Identifying patterns of immune-related disease: use in disease prevention and management

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Background: **Childhood susceptibility to diseases linked with immune dysfunction affects over a quarter of the pediatric population in some countries. While this alone is a significant health issue, the actual impact of immune-related diseases extends over a lifetime and involves additional secondary conditions. Some co-morbidities are well known (e.g., allergic rhinitis and asthma). However, no systematic approach has been used to identify life-long patterns of immune-based disease where the primary condition arises in childhood. Such information is useful for both disease prevention and treatment approaches.**

Data sources: **Recent primary research papers as well as review articles were obtained from PubMed, Chem Abstracts, Biosis and from the personal files of the authors. Search words used were: the diseases and conditions shown Figs. 1 and 2 in conjunction with comorbid, comorbidities, pediatric, childhood, adult, immune, immune dysfunction, allergy, autoimmune, inflammatory, infectious, health risks, environment, risk factors.**

Results: **Childhood diseases such as asthma, type-1 diabetes, inflammatory bowel disease, respiratory infections /rhinitis, recurrent otitis media, pediatric celiac, juvenile arthritis and Kawasaki disease are examples of significant childhood health problems where immune dysfunction plays a significant role. Each of these pediatric diseases is associated with increased risk of several secondary conditions, many of which appear only later in life. To illustrate, four prototypes of immune-related disease patterns (i.e., allergy, autoimmunity, inflammation and infectious disease) are shown as tools for: 1) enhanced disease prevention; 2) improved management of immune-based pediatric diseases; and 3) better recognition of underlying pediatric immune dysfunction.**

Conclusions: **Identification of immune-related disease patterns beginning in childhood provides the framework for examining the underlying immune dysfunctions that can contribute to additional diseases in later life. Many pediatric diseases associated with dysfunctional immune responses have been linked with an elevated risk of other diseases or conditions as the child ages. Diseases within a pattern may be interlinked based on underlying immune dysfunctions and/or current therapeutic approaches for managing the entryway diseases. It may be beneficial to consider treatment options for the earliest presenting diseases that will concomitantly reduce the risk of immune-linked secondary conditions. Additionally, improved disease prevention is possible with more relevant and age-specific immune safety testing.**

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Introduction

During prenatal and neonatal development, one time maturation events occur within the immune system (e.g., maturation of mucosal immune capacity in the lung and gastrointestinal tract) that can establish the host interaction pattern with disease challenges across a lifetime. For this reason, effective management of the immune system that leads to better health needs to begin early. The benefits of encouraging this type of management in the pediatric and OB/GYN settings were recently discussed.[1] Environmental exposures to chemicals, drugs and physical factors combined with a child's genetic background, can affect the course of immune maturation creating problematic imbalances that can affect the health of every physiological system. The pediatrician plays a pivotal role in this immune management strategy because

actions taken during the perinatal and neonatal periods of childhood development can affect the risk of later-life immune-related diseases.

The scope of pediatric-immune-based diseases

Immune-based diseases impact in excess of 25% of the pediatric population in some countries.[2] Among those of concern are childhood asthma and allergies, type 1 diabetes, juvenile arthritis, otitis media, late-onset sepsis, childhood leukemia, pediatric celiac and Kawasaki disease. For some diseases, such as childhood asthma, specific environmental risk factors have been identified such as maternal smoking[3] and traffic-related air pollution.[4] However, known environmental risk factors do not account completely for recent increases observed in some immune-related pediatric diseases (i.e., childhood asthma and allergies).[5,6] The problem in identifying early-life immune risk factors is not surprising since current safety testing approaches for chemicals and drugs are not designed to detect these types of health risks.[7,8]

The actual impact of pediatric immune dysfunction on health is even greater than may be obvious. This is because pediatric immune and inflammatory diseases rarely occur in isolation. Instead their occurrence is usually associated with specific childhood vulnerabilities or host response processes that by their very nature impact the risk of additional later-life diseases. Predisposing risk for development of a secondary disease or condition following a primary pediatric diagnosis is not uncommon. In fact most pediatric diseases associated with misdirected, exaggerated or dysfunctional immune responses are associated with an elevated risk of additional diseases or conditions. These comorbid or secondary diseases can appear within a matter of days or, alternatively, they may not arise for decades. Identifying the patterns of immune-related diseases that begin during early life offers the opportunity to: 1) reduce the risk factors associated with the entire disease pattern (e.g., a pediatric atopic-allergy pattern that includes later-life diseases); 2) consider treatments addressing the life course of health risks as opposed to a single presenting condition; and 3) better examine underlying mechanisms of pediatric immune dysfunction.

Co-morbidities or secondary diseases

The occurrence of secondary diseases is common in the pediatric setting. For example, bacterial infection can follow certain respiratory viral infections and is a major cause of childhood antibiotic use. When the infant mounts a host response against a virus such as influenza, the nature, duration and intensity of the response itself can elevate the risk of other categories of microbial infection. For example, using a mouse model, Sun and Metzger[9] recently described that gamma-interferon in the lung, during the recovery phase of influenza infection, predisposes the airways to infection by extracellular bacteria (e.g., streptococcus).

