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Television watching, sleepiness, and adiposity

There is increasing evidence that there is a connection between sleep disturbance and obesity. In this issue of *The Journal*, Gaina et al evaluated a large population of Japanese children in a cross-sectional, school-based study. Twenty-five percent of children reported that they were almost always sleepy during the day, and 48% reported that they were often sleepy during the day. Increased daytime sleepiness was associated with higher body mass index and more time watching television and playing video games. The cross-sectional nature of the study does not allow us to determine which factors come first. In addition, the role of obstructive sleep apnea as a disrupter of sleep is not clear. Nevertheless, these results suggest that increased physical activity, decreased media time, and improved sleep habits might decrease daytime sleepiness and could lower the incidence of childhood obesity.

—Stephen R. Daniels, MD, PhD

Advanced pubertal status at age 11 and lower physical activity in adolescent girls

It has been known that physical activity tends to decline in girls during adolescence. However, factors which may accelerate this decline have not been extensively studied. In this issue, Baker et al evaluated the impact of timing of onset of puberty on levels of physical activity. They found that girls who experienced pubertal maturation at a younger age have lower levels of physical activity at age 13 than girls who matured at a slower pace. These girls with early maturation may also be at higher risk for the development of obesity. Further research is needed to better understand the mechanisms of the puberty-related decline. Clinicians can use these results to identify a group of girls at higher risk to decrease activity who would benefit from counseling on ways to remain active.

—Stephen R. Daniels, MD, PhD

Can City Park programs improve obesity?

The genesis of the childhood epidemic of obesity is clearly due to an overall decline of physical activity with a concomitant increase of dietary intake of calories. How to solve the problem of childhood obesity is much more complex. Some have wondered whether city parks could be part of an obesity prevention and treatment program. In this issue of *The Journal*, Bush et al studied a physical fitness and nutrition education program that was delivered in the City Park system of Houston, Texas. They found that children who were overweight and participated in the program had small decreases in their body weight and body mass index. The children also improved strength, flexibility, and endurance. These results suggest that for some children the involvement with programs in City Parks can be beneficial.

—Stephen R. Daniels, MD, PhD
A new larger look to inflammatory bowel disease

The current epidemic of childhood obesity and type 2 diabetes has generated a set of serious multi-systemic complications, heretofore not observed at this frequency in childhood. These have included obesity-related renal insufficiency, sleep apnea, steatohepatitis, and complicated orthopedic problems among others. Moreover, the obesity epidemic has spread beyond the wealthiest nations. Even in many developing countries, childhood obesity is now as common as malnutrition, changing the content of public health programs for optimal nutrition in children. In this issue of *The Journal*, Kugathasan et al uncover another alteration from the usual presentation of a classical childhood disease that is a direct result of the obesity epidemic. Weight loss and undernutrition are no longer the dominant nutritional presentation of Crohn’s disease and ulcerative colitis in North America. Rather, at presentation, <66% have normal body mass index (BMI) and obesity is twice as common as undernutrition in ulcerative colitis and half as common in Crohn’s disease. Changing body habitus in American children in general may now be altering the BMI of children with a variety of chronic diseases, changing the clinical phenotypes, and requiring that we expand our diagnostic criteria.

—Ronald J. Sokol, MD  
page 523

Long-term impact of adolescent dating violence

In this issue of *The Journal*, Ackard et al from the University of Minnesota have studied the long-term impact of adolescent dating violence on the behavioral and psychological health of male and female youth. The data were taken from Project EAT, an epidemiologic study of adolescent eating behaviors. Adolescent dating violence is associated with a greater likelihood of problematic health issues and increases non-specific risks toward behavior and psychological impairment amongst youth, particularly amongst females.

—Robert W. Wilmott, MD  
page 476

Family connectedness

Childhood sexual abuse produces scars which last well into adulthood. One of the known long-term outcomes of this trauma is suicidal ideation and actual completed suicide. Once abuse has been diagnosed and its immediate consequences addressed, it would be helpful for practitioners to know of interventions which could mitigate its long-term adverse outcomes.

