Childhood Atopic Diseases and Early Life Circumstances: An Ecological Study in Cuba

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Abstract

Background: Children are especially vulnerable during periods of resource shortage such as economic embargoes. They are likely to suffer most from poor nutrition, infectious diseases, and other ensuing short-term threats. Moreover, early life circumstances can have important consequences for long-term health. We examined the relationship between early childhood exposure to the Cuban economic situation in the nineties and the occurrence of atopic diseases later in childhood.

Methodology/Principal Findings: A cross-sectional study of 1321 primary schoolchildren aged 4–14 was conducted in two Cuban municipalities. Asthma, allergic rhinoconjunctivitis and atopic dermatitis were diagnosed using the International Study of Asthma and Allergies in Childhood questionnaire. Children were divided into three groups of exposure to the economic situation in the nineties according to birth date: (1) unexposed; (2) exposed during infancy; (3) exposed during infancy and early childhood. Associations were assessed using multiple logistic regression models. Exposure during infancy had a significant inverse association with the occurrence of asthma (OR 0.56, 95% CI 0.33–0.94) and allergic rhinoconjunctivitis (OR 0.46, 95% CI 0.25–0.85). The associations were stronger after longer exposure, i.e., during infancy and early childhood, for asthma (OR 0.40, 95% CI 0.17–0.95) and allergic rhinoconjunctivitis (OR 0.29, 95% CI 0.11–0.77). No significant associations were found for atopic dermatitis.

Conclusions/Significance: Exposure to the economic situation in the nineties during infancy and early childhood was inversely associated with asthma and allergic rhinoconjunctivitis occurrence later in childhood. We hypothesize that factors related to this period, such as infectious diseases and undernutrition, may have an attenuating effect on atopic disease development. The exact cause and underlying mechanisms need to be further elucidated.

Introduction

Economic crises can have a negative impact on health [1,2]. In Cuba, a period of great economic challenges, known as the “Special Period”, affected the country in the early 1990s. The United States instituted an economic blockade against the island in 1961. This embargo, along with the collapse of the Soviet Union and the Eastern European socialist block in the late 1980s, reduced Cuban foreign trade by 80%. Multiple economic constraints evolved which further deteriorated when the U.S. intensified their sanctions in the early 1990s. The situation improved during 1995–1996 and especially from 1996 on, but complete economic recovery was not reached until after 2000 [3–6].

The economic problems affected the health of the Cuban population in various ways, due to a sudden shortage of essential products such as food, energy, drugs and medical equipment [3–5]. Approximately half of the food needed to meet caloric and protein needs was imported. Therefore, the decline in food imports combined with an already low food production within Cuba resulted in a 40% reduction in the availability of nutritional energy per capita [3–6]. Furthermore, diet quality, composition and patterns were affected [5]. Vitamin deficiencies led to an increase of anaemia in pregnant women and infants and an epidemic of optic neuropathy predominantly among males [3,7,8]. The incidence of tuberculosis increased as did the mortality rates from infectious and parasitic disorders, and influenza and pneumonia [3]. Although the economic crisis in Cuba was severe, the harmful effects on general public health were reduced to a minimum due to appropriate economic and social measures taken by the government to counter the crisis [9]. For example, vulnerable groups like children, women, and the elderly were prioritized for protection against nutritional deficiencies [3].

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Children under the age of five are especially vulnerable during economic embargoes. They are likely to suffer most from poor nutrition, increased infectious disease risk, and other ensuing short-term threats [2,10]. Moreover, early life circumstances may have serious consequences for long-term health, such as cardiovascular and other chronic diseases [11,12]. Previous research on the health impact of economic crises mostly focused on morbidity, mortality, impact on health care, and nutritional status during and shortly after a crisis [13–16]. Longer term consequences, like altered chronic disease occurrence, have been studied less and mostly in adults [11].

In this ecological study, we examined the relationship between early childhood exposure to the Cuban economic situation in the nineties and the occurrence of atopic diseases later in childhood. Possible contributing factors and underlying mechanisms for this association will be discussed.

**Methods**

**Study Design**

A cross-sectional study was conducted in 1321 primary schoolchildren of two municipalities in Cuba: San Juan y Martínez (SJM) in Pinar del Rio (December 2003), a province in the west of Cuba, and Fomento in Sancti Spiritus (May 2004), a province in the centre of Cuba. Rural and urban primary schools were randomly selected from SJM (N = 5) and Fomento (N = 14). All children were included in the study, i.e. 398 children from SJM and 923 children from Fomento. Data on atopic diseases, other relevant health and environmental factors, and demographic characteristics were collected. Further details have been described elsewhere [17,18].