A similar relationship has been reported between viral infection, inflammatory responses and specific cytokine production for the risk of bacteria-related otitis media.[10,11] Additionally, pediatric respiratory allergy can predispose toward an increased risk of otitis media with effusion.[12-14] While relationships such as those among respiratory viral and bacterial infections are well known to the pediatric community, others may be far less obvious. This is particularly true when: 1) the timeline for onset of the "second" disease/condition occurs years to decades after the initial pediatric diagnosis; and 2) either the primary or secondary disease is more commonly associated with a particular target organ rather than with immune dysfunction (e.g., atherosclerosis as cardiovascular disease, inflammatory bowel disease as a gastrointestinal disease or multiple sclerosis as a neurological disorder).

Identifying disease patterns

In a recent article, Dietert and Zelikoff[2] examined the associated risks between 28 different diseases and conditions where the initial diagnosis was made for a pediatric-onset immune-related condition. Relationships among the diseases and conditions were described in a 28×28 checkerboard that covered both pediatric-onset and adult onset-diseases. When supplemented with additional research and clinical information, this matrix provides a basis for the identification of fundamental patterns of immune-based diseases that can be connected with underlying pediatric immune dysfunction. The connections among diseases may in fact prove to be immunologically-based and potentially complex in nature.

Pediatric immune dysfunction can take many forms that involve different combinations of cell types and affect acquired and innate immunity, as well as inflammatory responses and tissue homeostasis. Additionally, more than one type of dysfunction can coexist following a specific immune insult.[15-19] By identifying patterns of immune-based diseases beginning in childhood, the connections between pediatric immune dysfunction and a lifetime of interrelated health risks can be better understood. The purpose of this review is to present examples of four basic patterns of immune-related disease and to discuss the benefits of approaching these diseases as unified patterns rather than as isolated conditions. This is a potentially useful step towards enhanced disease prevention, improved health management and a better mechanistic understanding of

immunologically-based diseases. A detailed consideration of pediatric immune dysfunction is beyond the scope of this review. But examples describing how specific pediatric immune dysfunction can explain associated health risks within a pattern are provided later in this paper. To our knowledge this is the first attempt to organize pediatric and later-life diseases using an immunological matrix.

Four examples of immune-related disease patterns

Examples of four immune-related pediatric disease patterns resulting in heightened risks of later onset diseases are shown in Figs. 1[20-36] and 2[37-50]. These include: 1) allergy; 2) autoimmunity; 3) inflammation; and 4) infection. Note that by itself, each of the four primary conditions shown in Figs. 1 and 2 (asthma, type 1 diabetes, inflammatory bowel disease, recurrent respiratory infections) represents a significant pediatric health concern. But when these individual pediatric diseases are also seen as potential entryways that facilitate multiple chronic diseases and conditions in later life, they take on an added level of concern. It should be noted that while all diseases depicted as interlinked in Figs. 1 and 2 are from studies showing statistically significant disease associations, it does not mean that the risks of secondary diseases are of equal importance. Some of the co-morbidities represent a more significant health risk than others. However, these disease patterns show clearly that prevention and/or treatment of the primary immune-related conditions in the pediatric setting is a critical focal point for the child's subsequent health concerns.

It is useful to recognize that not all pediatric immune-based diseases cluster together in a single group. Instead they fall into distinct categories based on the pediatric entryway disease. For example, the two primary or core diseases shown in Fig. 1 (i.e., allergic asthma and type 1 diabetes) are thought to be brought about by different types of immune responses. Children with asthma are prone to other Th2-driven, IgE-related allergic conditions (i.e., atopic dermatitis and allergic rhinitis). In contrast, children with type 1 diabetes are more likely to experience other autoimmune and inflammatory diseases linked with the same immune dysregulation as occurs with the diabetes but not necessarily with an allergy pattern.[35,51,52] In fact several studies reported that children with type 1 diabetes are not at a higher risk for asthma.[53,54] So the allergy-asthma vs. autoimmune-type 1 diabetes clusters shown in Fig. 1 are readily separable patterns both for the immunological basis for the core diseases as well as for the elevated risk of additional diseases.

Of note is the fact that the reported elevated risk of

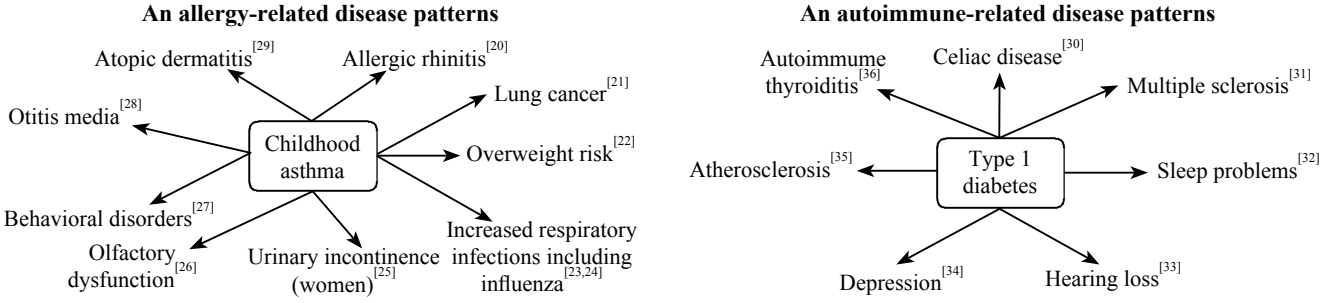

Fig. 1. Two examples of patterns of immune-related diseases. Both an allergy-related example (left) and an autoimmune-related example (right) are presented. The primary pediatric-onset immune-related disease is indicated in the center of each pattern. Secondary diseases and conditions that may arise either simultaneously or later in life and are connected to the primary disease by elevated risk are shown via arrows.