In this issue of *The Journal*, Eisenberg et al provide some potential insights into this issue. Drawing from a survey of over 80,000 children in Minnesota schools, this group confirmed that sexual abuse was common (over 5% of respondents) and was often accompanied by suicidal ideation and actual attempts. The authors determined, however, that some potentially modifiable factors significantly attenuated these risks. Foremost among these was what they called “family connectedness”—a measure associated with the sense that parents were present, available to talk, and demonstrated care and respect for privacy. This study is must reason for anyone involved in the counseling of abused children and their families.

—Thomas R. Welch, MD  
page 482
“Programmed” futures

The Barker hypothesis relates decreased size at birth to adverse cardiovascular outcomes as an adult. The original observations focused primarily on infants born small at term. There is accumulating information suggesting that preterm infants also may be at risk of cardiovascular and metabolic abnormalities as they age. In this issue of The Journal, Mikkola et al report on a 5-year follow-up of cardiovascular function in AGA and SGA very low birth weight infants in comparison with term infants. This cohort of preterm infants had increased cardiac workload and compromised hemodynamic adaptation in the first weeks of life relative to term infants. Now at 5 years, they have abnormal measurements for heart wall and chamber sizes as well as alterations in microvascular perfusion in response to sodium nitroprusside and acetylcholine. Strengths of the study are the sequential evaluation of a cohort of infants and the use of provocations to tease out differences in microvascular perfusion. The long-term importance of the detected differences will require further study at older ages. However, this study is another demonstration that fetal and/or early life events can “program” physiological responses in later life.

—Alan H. Jobe, MD, PhD

Incidence of childhood leukemia stable in Nordic countries over two decades

Using a well-established cancer registry and capturing data of the entire population of Nordic countries, Svendsen et al report that incidence of childhood leukemia rose until 1983 and has been stable since. Data on incidence by birth cohort showed rise to birth in 1980, with sustained incidence but no further rise since. This database, spanning a quarter-century, and less likely than others to have biases of case ascertainment and diagnosis, provides two possible “saturation” points in time for epidemiologists and cancer researchers to consider in hypothesis exploration.

—Sarah S. Long, MD

Abnormal head ultrasounds and neurodevelopmental outcome

Severe intracranial hemorrhage and periventricular leukomalacia are believed to be strong predictors of poor neurodevelopmental outcome in extremely immature infants. The article by Broitman et al examines the ability of head ultrasounds, obtained during routine care to accurately predict neurodevelopmental outcomes. The authors compared the predictive capabilities of the commonly used ultrasound classification system (that considers increasing grades of IVH as a progression of a single disease) with clinical risk factors alone. Their study shows that head ultrasounds do not reliably predict neurodevelopmental impairment in survivors. When controlled for clinical variables and timing of the exam, only periventricular leukomalacia diagnosed closer to 36 weeks and shunt placement were significantly associated with subsequent neurodevelopmental impairment. Both the high prevalence of neurodevelopmental impairment in infants with no or minor grades of intracranial hemorrhage, and the frequent absence of severe impairment despite grade IV hemorrhage or periventricular leukomalacia, indicate that head ultrasound findings may not be as useful in predicting neurodevelopmental outcome as previously believed.

—Ronald I. Clyman, MD
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Morbidity and Mortality in Late-Preterm Infants: More than Just Transient Tachypnea!
Lucky Jain, MD, Atlanta, Georgia

Bronchodilator Response: Another Piece in the Asthma Mosaic
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Parenting Stress and Childhood Impairment
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Early Umbilical Cord Clamping Contributes to Elevated Blood Lead Levels among Infants with Higher Lead Exposure

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50 Years Ago in The Journal of Pediatrics—Medical Progress: Hyaline Membrane Disease

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Park-Based Obesity Intervention Program for Inner-City Minority Children

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Janice F. Davis, BA, and Paul Graham Fisher, MD, Palo Alto, California

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Alexandru Gaina, MD, PhD, Michikazu Sekine, MD, MSc, PhD, Shimako Hamanishi, MHPEd, Xiaoli Chen, MPH, PhD, Hongbing Wang, MD, PhD, Takashi Yamagami, MD, and Sadanobu Kagamimori, MD, PhD, Toyama, Japan

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Vladimir K. Bakalov, MD, Thomas Shawker, MD, Irene Ceniceros, BS, and Carolyn A. Bondy, MD, Bethesda, Maryland

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Metabolic Cardiomyopathy and Mitochondrial Disorders in the Pediatric Intensive Care Unit

