.01$).

GNP was positively correlated with the incidence of type 1 diabetes and with symptoms of asthma in European (r_{sp} : 0.53 and 0.69; $p = 0.001$ and $p < 0.0001$, respectively; Fig. 1) and extra-European countries (r_{sp} : 0.44 and 0.46; $p = 0.04$ for both diseases).

Infant mortality rate was inversely correlated with GNP (r_{sp} : -0.87 ; $p < 0.0001$) and with the occurrences of the two diseases in Europe (r_{sp} : -0.66 , $p < 0.0001$ for type 1 diabetes; r_{sp} : -0.51 , $p = 0.01$ for asthma; Fig. 2). In extra-European countries, a significant relationship was found between infant mortality and GNP (r_{sp} : -0.88 ; $p < 0.0001$). Infant mortality was inversely correlated with the occurrence of asthma (r_{sp} : -0.46 ; $p = 0.03$); a trend towards a negative correlation between infant mortality and type 1 diabetes was also found, although no statistical significance was reached (r_{sp} : -0.21 ; $p = 0.31$).

Discussion

Our analysis indicates that type 1 diabetes and asthma symptoms are positively associated with the GNP at the population level in both European and extra-European countries, confirming previous findings from EURODIAB and ISAAC Studies (8, 9). In agreement with this observation, countries with low infant mortality rates tend to have a higher incidence of these immune-mediated diseases. Moreover, a positive association between the occurrence of the two diseases at the population level was confirmed, evaluating the prevalence of asthma and the incidence of type 1 diabetes in both European and extra-European children.

In 2001 the EURODIAB collaborative group, using prospective, geographically defined registers of children with type 1 diabetes diagnosed under 15 yr of age, analysed the relationship between the disease incidence and several health and economic indicators. The results showed that

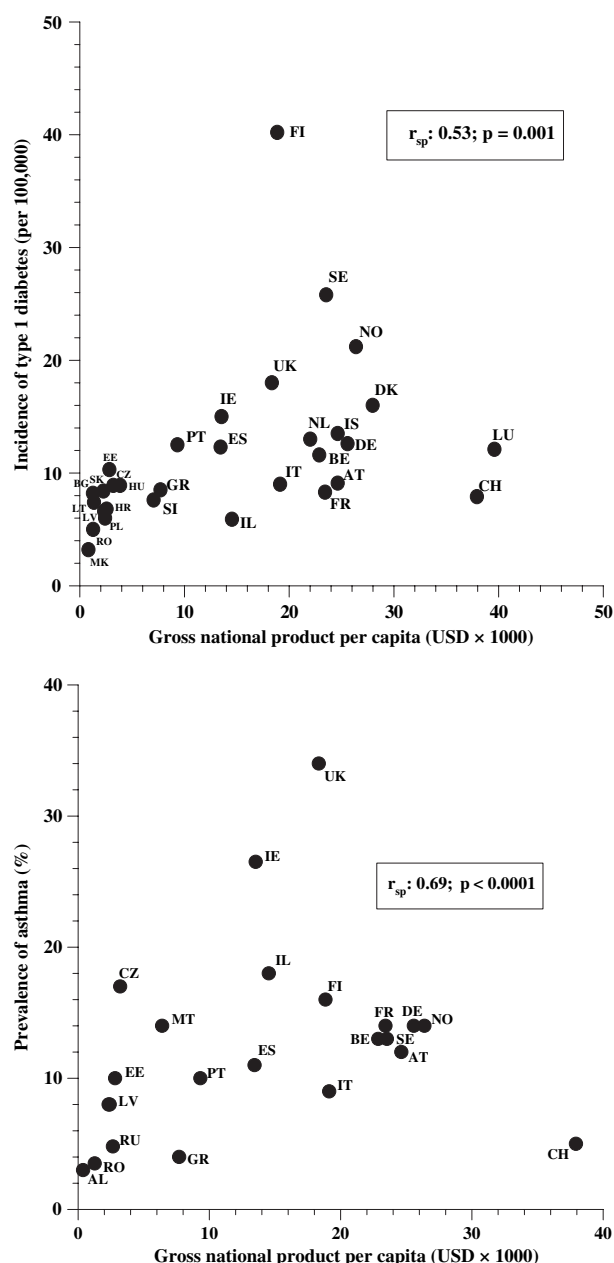


Fig. 1. Gross national product (GNP) was positively correlated with the incidence of type 1 diabetes and with symptoms of asthma in European countries. AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IL, Israel; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MK, Macedonia; MT, Malta; NL, Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RU, Russian Federation; SE, Sweden; SK, Slovak Republic; SI, Slovenia; UK, United Kingdom.

indicators of national prosperity, such as infant mortality and gross domestic product, were significantly correlated with diabetes incidence rate and suggested that the wide variation in type

1 diabetes incidence rates within Europe could reflect differences in environmental risk factors (3). Except some areas where genetic factors have a main role, such as Madeira and Sardinia, analysis of type 1 diabetes incidence suggests a possible link with socio-economic status, leading to the hypothesis that it is a wealth-related disease (8).