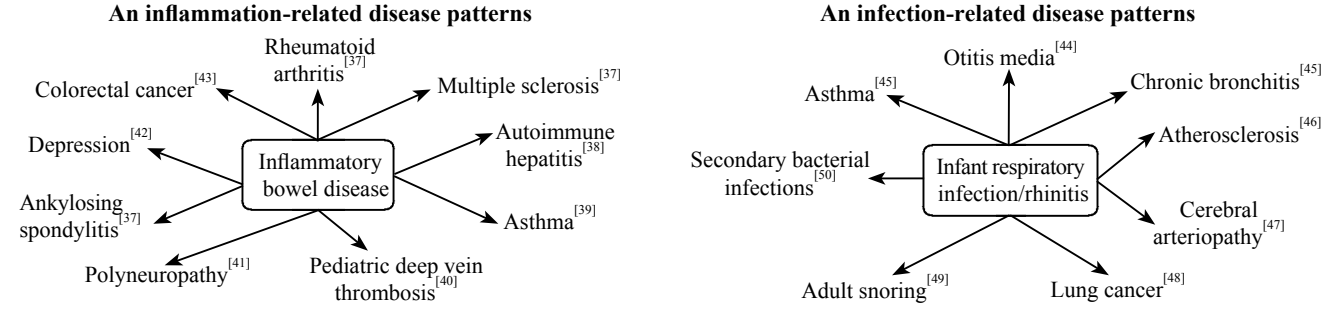

Fig. 2. Two examples of patterns of immune-related diseases. Both an inflammation-related example (left) and an infection-related example (right) are presented. The primary pediatric-onset immune-related disease is indicated in the center of each pattern. Secondary diseases and conditions that may arise either simultaneously or later in life and are connected to the primary disease by elevated risk are shown via arrows.

lung cancer among asthmatics (Fig. 1) does not extend to those with other allergies where the risk appears to be reduced.[21] Given the ramifications of prolonged tissue inflammation in the lungs, the asthma-lung cancer association is not surprising.

A similar relationship of chronic inflammation may explain, in part, the connection between inflammatory bowel disease and later-life colorectal cancer (Fig. 2). Sleep disorders seem to be associated with both autoimmune and inflammatory diseases; dysregulation of cytokine production may contribute to both adverse outcomes.[55-58] In fact the relationship between elevated production of proinflammatory cytokines and sleep disorders appears to be bidirectional. The cytokines interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha can regulate sleep patterns.[59,60] Additionally, IL-6 appears to play a role in sleep-wake cycles.[61] In the reciprocal relationship, sleep loss can result in elevated production of TNF-alpha and IL-6.[62] Likewise, depression is associated with a number of autoimmune and inflammatory conditions including multiple sclerosis,[63] type 1 diabetes,[34] juvenile arthritis,[64] endometriosis[65] and sarcoidosis.[66] The mechanisms connecting other conditions such as the association between childhood asthma and behavioral disorders may be less obvious in terms of a mechanistic basis.

Additional patterns

The four sample patterns described in this review are only meant to serve as prototype examples. They are intended to illustrate significant childhood immune-based diseases and the way in which pediatric diseases may be linked with the risk of later-life illnesses. Data are available for the identification of additional immune-based patterns beginning in childhood. For example, pediatric celiac disease and recurrent otitis media both have their own spheres of probable secondary conditions. Celiac disease, particularly in early life, has been linked with additional conditions such as autoimmune liver disease,[67] additional autoimmune diseases,[68] dental carries,[69] bone problems,[70] non-Hodgkins lymphoma[71] and neurological complications.[72,73] Recurrent otitis media is linked with adolescent[74] and adult[75] snoring. An additional childhood autoimmune condition, Kawasaki disease, is linked with carotid atherosclerosis as a later disease concern.[76]

Another important childhood disease, childhood acute lymphoblastic leukemia (cALL), also appears to be connected to immune dysfunction.[77-79] In this case, although a prototype model has yet to be identified, available data suggest that cALL is likely to be placed into a pattern that emphasizes infectious disease/dysfunctional responses. In contrast, cALL is unlikely to fall within a pattern of diseases where the primary or core condition is allergy/atopy. This is based on the fact that Hughes and colleagues[78] reported that childhood allergy (particularly atopic dermatitis and allergic rhinitis) is associated with a reduced rather than an elevated risk of cALL. These findings further emphasize the need for pediatricians to understand and utilize immune dysfunctional disease patterns.

Using disease patterns in prevention and management

Identification of immune-based disease patterns can be useful in disease prevention by encouraging strategies to help parents and their children avoid already established risk factors. Pattern identification can also be used in the pediatric setting to design disease management approaches that take into account the lifetime of potential health risks.

For example in the context of disease prevention, early-life exposure to polychlorinated biphenyls (PCBs) has been reported to increase susceptibility to respiratory infections[80-82] and to reduce responses to childhood vaccination.[83] We now know that increased susceptibility to respiratory infections is a potential core or first pediatric condition seen in one type of infectious disease pattern of immune dysfunction (Fig. 2). However, this pattern is far more than a single childhood illness. Instead it is a susceptibility pattern associated with a higher risk of several later-life diseases. Such information provides even greater health impetus to minimize prenatal/neonatal exposure to PCBs. The actual health risks seem likely to extend well beyond those primary diseases seen in young children, and the benefits of avoiding problematic exposure are greater than the previously understood.