Jason M. Kane, MD, FAAP, Janet Rossi, MD, FAAP, Sabrina Tsao, MBBS, MRCP (UK), and Barbara K. Burton, MD, FAAP, Chicago, Illinois

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Ailsa Goulding, PhD, FACN, Andrea M. Grant, MSc, Rachael W. Taylor, PhD, Sheila M. Williams, DSc, Winsome R. Parnell, PhD, Noela Wilson, PhD, and Jim Mann, DM, PhD, FRACP, Dunedin, New Zealand

Ratio of High-, Medium-, and Low-Molecular Weight Serum Adiponectin to the Total Adiponectin Value in Children

Rimei Nishimura, MD, MPH, Aya Morimoto, MD, Toru Matsudaira, MD, Yumi Miyashita, MD, Hironari Sano, MD, Takako Shirasawa, ME, Eiko Takahashi, MD, PhD, and Naoko Tajima, MD, MsHyg, Tokyo, Japan, and Pittsburgh, Pennsylvania


Anne Louise Svendsen, PhD, Maria Feychting, PhD, Lars Klaeboe, PhD, Froydis Langmark, MD, and Joachim Schütz, PhD, Copenhagen, Denmark, Stockholm, Sweden, and Oslo, Norway

INSIGHTS

Complete Vascular Ring

Shyh-Jye Chen, MD, PhD, and Kao-Lang Liu, MD, Taipei, Taiwan
Factors Influencing Capillary Refill Time
Michael Eisenhut, MD, Luton, Bedfordshire, United Kingdom

Reply
Jennifer Evans, MD, MRCP, Kumasi, Ghana

Neurologic Complications in Children Hospitalized with Influenza: Comparison Between USA and Hong Kong
Brian HY Chung, MBBS (Hons), MRCPCH, DCH, FHKAM, Anita MC Tsang, MBBS, MRCP, DCH, FHKAM, and Virginia CN Wong, MBBS, MRCP, FRCP, FRCPCH, DCH, FHKAM, FHKCPaed, Hong Kong

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Reply
Amir Kugelman, MD, Arieh Riskin, MD, and David Bader, MD, MHA, Haifa, Israel

The Importance of Avoiding Head Flexion in Preterm Infants
Shirley L. Tonkin, MBChB, Christine G. McIntosh, MBChB, and Alistair J. Gunn, MBChB, PhD, Auckland, New Zealand

Information for Readers
Announcements
Guide for Authors
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December 2007

**Hot Topics in Neonatology.** December 2-4, 2007, Omni Shoreham Hotel, Washington, DC. Sponsored by Neonatal Research and Technology Assessment, Inc. (NRTA). Premier, exciting, interactive annual conference for neonatologists from around the world. Average 1400 attendees, 25+ speakers and guest discussants. Chairman, Dr. Jerold F. Lucey, Wallace Professor of Neonatology, Burlington, Vermont, Editor-in-Chief, Pediatrics. For more information, contact Gail Murphy, Neonatal Research and Technology Assessment, Inc; phone 802-865-2283; E-mail: info@hottopics.org; Website: www.hottopics.org.

February 2008

**Lysosomal Disease Network: WORLD Symposium 2008 (We’re Organizing Research on Lysosomal Diseases).** February 13-15, 2008, University of Minnesota, The Venetian Hotel, Las Vegas, Nevada. Newborn Screening/Gaucher Disease/Fabry Disease/Mucopolysaccharidosis/Batten Disease/Pompe Disease/Mucolipidosis/Sphingolipidoses/Oligosaccharidosis. Determination of AMA credits pending. For more information: Office of Continuing Medical Education, University of Minnesota; phone: 612-626-7600 or 800-766-8636; E-mail: cme@umn.edu; Websites: www.LysosomalDiseaseNetwork.org or www.cmecourses.umn.edu.

May 2008

**9th Congress of the European Society for Pediatric Dermatology (ESPD).** May 15-17, 2008, Athens Hilton Hotel, Athens, Greece. Sponsored by The European Society for Pediatric Dermatology. For more information, contact Mrs. Penelope Mitroyianni, Erasmus Conferences Tours & Travel; phone 0030 210 7257693; E-mail: info@espd2008.com; Website: www.espd2008.com.