**Ethics Statement**

Informed written consent was obtained from the parents or guardians of each participating child. This study is part of a larger investigation on atopic diseases and helminth infections in Cuban children, for which approval was obtained from the Ethical Committees of the Prince Leopold Institute of Tropical Medicine in Antwerp, Belgium, the Pedro Kouri Institute (IPK) of Tropical Medicine and the National Institute for Hygiene, Epidemiology and Microbiology (INHEM) in Havana, Cuba.

**Atopic Diseases**

Atopic disease occurrence, i.e. asthma, allergic rhinoconjunctivitis and atopic dermatitis, was determined by means of the standard Spanish version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [19], whereby a parent or guardian of each child was interviewed by a trained local team member. ISAAC definitions of atopic diseases were used in this study: current asthma, shortened to ‘asthma’ throughout the text, was defined as an affirmative answer to the second ISAAC core asthma question on current wheeze [20]; allergic rhinoconjunctivitis was defined as an affirmative answer to the second and third core questions of the ISAAC modules on rhinitis [21]; and atopic dermatitis was defined as an affirmative answer to the second and third core questions of the ISAAC modules on eczema [22].

**Exposure to Economic Situation**

Exposure to the Cuban economic situation in the nineties was determined using the child’s date of birth. None of the children in our study group were born before 1990. The gross domestic product (GDP) dropped dramatically starting in 1990 [4]. As the situation improved during 1995–1996 [5,6], the exposure period was set from January 1st 1990 until January 1st, 1996. Children were divided into three groups: (1) exposed during infancy (<24 months) and early childhood (2–6 year), i.e. born before January 1st, 1994; (2) exposed only during infancy, i.e. born from January 1st, 1994 till January 1st, 1996; and (3) unexposed, i.e. born from January 1st, 1996 and later.

**Covariates**

Demographic variables considered were sex, age (in years), municipality (SJM vs. Fomento) and area of residence (rural vs. urban). Socio-economic variables were monthly household income (250 pesos (~ 7 euro/month or less vs. more than 250 pesos/month) and education level of the parents (less grade 12 vs. grade 12 or higher). Perinatal variables considered were low birth weight (LBW), i.e. a birth weight less than 2500 gram (yes or no), and premature birth, i.e. a gestational age of less than 37 weeks (yes or no). The variables included regarding the first year of life were breastfeeding for more than six months (yes or no) and antibiotics use (yes or no). All these variables were collected by means of a structured parental questionnaire.

**Statistical Analysis**

Statistical analyses were conducted using SPSS (SPSS Inc., Chicago, IL, USA) version 17.0 for Windows. A P-value of 0.05 or less was regarded as statistically significant. Characteristics of the study population are given as numbers and percentages, except age which is given as median and its interquartile range (IQR). Differences in the covariates between the three exposure groups were tested using the Chi-square test, except age for which the Kruskal-Wallis test was used. Univariate logistic regression models were performed to assess crude associations between exposure to the economic situation in the nineties and atopic disease outcomes with the unexposed group as the reference. Subsequently, the covariates were entered using a stepwise forward approach to examine possible confounding or effect modification. Only relevant confounders, i.e. which satisfied a change-in-estimate criterion of ≥10% [23], and significant effect modifiers were included in the final multiple logistic regression model.

To test the robustness of the results, sensitivity analyses were performed: the two cut-off dates that distinguished the three groups were shifted forward for three and six months, and the ‘transition groups’ with a range of six months before and after both cut-off dates were removed, and associations were re-assessed.

**Results**

All 1321 children were included in the analysis. The participating children were aged 4 till 14 (median 8 years) and consisted of 678 boys (51%) and 643 girls (49%). The response rate to the questionnaires was 100%. Characteristics of the study population according to their exposure to the economic situation in the nineties are shown in Table 1. The three groups significantly differed from each other on age, municipality, and education level of the mother.

Based on the parental ISAAC questionnaire 279 of the 1321 children (21.1%) were diagnosed with asthma, 180 (13.6%) with allergic rhinoconjunctivitis, and 110 (8.3%) with atopic dermatitis. The percentages of positives for the different atopic diseases according to exposure status (Figure 1) show that (longer) exposure to the economic situation in the nineties corresponds with decreased atopic disease occurrence.