Some individual hazards for the developing immune system appear to be capable of promoting more than one of the immune dysfunction disease patterns discussed in this review. For example, evidence suggests that early life exposure to 2, 3, 7, 8 tetrachlorodibenzo-p-dioxin (TCDD, dioxin) can cause reduced host defense against viral infections,[84] increased tissue inflammation,[18,85] and increased risk of autoimmunity;[19,86] the latter disease is linked to a disruption of thymic selection of T cells.[19] In another example, prenatal and neonatal exposure to tobacco smoke (TS) can play a role in multiple immune dysfunction patterns in the offspring. Based on entry diseases the most apparent patterns are an allergy-asthma[87,88] and a respiratory infection[89-91] pattern. However, based on known disease associations with TS exposure, there is the suggestion that autoimmune[92] and inflammatory disease[93,94] patterns may also be promoted. This ability of TS to instigate

multiple immune dysfunctional disease patterns is not necessarily surprising since TS is a mixture of many well-established immunotoxicants (e.g., heavy metals, benzene, polycyclic aromatic hydrocarbons), and each individual toxicant can produce its own specific damage to the developing immune system.

Based on existing knowledge it is clear that early-life exposure to a single environmental risk factor can promote a cluster of chronic diseases all linked to a single pattern of immune dysfunction. In some cases (e.g., TCDD, TS) it can also promote more than one pattern of immune-related diseases. This should provide an added impetus for protecting children from known immunotoxic risks that can contribute to disease not only in children but also in adults.

An important aspect of immune dysfunction prevention is that the gap in immune safety testing information for pregnant women and children be addressed. It is obvious that we know far less about the immunological safety of chemicals and drugs for these sensitive subpopulations than for adults. Pediatricians can help to close this safety gap by insisting that age-relevant safety information be available for their procedures. For example, do we really know the optimum timing for childhood vaccinations when it comes to overall immune safety? Recent studies raise doubts. McDonald and colleagues[95] reported that earlier-age protocols of vaccination with diphtheria-pertussis-tetanus (DPT) are associated with an increased risk of childhood asthma. Childhood vaccination is a foundation stone for pediatric disease prevention. However, whether the current timing of childhood vaccinations necessarily optimizes overall immune function in children is not known. Ideally, decisions on the timing of vaccinations should be based on managing the immune system and disease risks over a lifetime and not just in the short term. It is important to know that, in using a specific regimen for preventing childhood infectious diseases, we do not put children at greater risk for asthma and potentially the entire pattern of allergy-asthma-linked diseases that can appear in later life (Fig. 1).

Prevention and disease management intersect in ways that allow pediatricians to use immune-based disease patterns in considering the management of an entryway disease. For example, knowledge of likely secondary conditions in later life may influence which of several options pediatricians choose for managing a primary disease such as asthma, celiac disease, inflammatory bowel disease or recurrent otitis media. An example where immune management decisions might affect secondary disease risk can be found in the topic of depression as a secondary outcome associated with certain primary autoimmune and inflammatory pediatric diseases. One can envision some pediatric treatment courses that address only the presenting autoimmune or inflammatory symptoms, but leave the underlying immune dysfunction (e.g., predisposition for cytokine misregulation) present to emerge as later-life depression. Additionally, some courses of treatment, such as prolonged corticosteroid therapy, may contribute to the risk of secondary conditions such as depression.[96] Alternative treatments that may be available to address both the immediately presenting symptoms as well as the underlying immune-based dysfunction would be preferable. Knowledge of those patterns of immune-related disease would be useful for considering such decisions.

Using disease patterns to study pediatric immune dysfunction

While a detailed review of pediatric immune dysfunction will not be considered here, it is useful to illustrate how the identification of patterns of immune-related disease can provide a framework for considering underlying immune dysfunction. For example, as one of the core diseases in Fig. 1, childhood asthma can involve both T-helper (Th2)-driven IgE allergic responses and inappropriate inflammation of the airways. The immune mechanism of mounting allergic IgE responses connects the pediatric asthma to other atopic conditions shown in Fig. 1 (i.e., allergic rhinitis and atopic dermatitis). In contrast, the elevated risk of later-life lung cancer associated with asthma is unlikely to be associated with hyper-IgE production. Instead, chronic misregulated inflammation in the airways and cumulative oxidative damage in the lungs is the putative underlying mechanism of immune dysfunction that connects childhood asthma to later-life lung cancer.

Entryway immune-related diseases of childhood can feature more than one underlying immune dysfunction. In fact, misregulated inflammation is common to several of the patterns illustrated in this review. This is not surprising as inflammation is among the most common adverse outcome of pollutant-associated developmental immunotoxicity.[18,97,98] In certain cases it can be challenging to determine whether a later-life health risk is connected directly to the entryway pediatric disease or to a commonly-employed treatment protocol. However, the identification of existing patterns of immune-related disease is a useful first step towards dissecting these relationships.