**2007-2008 Certifying Examinations of the American Board of Pediatrics**

111 Silver Cedar Court, Chapel Hill, NC 27514-1513 telephone: 919-929-0461 fax: 919-918-7114 or 919-929-9255 Website: www.abp.org

All applicants for certifying examinations must complete applications online during the registration periods. The final month of each registration requires payment of a late fee. The requirements for online applications may be found on the ABP Website ([www.abp.org](http://www.abp.org)) or may be obtained by contacting the ABP. Additional information including eligibility requirements and registration dates may be found on the ABP Website.
There are deep concerns about an inadequate supply of future academic pediatricians and pediatric subspecialists.\textsuperscript{1–4} It is hoped that, by better understanding the professional values that impact career choice of medical students and pediatric residents, we could more effectively address workforce shortages\textsuperscript{5,6} in pediatric subspecialties.

One of the remarkable demographic shifts in medicine over the last 2 decades has been the steady increase of female medical students and pediatric trainees.\textsuperscript{7} Yet, we know very little about the professional values of future pediatricians and whether there are significant differences in values by sex.\textsuperscript{8} The purpose of this study was to define the values of medical students in relation to medical specialty choice and sex.

**METHODOLOGY**

The study participants included recently graduated medical students registered to use the Careers in Medicine (CiM) Web site, operated by the Association of American Medical Colleges (AAMC).\textsuperscript{9} CiM is a comprehensive career planning program available to students from all U.S. and Canadian medical schools. The site contains online career assessment resources and specialty information to help medical students choose their residency. The participants selected for this study had been in residency training for 2 years or less.

The Physician Values in Practice Scale (PVIPS) is a measure of personal values related to the practice of medicine.\textsuperscript{8} This 35-item inventory was developed for and validated on medical students from U.S. medical schools. The PVIPS helps students identify what is most important to them about being a physician and which aspects of the profession they find the most personally satisfying. It measures 6 important values: Prestige (the desire to be recognized by others as a top physician), Service (the desire to care for others regardless of financial gains or other rewards), Autonomy (the importance of freedom, independence, and control over clinical decision making), Lifestyle (a desire for a predictable and stable work schedule), Management (the desire to supervise and have responsibility for others), and Scholarly Pursuits (the desire to engage in clinical or basic research and scholarship activities, academic medicine, and teaching).

The PVIPS reports reliability estimates ranging from .77 to .88 with an overall Cronbach’s alpha coefficient of .83.\textsuperscript{10} Each question begins with the statement “In my medical career it will be important that I . . . .” The questions are rated using a Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). The PVIPS is administered online as part of the CiM career planning service of the AAMC.

The PVIPS results were obtained from the CiM Web site for medical students who had completed the survey before graduation and begun residency training within the previous 2 years. The participants were assigned to 1 of 2 groups on the basis of area of specialization chosen. Because the AAMC tracks residency choice in a number of medical disciplines (including pediatrics), students who selected pediatrics were assigned to 1 group, and “all other” students were assigned to the second group consisting of the remaining residencies (psychiatry, surgery, obstetrics-gynecology, internal medicine, and family medicine). Demographic data were collected from both groups.

**ANALYSIS**

Two multivariate analyses of variance were conducted to assess differences between the pediatrics resident group and the “all other” group, followed by an analysis of differences between male and female pediatric students who entered pediatric residency.

**RESULTS**

Of the 3328 residents in the study (45% male and 55% female), 350 (10.5%) belonged to the pediatrics group, and 2978 (89.5%) were assigned to the “all other” group. As shown in the Table (available at www.jpeds.com), pediatrics residents scored significantly higher than other residents on Service, and lower on Autonomy, Management, and Prestige. No differences were found between these groups in the Lifestyle and Scholarly Pursuits categories.

In the second analysis, we examined sex differences in the values...
of residents belonging to the pediatrics group and the “all other” group. The pediatrics group yielded a total of 350 participants, with 27% men and 73% women, and the “all other” group was comprised of 47% men and 53% women. Among future pediatricians, significant differences were found between men and women on all values except Management, with men scoring higher on the values of Autonomy, Prestige, and Scholarly Pursuits, and women scoring significantly higher on Lifestyle and Service (Figure 1; available at www.jpeds.com). The largest variation in values between sexes was found in Scholarly Pursuits. Among the “all other” group, significant differences were found between men and women on all values except Lifestyle, with men scoring higher on the values of Autonomy, Management, Prestige, and Scholarly Pursuits, and women scoring significantly higher on Service (Figure 2; available at www.jpeds.com). Women in both the pediatrics group and the “all other” group value Service to a greater extent than their male counterparts. Furthermore, both groups of female trainees place significantly lower emphasis on the value of Scholarly Pursuits as compared with male trainees. However, in the pediatrics group, women scored significantly higher than men on Lifestyle, even though there was not a statistically significant difference between men and women from the “all other” group on the value of Lifestyle.