Table 2 shows the crude and adjusted ORs of the two groups exposed to the economic situation in the nineties for the different
atopic diseases compared to the unexposed group. The adjusted ORs confirmed the observations of Figure 1, with significant associations between exposure and asthma and allergic rhinoconjunctivitis. These associations tended to be stronger for longer exposure, i.e. during both infancy and early childhood. However, the differences between the two exposure groups were not significant. No significant association was found between exposure and atopic dermatitis.

The sensitivity analysis by shifting forward the cut-off dates confirmed the general trend found for asthma and allergic rhinoconjunctivitis (Table S1). As expected, removing the transition groups slightly strengthened most associations (Table S2). Only for atopic dermatitis the results were altered after sensitivity analysis, confirming the instability of the original results for atopic dermatitis due to the small group sizes (Table S1 and S2).

Table 1. Characteristics of study population according to exposure to the Cuban economic situation in the nineties.

|                             | Unexposed | Exposed during infancy | Exposed during infancy and early childhood | N  | P-value* |
|-----------------------------|-----------|------------------------|--------------------------------------------|----|----------|
| Number of children          | 541       | 400                    | 380                                        | 1321|          |
| Sex (male)                  | 265 (49.0%)| 202 (50.5%)            | 211 (55.5%)                                | 1321| 0.14     |
| Age (years)                 | 6 (1)     | 9 (1)                  | 11 (1)                                     | 1321| <0.001   |
| Municipality (Fomento)      | 375 (69.3%)| 259 (64.8%)            | 289 (76.1%)                                | 1321| 0.003    |
| Area of residence (urban)   | 280 (51.8%)| 210 (52.5%)            | 200 (52.6%)                                | 1321| 0.96     |
| Family income (>250 peso/month) | 249 (46.2%)| 182 (45.8%)            | 162 (43.1%)                                | 1312| 0.62     |
| Education level father (>12 grades) | 239 (44.8%)| 181 (46.5%)            | 159 (42.4%)                                | 1297| 0.51     |
| Education level mother (>12 grades) | 261 (48.6%)| 204 (51.1%)            | 151 (39.9%)                                | 1314| 0.004    |
| LBW (<2500 g)               | 51 (9.5%)  | 51 (13.0%)             | 31 (8.3%)                                  | 1304| 0.07     |
| Premature birth (<37 weeks) | 37 (6.8%)  | 29 (7.3%)              | 23 (6.1%)                                  | 1321| 0.80     |
| Breastfeeding (>6 months)   | 284 (52.7%)| 198 (49.7%)            | 181 (47.9%)                                | 1315| 0.34     |

Data are given as numbers and percentage, except age which is given as median (IQR).
Statistically significant differences are given in bold and borderline significant differences in italic.
*Chi-square test for difference between the three exposure groups, expect for age which was done by Kruskal-Wallis test.
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Figure 1. Atopic diseases according to exposure status to the Cuban economic situation in the nineties. (asthma resp. 28.5%, 18.8% and 13.2%; allergic rhinoconjunctivitis resp. 16.6%, 12.3% and 10.8%; atopic dermatitis resp. 9.8%, 8.5% and 6.1%).
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Discussion

So far most studies on the impact of economic crises on health have focused on immediate health consequences during or shortly after the crisis [4,5,13–16]. Longer term health consequences like chronic diseases have been investigated to a lesser extent. Here, we studied the effects of the Cuban economic situation in the nineties on the occurrence of atopic diseases in Cuban children 10 years later. We observed that exposure to the economic circumstances during infancy and early childhood had an attenuating effect on atopic disease development later in childhood.

A few limitations of this study should be noted. Firstly, all ecological studies are potentially prone to the so-called ‘ecological fallacy’, and our study findings should thus be interpreted cautiously. Although we checked for potential confounders, we cannot exclude that unknown or unmeasured contemporary factors not related to the economic situation may have influenced the study results. Our atopic disease data are based on the ISAAC questionnaire, which has become the standard diagnostic method in childhood epidemiology of atopic diseases worldwide [19]. Nevertheless, questionnaires have important inherent limitations, such as information and recall bias, which should be kept in mind when interpreting the data. Also, an independent trend of increasing atopic diseases prevalence over time, like in the Western world, cannot be ruled out [24]. Moreover, we used GDP to define the period of exposure, as this seems to be the most objective and well-documented proxy for exposure to the Cuban economic situation in the nineties. However, we do realize that GDP is an indirect measure of exposure. Thus, the possibility remains that our conclusions are based on an inaccurate assumption of how GDP translates into exposure to the economic circumstances. Also, we did not take severity of the economic situation into account, e.g. the first years of the exposure period may have been less severe than the following years, resulting in differences in impacts on health in infancy and childhood. However, such data are scarce, and usually report on one aspect, such as per capita calorie consumption or low birth weight prevalence [3,3], so we could not to take this aspect into account.