Conclusions

Immune-related diseases, including allergy, asthma, autoimmunity, leukemia and susceptibility to infectious diseases, represent a significant proportion of all pediatric diseases. Historically most of these diseases have been considered either in isolation or as narrowly-grouped

diseases (e.g., the atopic triad). Additionally, some diseases are recognized equally by the compromised tissue targeted by the immune insult (e.g., inflammatory bowel disease) as by the immune dysfunction-basis for the disease. The danger in this is that treatments may focus narrowly on the presenting organ-related symptoms leaving the underlying immune dysfunction in place to contribute to later-life disease. Identification of patterns of immune-related diseases starting in childhood provides a useful step towards identifying and addressing underlying immune problems that may continue to trigger chronic disease across decades of life.

This review, that has provided four examples of patterns of immune-related diseases, should emphasize the importance of preventing the primary condition that presents early in life. Such information should encourage the treatments that help reduce the risk of some later-life conditions.

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References

1 Dietert RR, Piepenbrink MS. The managed immune system: protecting the womb to delay the tomb. Hum Exp Toxicol 2008; 27:129-134.
2 Dietert RR, Zelikoff JT. Pediatric immune dysfunction and health risks following early-life immune insult. Curr Pediatr Rev 2009;5:36-51.
3 Karmaus W, Dobai AL, Ogbuanu I, Arshard SH, Matthews S, Ewart S. Long-term effects of breastfeeding, maternal smoking during pregnancy, and recurrent lower respiratory tract infections on asthma in children. J Asthma 2008;45:688-695.
4 Kim JJ, Huen K, Adams S, Smorodinsky S, Hoats A, Malig B, et al. Residential traffic and children's respiratory health. Environ Health Perspect 2008;116:1274-1279.
5 Yeatts K, Sly P, Shore S, Weiss S, Martinez F, Geller A, et al. A brief targeted review of susceptibility factors, environmental exposures, asthma incidence, and recommendations for future asthma incidence research. Environ Health Perspect 2006;114: 634-640.
6 Selgrade MK, Lemanske RF Jr, Gilmour MI, Neas LM, Ward MD, Henneberger PK, et al. Induction of asthma and the environment: what we know and need to know. Environ Health Perspect 2006;114:615-619.
7 Dietert RR. Developmental immunotoxicity (DIT) in drug safety testing: matching DIT testing to adverse outcomes and childhood disease risk. Curr Drug Saf 2008;3:216-226.
8 Dietert RR. Developmental immunotoxicology: focus on health risks. Chem Res Toxicol 2009;22:17-23.
9 Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 2008;14:558-564.
10 Alper CM, Winther B, Mandel EM, Hendley JO, Doyle WJ. Rate of concurrent otitis media in upper respiratory tract infections with specific viruses. Arch Otolaryngol Head Neck Surg 2009;135:17-21.
11 Beder LB, Hotomi M, Ogami M, Yamauchi K, Shimada J, Billal DS, et al. Clinical and microbiological impact of human bocavirus on children with acute otitis media. Eur J Pediatr 2009; 168:1365-1372.
12 Yeo SG, Park DC, Eun YG, Cha CI. The role of allergic rhinitis in the development of otitis media with effusion: effect on eustachian tube function. Am J Otolaryngol 2007;28:148-152.
13 Luong A, Roland PS. The link between allergic rhinitis and chronic otitis media with effusion in atopic patients. Otolaryngol Clin North Am 2008;41:311-323, vi.
14 Marseglia GL, Pagella F, Caimmi D, Caimmi S, Castellazzi AM, Poddighe D, et al. Increased risk of otitis media with effusion in allergic children presenting with adenoiditis. Otolaryngol Head Neck Surg 2008;138:572-575.
15 Luebke RW, Copeland CB, Bishop LR, Daniels MJ, Gilmour MI. Mortality in dioxin-exposed mice infected with influenza: mitochondrial toxicity (reye's-like syndrome) versus enhanced inflammation as the mode of action. Toxicol Sci 2002;69:109-116.
16 Vorderstrasse BA, Cundiff JA, Lawrence BP. A dose-response study of the effects of prenatal and lactational exposure to TCDD on the immune response to influenza a virus. J Toxicol Environ Health A 2006;69:445-463.
17 Mustafa A, Holladay SD, Goff M, Witonsky SG, Kerr R, Reilly CM, et al. An enhanced postnatal autoimmune profile in 24 week-old C57BL/6 mice developmentally exposed to TCDD. Toxicol Appl Pharmacol 2008;232:51-59.
18 Hogaboam JP, Moore AJ, Lawrence BP. The aryl hydrocarbon receptor affects distinct tissue compartments during ontogeny of the immune system. Toxicol Sci 2008;102:160-170.
19 Ishimaru N, Takagi A, Kohashi M, Yamada A, Arakaki R, Kanno J, et al. Neonatal exposure to low-dose 2,3,7, 8-tetrachlorodibenzo-p-dioxin causes autoimmunity due to the disruption of T cell tolerance. J Immunol 2009;182:6576-6586.
20 de Andrade CR, da Cunha Ibiapina C, Gonçalves Alvim C, Fernandes Fontes MJ, de Lima Belizário Facury Lasmar LM, Moreira Camargos PA. Asthma and allergic rhinitis co-morbidity: a cross-sectional questionnaire study on adolescents aged 13-14 years. Prim Care Respir J 2008;17:222-225.
21 Sherman PW, Holland E, Sherman JS. Allergies: their role in cancer prevention. Q Rev Biol 2008;83:339-362.
22 Bender BG, Fuhlbrigge A, Walders N, Zhang L. Overweight, race, and psychological distress in children in the Childhood Asthma Management Program. Pediatrics 2007;120:805-813.
23 Jacobson JS, Goldstein IF, Canfield SM, Ashby-Thompson M, Husain SA, Chew GL, et al. Early respiratory infections and asthma among New York City Head Start children. J Asthma 2008;45:301-308.
24 Miller EK, Griffin MR, Edwards KM, Weinberg GA, Szilagyi PG, Staat MA, et al. Influenza burden for children with asthma. Pediatrics 2008;121:1-8.
25 Van Gerwen M, Schellevis F, Lagro-Janssen T. Comorbidities associated with urinary incontinence: a case-control study from