Our analysis shows similar data for the occurrence of asthma, in agreement with previous studies related to risk factors for atopy among children. Low socio-economic level and overcrowding are independently protective against atopy among schoolchildren (1). Allergic disorders are typical of wealthy and westernized societies, although the risk of asthma symptoms is not exclusively linked to affluence. Stewart et al. analysed data from the ISAAC study and found a statistically significant positive association between wheezing in the last 12 months and GNP per capita in the 13–14-yr age group, but not in the 6–7-yr age group (9). According to the authors, the positive associations between GNP per capita and asthma symptoms was of only moderate strength, suggesting that the environmental factors are not just related to the wealth of the country.

Our findings confirm that two important health-related indicators, such as GNP and infant mortality rate, are common factors to consider in the epidemiological risk evaluation for immune-mediated diseases. The hygiene hypothesis, proposed at first to explain the rising trend of atopy, suggests that a limited exposure to bacterial and viral pathogens during early childhood results in insufficient stimulation of Th1-cells and consequent expansion of Th2-cells, which predisposes to allergy (1, 2). However, the increase in asthma and allergies has been paralleled by an increase in the incidence of type 1 diabetes, a Th1-mediated disease. It seems indeed that common underlying factors predispose to the increase in Th2- and Th1-mediated diseases. A likely explanation, rather than the Th1/Th2 balance, is that repeated early contacts with infectious agents can induce regulatory T cells that control T cell-mediated responses against common allergens or self-antigens. According to Kemp and Björkstén (10), the available epidemiological evidence does not provide support for a mechanism of early life immune deviation and the main environmental influences on the development of atopic disease are likely to occur throughout life. The need for a continuous pressure on the immune system in order to avoid the development of allergic and autoimmune disorders is supported by the epidemiological

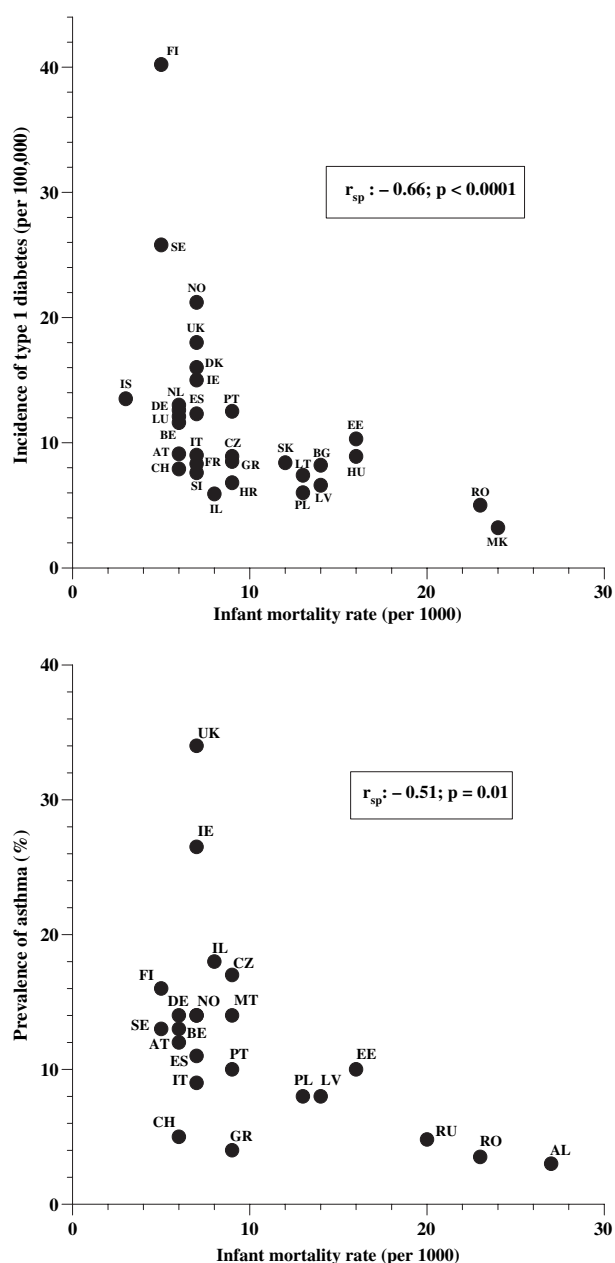


Fig. 2. Infant mortality rate was inversely correlated with gross national product (GNP) and with the occurrences of the two diseases in Europe. AL, Albania; AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IL, Israel; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MK, Macedonia; MT, Malta; NL, Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; RU, Russian Federation; SE, Sweden; SK, Slovak Republic; SI, Slovenia; UK, United Kingdom.

observations on migrants from developing countries to industrialized and affluent societies. In fact, an increase in asthma and type 1 diabetes occurrence has been observed in populations

migrating from areas of low disease incidence to countries with higher incidence (11, 12).

An alternative explanation is that affluent societies have the resources to save the children with bronchial asthma and type 1 diabetes and therefore, the observed increase in the occurrence of these two disorders might be simply the consequence of better sanitation. However, we believe that this explanation is unlikely because several epidemiological surveys carried out in affluent countries have shown that the increase in the occurrence in bronchial asthma and type 1 diabetes in the last decades has been real and not due to more accurate diagnosis and better cure with increased survival.

Although GNP is a surrogate marker for many societal and lifestyle differences, such as diet, pollutant exposure and housing conditions, it is notable that a high socio-economic status implies a reduced or delayed exposure to infectious agents. The reduced pressure of infectious agents on the immune system throughout life might lead to an impaired generation of regulatory T cells increasing the susceptibility to immune-mediated disorders.

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