Although we corrected for age, we are aware that this cannot completely adjust for age-related trends in the prevalence of atopic diseases. However, the adjusted effects we found show that older children are less likely to have asthma and allergic rhinoconjunctivitis and more likely to have atopic dermatitis. Therefore, these effects are different or even opposite of the normal age trends, suggesting that the effect of the economic circumstances is genuine. Finally, since it is difficult to determine an exact end point for the exposure period, the chosen cut-off date (January 1st, 1996) is somewhat arbitrary and therefore possible misclassification cannot be ruled out. Nevertheless, we believe that our results are robust, as demonstrated by the sensitivity analyses, and do indicate an inverse association between atopic diseases in today’s Cuban schoolchildren and exposure to the economic circumstances in the nineties.

The associations found suggest an attenuating effect of factors related to the economic situation on atopic disease development. Below we speculate on potential factors and mechanisms underlying the observed associations.

During Cuba’s Special Period there were two important health trends. One was a small and temporary rising in mortality rates from infectious and parasitic disorders and increased incidence of tuberculosis [3,25]. Even though we do not have exact data on other infectious disease incidences, it is very likely that these were elevated as well, since infectious pathogens normally thrive during natural disasters, civil unrest or economic upheaval [26–28]. The relationship between infection and atopic diseases has been subject of many studies and originates from the so-called hygiene hypothesis which could explain our results. According to this hypothesis, early childhood infections can down-regulate inflammatory immune responses, thereby suppressing allergic disorders [29]. The rise in infectious disease rates during the 1990s may thus as such have had an attenuating effect on the development of atopic diseases as observed in our study.

The other major health trend during Cuba’s special period was the declining nutritional status of the population with caloric restrictions, marginal vitamin deficiencies in children and high

| Table 2. Crude and adjusted odds ratio’s (OR) with 95% confidence intervals (CI) of exposure to the Cuban economic situation in the nineties for the different atopic diseases. |
|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | Crude OR (95% CI) | P-value | Adjusted OR (95% CI) | P-value |
|--------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Asthma** | | | | | |
| Unexposed | 1.0 | | | | |
| Exposed during infancy | 0.58 (0.42–0.79) | 0.001 | 0.56 (0.33–0.94) | 0.03 |
| Exposed during infancy and early childhood | 0.38 (0.27–0.54) | <0.001 | 0.40 (0.17–0.95) | 0.04 |
| **Allergic rhinoconjunctivitis** | | | | | |
| Unexposed | 1.0 | | | | |
| Exposed during infancy | 0.70 (0.48–1.02) | 0.06 | 0.46 (0.25–0.85) | 0.01 |
| Exposed during infancy and early childhood | 0.61 (0.41–0.90) | 0.01 | 0.29 (0.11–0.77) | 0.01 |
| **Atopic dermatitis** | | | | | |
| Unexposed | 1.0 | | | | |
| Exposed during infancy | 0.86 (0.55–1.35) | 0.51 | 1.58 (0.72–3.44) | 0.25 |
| Exposed during infancy and early childhood | 0.59 (0.36–0.99) | 0.04 | 1.86 (0.52–6.65) | 0.34 |

Statistically significant associations are given in bold and borderline significant associations in italic.

*Adjusted for age & municipality.

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anemia rates in infants and pregnant women [3,5]. Several studies have been carried out and different hypotheses have been put forward on the relationship between nutritional status and atopic diseases. According to the Barker hypothesis, undernutrition in early-life, by altering the body’s metabolism, is positively associated with (risk factors for) chronic diseases in adulthood in general [10,30,31] and with asthma specifically by impairing lung development [32,33]. Furthermore, several dietary hypotheses postulate that diet changes, e.g. reduced antioxidant intake, increases the risk for asthma and other atopic diseases, but the available evidence is inconclusive [34,35]. Neither of these hypotheses are in line with our study results, possibly due to differences in study groups, i.e. schoolchildren from a resource poor country versus adults and populations from resource rich countries, respectively. A number of studies have been devoted to the relationship between obesity and the occurrence of asthma, although the underlying mechanisms are still unresolved [36,37]. In Cuba suggesting that obesity increases the risk of asthma, although the relationship between obesity and the occurrence of asthma, geographical distribution, with the same individuals often experiencing both disease states simultaneously [39]. Their co-existence has been explained by two causal pathways: infection leads to undernutrition and alternatively undernutrition increases susceptibility to infection [39,40], with a strong involvement of the immune system [38,40], which in turn underlies atopic disease pathology [41,42]. The observed inverse relationship between atopic diseases and exposure to the economic situation in the nineties of our study group may thus well be the result of some immuno-regulated effect of a synergistic interplay between infection and undernutrition on the development of atopic disease.