the Second Dutch National Survey of General Practice. J Am Board Fam Med 2007;20:608-610.
26 Litvack JR, Fong K, Mace J, James KE, Smith TL. Predictors of olfactory dysfunction in patients with chronic rhinosinusitis. Laryngoscope 2008;118:2225-2230.
27 Blackman JA, Gurka MJ. Developmental and behavioral comorbidities of asthma in children. J Dev Behav Pediatr 2007; 28:92-99.
28 Bentdal YE, Nafstad P, Karevold G, Kvaerner KJ. Acute otitis media in schoolchildren: allergic diseases and skin prick test positivity. Acta Otolaryngol 2007;127:480-485.
29 Willis-Owen SA, Morar N, Willis-Owen CA. Atopic dermatitis: insights from linkage overlap and disease co-morbidity. Expert Rev Mol Med 2007;9:1-13.
30 Larsson K, Carlsson A, Cederwall E, Jönsson B, Neiderud J, Jonsson B, et al. Annual screening detects celiac disease in children with type 1 diabetes. Pediatr Diabetes 2008;9:354-359.
31 Nielsen NM, Westergaard T, Frisch M, Rostgaard K, Wohlfahrt J, Koch-Henriksen N, et al. Type 1 diabetes and multiple sclerosis: a Danish population-based cohort study. Arch Neurol 2006;63:1001-1004.
32 Jauch-Chara K, Schmid SM, Hallschmid M, Born J, Schultes B. Altered neuroendocrine sleep architecture in patients with type 1 diabetes. Diabetes Care 2008;31:1183-1188.
33 Elamin A, Fadlallah M, Tuevmo T. Hearing loss in children with type 1 diabetes. Indian Pediatr 2005;42:15-21.
34 Gendelman N, Snell-Bergeon JK, McFann K, Kinney G, Paul Wadwa R, Bishop F, et al. Prevalence and correlates of depression in individuals with and without type 1 diabetes. Diabetes Care 2009;32:575-579.
35 Devaraj S, Cheung AT, Jialal I, Griffen SC, Nguyen D, Glaser N, et al. Evidence of increased inflammation and microcirculatory abnormalities in patients with type 1 diabetes and their role in microvascular complications. Diabetes 2007;56:2790-2796.
36 Fröhlich-Reiterer EE, Hofer S, Kaspers S, Herbst A, Kordonouri O, Schwarz HP, et al. Screening frequency for celiac disease and autoimmune thyroiditis in children and adolescents with type 1 diabetes mellitus—data from a German/Austrian multicentre survey. Pediatr Diabetes 2008;9:546-553.
37 Cohen R, Robinson D Jr, Paramore C, Fraeman K, Renahan K, Bala M. Autoimmune disease concomitance among inflammatory bowel disease patients in the United States, 2001-2002. Inflamm Bowel Dis 2008;14:738-743.
38 Saich R, Chapman R. Primary sclerosing cholangitis, autoimmune hepatitis and overlap syndromes in inflammatory bowel disease. World J Gastroenterol 2008;14:331-337.
39 Weng X, Liu L, Barcellos LF, Allison JE, Herrinton LJ. Clustering of inflammatory bowel disease with immune mediated diseases among members of a northern california-managed care organization. Am J Gastroenterol 2007;102:1429-1435.
40 Vu LT, Nobuhara KK, Lee H, Farmer DL. Determination of risk factors for deep venous thrombosis in hospitalized children. J Pediatr Surg 2008;43:1095-1099.
41 Oliveira GR, Teles BC, Brasil EF, Souza MH, Furtado LE, de Castro-Costa CM, et al. Peripheral neuropathy and neurological disorders in an unselected Brazilian population-based cohort of IBD patients. Inflamm Bowel Dis 2008;14:389-395.
42 Szigethy E, Levy-Warren A, Whitton S, Bousvaros A, Gauvreau K, Leichtner AM, et al. Depressive symptoms and inflammatory bowel disease in children and adolescents: a cross-sectional study. J Pediatr Gastroenterol Nutr 2004;39:395-403.