**DISCUSSION**

Our study examined values in medical students in relation to medical specialty choice and sex. Although our sample size of medical students choosing pediatrics was relatively small and could have introduced bias to the analyses, it was representative of the relative number of women in pediatrics training programs (73% of respondents were women vs 70% of pediatric residents were women in 2002). The analyses of values data by career choice and sex uncovered highly significant differences discussed below.

Autonomy was the top-ranked value overall among medical students. Although women in pediatrics placed somewhat lower importance on Autonomy relative to male counterparts, medical professionals clearly value their freedom, independence, and control over clinical decision making.

After Autonomy, the values of Service and Lifestyle were most important to male and female respondents from both groups. Students selecting pediatrics training placed significantly higher value on Service, that is the desire to care for others regardless of financial gains or other rewards, and women rated it significantly more important than men. Although lifestyle was regarded highly by all residents, regardless of specialty, women in the pediatrics group rated it significantly higher than men in pediatrics. These data are consistent with the view that women may be somewhat more conflicted with the responsibility of being a physician and the future added responsibility of starting a family. Moreover, pediatrics trainees did not think that the desire to be recognized by others as a top physician (Prestige) was as important as trainees in other disciplines.

It is perhaps not surprising that Management issues were of least importance across the board, given that undergraduate medical education and residency training generally do not devote substantial attention to the intricacies of healthcare business. However, in view of the importance of such concerns in all specialties, it would be appropriate for newly graduating physicians, including pediatricians, to be concerned about these issues. Experienced practitioners who have entered private practice or group practice with no training in management have had to learn the hard way how to run a business, hire and fire, and work several days a week to support the office overhead before they start earning for themselves.

Although most medical students have been taught primarily in academic settings and are continually exposed to scholarship, they ranked Scholarly Pursuits second to last overall and third among students entering pediatrics residency. These findings are of concern in regard to the trend for academic medicine and academic pediatrics, particularly among female trainees. It may be that current role models underestimate the importance of scholarship in academic environments that stress clinical quotas over publications. The low numbers of women in academic leadership roles also confounds the perceptions of our students, especially among female students. Additional research is needed to better understand why scholarship is so relatively unimportant to students, particularly among women who have selected pediatrics as careers. In addition, because candidates for all pediatric subspecialty training may be increasingly female, the lower value for Scholarly Pursuits may have significant workforce implications for the future of academic pediatrics.

One proposed strategy to enhance the value of scholarship might be to link scholarly activities more closely with high-ranked values such as Autonomy, Lifestyle, and Service. Mentors may be most effective as role models by demonstrating a passion for their work and connectivity between autonomy and scholarship, for example. The national emphasis on enhancing clinical and translational research creates a platform for mentors to demonstrate how patient care (Service) is inextricably linked to science (Scholarly Pursuits) by moving discoveries from the bench to the clinic, and then to the community. Evidence suggests that physicians entering academic medicine with mentors are more likely to have productive careers in research in addition to reporting an overall higher level of career satisfaction. With the guidance of a mentor, perhaps medical students entering pediatrics training programs can realize the rewards of conducting research and publishing studies in peer-reviewed journals. The ability to convey compassion and be an excellent teacher in academic pediatrics may be increasingly important to getting the attention of promising young investigators who may desire a more predictable and stable work schedule than previous generations of trainees.

**NEX T STEPS**

The focus of this report has been on values and sex, with emphasis on differences in students who select pediatrics careers. It is important to note that the duty to nurture new pediatricians rests primarily with Silent (born before 1946), Baby Boomer (born 1946-1964), and Generation X (born 1964-1980) mentors and advisors, who may have significantly different values than the medical students. These generational differences must be characterized, acknowledged, and understood to foster career development of the next generation of pediatricians and to address workforce shortages in pediatric neurology and other disciplines.