To our knowledge no studies have been carried out so far about the effect of concurrent undernutrition and infection on atopic disease.

Within the limitations of an ecological analysis, our findings indicate an inverse relationship between exposure to the Cuban economic situation in the nineties during infancy and early childhood and asthma and allergic rhinoconjunctivitis occurrence later in childhood. These results suggest that factors related to this period may have an attenuating effect on atopic disease development. We hypothesized that increased levels of infectious disease incidence and undernutrition during this special period may have been influential factors, either separately or concurrently. However, the exact cause and underlying mechanisms for the observed relationship need to be further elucidated.

Supporting Information

Table S1 Adjusted odds ratio’s (OR) with 95% confidence intervals (CI) of exposure to the Cuban economic situation in the nineties for the different atopic diseases if cut-off date is shifted three or six months forward. (DOC)

Table S2 Adjusted odds ratio’s (OR) with 95% confidence intervals (CI) of exposure to the Cuban economic situation in the nineties for the different atopic diseases if transition groups around the cut-off dates are removed. (DOC)

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Author Contributions

Conceived and designed the experiments: KP MBG PS SDW. Performed the experiments: SDW RJD. Analyzed the data: SDW JWRT. Wrote the paper: SDW MCP MBG PS. Interpreted the data: SDW JWRT MCP PS. Drafted the manuscript: SDW. Critical revision of the manuscript: SDW KP MCP JWRT RJD MBG PS. Approved the final version of the published manuscript:SDW KP MCP JWRT RJD MBG PS.

References

1. Abel-Smith B (1996) The world economic crisis. Part 1: Repercussions on health. Health Policy Plan 1: 202–213.
2. Garfield R, Devin J, Fauey J (1995) The health impact of economic sanctions. Bull NY Acad Med 72: 454–469.
3. Garfield R, Santana S (1997) The impact of the economic crisis and the US embargo on health in Cuba. Am J Public Health 87: 15–20.
4. Nayeri K, Lopez-Pardo CM (2005) Economic crisis and access to care: Cuba’s health care system since the collapse of the Soviet Union. Int J Health Serv 35: 797–816.
5. Rodriguez-Ojea A, Jiménez S, Berdasco A, Esquivel M (2002) The nutrition transition in Cuba in the nineties: an overview. Public Health Nutr 5: 129–133.
6. Franco M, Oruénez P, Caballero B, Tapias Granados JA, Lazo M, et al. (2007) Impact of energy intake, physical activity, and population-wide weight loss on cardiovascular disease and diabetes mortality in Cuba, 1980–2005. Am J Epidemiol 166: 1374–1380.
7. Hedges TR, Hirano M, Tucker K, Caballero B (1997) Epidemic optic and peripheral neuropathy in Cuba: a unique geopolitical public health problem. Surv Ophthalmol 41: 341–353.
8. Centers for Disease Control and Prevention (1994) Epidemiic neuropathy—Cuba, 1991–1994. MMWR Morb Mortal Wkly Rep 43: 183, 189–192.
9. De Vos P (2005) “No one left abandoned”: Cuba’s national health system since the 1959 revolution. Int J Health Serv 35: 189–207.
10. Garfield R (1997) The impact of economic embargoes on the health of women and children. J Am Med Womens Assoc 52: 181–184, 198.
11. Painter RC, Roseboom TJ, Birker OP (2005) Prenatal exposure to the Dutch famine and disease in later life: an overview. Reprod Toxicol 20: 345–352.
12. Galobardes B, Smith GD, Lynch JV (2006) Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol 16: 91–104.
13. Waters H, Saadah F, Pradhan M (2003) The impact of the 1997–98 East Asian economic crisis on health and health care in Indonesia. Health Policy Plan 18: 172–181.
14. Khang YH, Lynch JW, Kaplan GA (2003) Impact of economic crisis on cause-specific mortality in South Korea. Int J Epidemiol 34: 1301–1303.
15. Hopkins S (2006) Economic stability and health status: evidence from East Asia before and after the 1990s crisis. Health Policy 75: 347–357.
16. Waters H, Saadah F, Suryabandar S, Heywood P (2004) Weight-for-age malnutrition in Indonesian children, 1992–1999. Int J Epidemiol 33: 599–595.
17. Wordemann M, Pohnlan K, Junco Diaz R, Menocal Heredia LT, Collado Madurga AM, et al. (2006) The challenge of diagnosing atopic diseases: outcomes in Cuban children depend on definition and methodology. Allergy 61: 1125–1131.
18. Wordemann M, Pohnlan K, Menocal Heredia LT, Junco Diaz R, Collado Madurga AM, et al. (2006) Prevalence and risk factors of intestinal parasites in Cuban children. Trop Med Int Health 11: 1813–1820.
19. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, et al. (1995) International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J 8: 483–491.
20. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee (1990) Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. Lancet 331: 1255–1253.
21. Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, et al. (1997) Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 8: 161–176.

22. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, et al. (1999) Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. J Allergy Clin Immunol 103: 125–130.

23. Sonis J (1998) A closer look at confounding. Fam Med 30: 584–588.

24. von Mutius E (1998) The rising trends in asthma and allergic disease. Clin Exp Allergy 28 Suppl 5: 45–49.

25. Ministerio de Salud Publica (2000) Anuario Estadistico de Salud en Cuba 2000. Havana. Available at: http://www.infomed.sld.cu/servicios/estadisticas/.

26. Ligon BL (2006) Infectious diseases that pose specific challenges after natural disasters: a review. Semin Pediatr Infect Dis 17: 36–43.

27. Mooren DM, Folkers GK, Fauci AS (2004) The challenge of emerging and re-emerging infectious diseases. Nature 430: 242–249.

28. Sturcke M, Stuckler D, Suk JE, Desai M, Senek M, et al. (2011) The impact of economic crises on communicable disease transmission and control: a systematic review of the evidence. PLoS One 6: e20724.

29. Wills-Karp M, Santeliz J, Karp CL (2001) The germless theory of allergic disease: revisiting the hygiene hypothesis. Nat Rev Immunol 1: 69–75.

30. Barker DJP, Godfrey KM (2004) Maternal Nutrition, Fetal Programming and Adult Chronic Disease. In: Gilbody MJ, Marugan BM, Kearney JM, Arab L, editors. Public Health Nutrition. 1st ed. Oxford: Blackwell Publishing Ltd.

31. Roseboom T, de Rooij S, Painter R (2006) The Dutch famine and its long-term consequences for adult health. Early Hum Dev 82: 485–491.

32. Lopuhaa CE, Roseboom TJ, Osmond C, Barker DJ, Ravelli AC, et al. (2000) Atopy, lung function, and obstructive airways disease after prenatal exposure to famine. Thorax 55: 555–561.

33. Shaheen SO, Sterne JA, Montgomery SM, Azima H (1999) Birth weight, body mass index and asthma in young adults. Thorax 54: 396–402.

34. Devereux G, Seaton A (2005) Diet as a risk factor for atopy and asthma. J Allergy Clin Immunol 115: 1109–1117.

35. Devereux G (2006) The increase in the prevalence of asthma and allergy: food for thought. Nat Rev Immunol 6: 869–874.

36. Shore SA, Johnston RA (2006) Obesity and asthma. Pharmacol Ther 110: 83–102.

37. Weiss ST (2005) Obesity: insight into the origins of asthma. Nat Immunol 6: 537–539.

38. Koski KG, Scott ME (2001) Gastrointestinal nematodes, nutrition and immunity: breaking the negative spiral. Annu Rev Nutr 21: 297–321.

39. Scrimshaw NS (2003) Historical concepts of interactions, synergism and antagonism between nutrition and infection. J Nutr 133: 316S-321S.

40. Bhaskaram P (2002) Micronutrient malnutrition, infection, and immunity: an overview. Nutr Rev 60: S40–45.

41. Ngoc PL, Gold DR, Tzianabos AO, Weiss ST, Celedon JC (2005) Cytokines, allergy, and asthma. Curr Opin Allergy Clin Immunol 5: 161–166.

42. Eisenbarth SC, Cassel S, Botomly K (2004) Understanding asthma pathogenesis: linking innate and adaptive immunity. Curr Opin Pediatr 16: 659–666.