43 Lin OS. Acquired risk factors for colorectal cancer. Methods Mol Biol 2009;472:361-372.
44 Fleming DM, Pannell RS, Elliot AJ, Cross KW. Respiratory illness associated with influenza and respiratory syncytial virus infection. Arch Dis Child 2005;90:741-746.
45 Ekici M, Ekici A, Akin A, Altinkaya V, Bulcun E. Chronic airway diseases in adult life and childhood infections. Respiration 2008;75:55-59.
46 Gurfinkel E, Lernoud V. The role of infection and immunity in atherosclerosis. Expert Rev Cardiovasc Ther 2006;4:131-137.
47 Amlie-Lefond C, Bernard TJ, Sébire G, Friedman NR, Heyer GL, Lerner NB, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. Circulation 2009;119:1417-1423.
48 Koh WP, Yuan JM, Wang R, Seow A, Lee HP, Yu MC. Chronic rhinosinusitis and risk of lung cancer in the Singapore Chinese Health Study. Int J Cancer 2008;123:1398-1402.
49 Franklin KA, Janson C, Gíslason T, Gulsvik A, Gunnbjörnsdottir M, Laerum BN, et al. Early life environment and snoring in adulthood. Respir Res 2008;9:63.
50 Heltzer ML, Coffin SE, Maurer K, Bagashev A, Zhang Z, Orange JS, et al. Immune dysregulation in severe influenza. J Leukoc Biol 2009;85:1036-1043.
51 Mantovani RM, Mantovani LM, Dias VM. Thyroid autoimmunity in children and adolescents with type 1 diabetes mellitus: prevalence and risk factors. J Pediatr Endocrinol Metab 2007;20:669-675.
52 Franzese A, Lombardi F, Valerio G, Spagnuolo MI. Update on coeliac disease and type 1 diabetes mellitus in childhood. J Pediatr Endocrinol Metab 2007;20:1257-1264.
53 Cakir M, Akcay S, Karakas T, Gedik Y, Okten A, Orhan F. Prevalence of atopy in children with type 1 diabetes mellitus, hepatitis B virus carriers, and healthy children: role of T helper 1 (Th1)-type immune response. Allergy Asthma Proc 2008;29: 166-170.
54 Gazit V, Tasher D, Hanukoglu A, Landau Z, Ben-Yehuda Y, Somekh E, et al. Atopy in children and adolescents with insulin-dependent diabetes mellitus. Isr Med Assoc J 2008;10:858-861.
55 Lorton D, Lubahn CL, Estus C, Millar BA, Carter JL, Wood CA, et al. Bidirectional communication between the brain and the immune system: implications for physiological sleep and disorders with disrupted sleep. Neuroimmunomodulation 2006; 13:357-374.
56 Mills PJ, von Känel R, Norman D, Natarajan L, Ziegler MG, Dimsdale JE. Inflammation and sleep in healthy individuals. Sleep 2007;30:729-735.
57 El-Sheikh M, Buckhalt JA, Granger DA, Erath SA, Acebo C. The association between children's sleep disruption and salivary interleukin-6. J Sleep Res 2007;16:188-197.
58 Kapsimalis F, Basta M, Varouchakis G, Gourgoulianis K, Vgontzas A, Kryger M. Cytokines and pathological sleep. Sleep Med 2008;9:603-614.
59 Cavadini G, Petrzilka S, Kohler P, Jud C, Tobler I, Birchler T, et al. TNF-alpha suppresses the expression of clock genes by interfering with E-box-mediated transcription. Proc Natl Acad Sci U S A 2007;104:12843-12848.
60 Krueger JM. The role of cytokines in sleep regulation. Curr Pharm Des 2008;14:3408-3416.
61 Morrow JD, Opp MR. Sleep-wake behavior and responses of interleukin-6-deficient mice to sleep deprivation. Brain Behav Immun 2005;19:28-39.
62 Irwin MR, Carrillo C, Olmstead R. Sleep loss activates cellular markers of inflammation: sex differences. Brain Behav Immun

2010;24:54-57.
63 Beiske AG, Svensson E, Sandanger I, Czujko B, Pedersen ED, Aarseth JH, et al. Depression and anxiety amongst multiple sclerosis patients. Eur J Neurol 2008;15:239-245.
64 Packham JC. Overview of the psychosocial concerns of young adults with juvenile arthritis. Musculoskeletal Care 2004;2:6-16.
65 Siedentopf F, Tariverdian N, Rücke M, Kentenich H, Arck PC. Immune status, psychosocial distress and reduced quality of life in infertile patients with endometriosis. Am J Reprod Immunol 2008;60:449-461.
66 Goracci A, Fagiolini A, Martinucci M, Calossi S, Rossi S, Santomauro T, et al. Quality of life, anxiety and depression in sarcoidosis. Gen Hosp Psychiatry 2008;30:441-445.
67 Caprai S, Vajro P, Ventura A, Sciveres M, Maggiore G; SIGENP Study Group for Autoimmune Liver Disorders in Celiac Disease Collaborators. Autoimmune liver disease associated with celiac disease in childhood: a multicenter study. Clin Gastroenterol Hepatol 2008;6:803-806.
68 Cosnes J, Cellier C, Viola S, Colombel JF, Michaud L, Sarles J, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. Clin Gastroenterol Hepatol 2008;6:753-758.
69 Avşar A, Kalayci AG. The presence and distribution of dental enamel defects and caries in children with celiac disease. Turk J Pediatr 2008;50:45-50.
70 Mora S. Celiac disease in children: impact on bone health. Rev Endocr Metab Disord 2008;9:123-130.
71 Catassi C, Fabiani E, Corrao G, Barbato M, De Renzo A, Carella AM, et al. Risk of non-Hodgkin lymphoma in celiac disease. JAMA 2002;287:1413-1419.
72 Vaknin A, Eliakim R, Ackerman Z, Steiner I. Neurological abnormalities associated with celiac disease. J Neurol 2004;251:1393-1397.
73 Fasano A, Catassi C. Coeliac disease in children. Best Pract Res Clin Gastroenterol 2005;19:467-478.
74 Gozal D, Kheirandish-Gozal L, Capdevila OS, Dayyat E, Kheirandish E. Prevalence of recurrent otitis media in habitually snoring school-aged children. Sleep Med 2008;9:549-554.
75 Franklin KA, Janson C, Gíslason T, Gulsvik A, Gunnbjörnsdottir M, Laerum BN, et al. Early life environment and snoring in adulthood. Respir Res 2008;9:63.
76 Cheung YF, O K, Woo CW, Armstrong S, Siow YL, Chow PC, et al. Oxidative stress in children late after Kawasaki disease: relationship with carotid atherosclerosis and stiffness. BMC Pediatr 2008;8:20.
77 Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. Nat Rev Cancer 2006;6:193-203.
78 Hughes AM, Lightfoot T, Simpson J, Ansell P, McKinney PA, Kinsey SE, et al. Allergy and risk of childhood leukaemia: results from the UKCCS. Int J Cancer 2007;121:819-824.
79 Dietert RR. Developmental immunotoxicity (DIT), postnatal immune dysfunction and childhood leukemia. Blood Cells Mol Dis 2009;42:108-112.
80 Weisglas-Kuperus N, Vreugdenhil HJ, Mulder PG. Immunological effects of environmental exposure to polychlorinated biphenyls and dioxins in Dutch school children. Toxiol Lett 2004;149:281-285.
81 Dallaire F, Dewailly E, Vézina C, Muckle G, Weber JP, Bruneau S, et al. Effect of prenatal exposure to polychlorinated biphenyls on incidence of acute respiratory infections in preschool Inuit children. Environ Health Perspect 2006;114:1301-1305.
82 Glynn A, Thuvander A, Aune M, Johannisson A, Darnerud PO, Ronquist G, et al. Immune cell counts and risks of respiratory infections among infants exposed pre- and postnatally to organochlorine compounds: a prospective study. Environ Health 2008;7:62.
83 Heilmann C, Grandjean P, Weihe P, Nielsen F, Budtz-Jørgensen E. Reduced antibody responses to vaccinations in children exposed to polychlorinated biphenyls. PLoS Med 2006;3:e311.
84 Head JL, Lawrence BP. The aryl hydrocarbon receptor is a modulator of anti-viral immunity. Biochem Pharmacol 2009;77:642-653.
85 Matsumura F. The significance of the nongenomic pathway in mediating inflammatory signaling of the dioxin-activated Ah receptor to cause toxic effects. Biochem Pharmacol 2009;77:608-626.
86 Gogal RM Jr, Holladay SD. Perinatal TCDD exposure and the adult onset of autoimmune disease. J Immunotoxicol 2008;5:413-418.
87 Goodwin RD, Cowles RA. Household smoking and childhood asthma in the United States: a state-level analysis. J Asthma 2008;45:607-610.
88 Wang L, Pinkerton KE. Detrimental effects of tobacco smoke exposure during development on postnatal lung function and asthma. Birth Defects Res C Embryo Today 2008;84:54-60.
89 Corsello G, Di Carlo P, Salsa L, Gabriele B, Meli L, Bruno S, et al. Respiratory syncytial virus infection in a Sicilian pediatric population: risk factors, epidemiology, and severity. Allergy Asthma Proc 2008;29:205-210.
90 Kwok MK, Schooling CM, Ho LM, Leung SS, Mak KH, McGhee SM, et al. Early life second-hand smoke exposure and serious infectious morbidity during the first 8 years: evidence from Hong Kong's "Children of 1997" birth cohort. Tob Control 2008;17:263-270.
91 Cheraghi M, Salvi S. Environmental tobacco smoke (ETS) and respiratory health in children. Eur J Pediatr 2009;168:897-905.
92 Jaakkola JJ, Gissler M. Maternal smoking in pregnancy as a determinant of rheumatoid arthritis and other inflammatory polyarthropathies during the first 7 years of life. Int J Epidemiol 2005;34:664-671.
93 Gunes T, Koklu E, Yikilmaz A, Ozturk MA, Akcakus M, Kurtoglu S, et al. Influence of maternal smoking on neonatal aortic intima-media thickness, serum IGF-I and IGFBP-3 levels. Eur J Pediatr 2007;166:1039-1044.
94 Geerts CC, Bots ML, Grobbee DE, Uiterwaal CS. Parental smoking and vascular damage in young adult offspring: is early life exposure critical? The atherosclerosis risk in young adults study. Arterioscler Thromb Vasc Biol 2008;28:2296-2302.
95 McDonald KL, Huq SI, Lix LM, Becker AB, Kozyrskyj AL. Delay in diphtheria, pertussis, tetanus vaccination is associated with a reduced risk of childhood asthma. J Allergy Clin Immunol 2008;121:626-631.
96 Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009;68:1119-1124.
97 Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. PLoS Genet 2007;3:e207.
98 Blossom SJ, Doss JC, Hennings LJ, Jernigan S, Melnyk S, James SJ. Developmental exposure to trichloroethylene promotes CD4+ T cell differentiation and hyperactivity in association with oxidative stress and neurobehavioral deficits in MRL+/+ mice. Toxicol Appl Pharmacol 2008;231:344-353.

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