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The authors would like to thank Dr. John B. Molidor from Michigan State University for bringing awareness to generational differences in values and Dr. Paul J. Hartung from Northeastern Ohio Universities College of Medicine for encouraging use of the Physician Values in Practice Scale in the study.

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Table. Mean PVIPS Scale scores, pediatrics residents vs all other residents

<table>
<thead>
<tr>
<th></th>
<th>Pediatrics residents*</th>
<th>All other residents†</th>
<th>Total‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomy§</td>
<td>3.69 ± 0.43</td>
<td>3.8 ± 0.44</td>
<td>3.79 ± 0.44</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>3.42 ± 0.76</td>
<td>3.41 ± 0.83</td>
<td>3.41 ± 0.83</td>
</tr>
<tr>
<td>Management</td>
<td>2.5 ± 0.62</td>
<td>2.58 ± 0.63</td>
<td>2.57 ± 0.63</td>
</tr>
<tr>
<td>Prestige§</td>
<td>2.89 ± 0.65</td>
<td>3.17 ± 0.67</td>
<td>3.14 ± 0.68</td>
</tr>
<tr>
<td>Scholarly Pursuits</td>
<td>2.57 ± 0.85</td>
<td>2.66 ± 0.86</td>
<td>2.65 ± 0.86</td>
</tr>
<tr>
<td>Service§</td>
<td>3.57 ± 0.58</td>
<td>3.36 ± 0.62</td>
<td>3.38 ± 0.62</td>
</tr>
</tbody>
</table>

Values by residency choice.
§Denotes values that were significantly different between groups. Autonomy (F = 10.410, df = 1, P < .001) and Prestige (F = 34.551, df = 1, P < .001) were significantly less important, whereas Service (F = 22.747, df = 1, P < .001) was significantly more important to future pediatricians.
* n = 350.
† n = 2978.
‡ n = 3328.

Figure 1. Values of students training in pediatrics. Comparing average PVIPS scale scores by gender shows statistically significant differences in values of Autonomy (P < .05), Lifestyle (P < .05), Prestige (P < .05), Scholarly Pursuits (P < .001), and Service (P < .05). Values in which significant differences were found, men tended to score higher than women on Autonomy, Prestige, and Scholarly Pursuits, although women scored higher on Lifestyle and Service. — , male; — , female.

Figure 2. Values of students training in all residencies excluding pediatrics. Comparing average PVIPS scale scores by gender shows statistically significant differences in values of Autonomy (P < .001), Management (P < .001), Prestige (P < .001), Scholarly Pursuits (P < .01), and Service (P < .001). Values in which significant differences were found, men tended to score higher than women on Autonomy, Management, Prestige, and Scholarly Pursuits, although women scored higher on Service. — , male; — , female.
Morbidity and Mortality in Late-Preterm Infants: More than Just Transient Tachypnea!

Concern about higher morbidity in late-preterm (34\(\frac{0}{7}\) to 36\(\frac{6}{7}\) weeks) infants has led to a flurry of recent publications with largely the same conclusions: late-preterm infants are more prone to problems related to delayed transition and overall immaturity, and they should therefore be treated differently than their more mature term counterparts.\(^{1-5}\) These observations have led to greater attention being paid to tracking short-term morbidity, healthcare costs, hospital stays, and issues such as re-hospitalization.\(^{5}\) However, widespread publicity has yet to make a measurable impact on the incidence of late prematurity; nearly 3 out of 4 preterm births occur at late-preterm gestations and this number is on the rise.\(^{6}\) It is estimated that nearly 250,000 late-preterm births occurred in the US in 2004; and although the problem appears to be widespread, similar estimates from other nations are not readily available.

A broad range of neonatal complications has been documented in the growing body of literature on late-preterm infants. These problems include delayed lung fluid clearance (transient tachypnea of the newborn), respiratory distress syndrome, pulmonary hypertension, apnea, temperature instability, hypoglycemia, jaundice, and poor feeding.\(^{6}\) Little, however, is known about the long-term impact of these “transitional issues” because there are no data repositories with information about outcomes, and, in spite of growing concern about the vulnerability of the late-preterm brain to white matter injury, systematic developmental assessments are seldom performed.

These publications notwithstanding, the obstetric community is yet to fully embrace the public health impact of late prematurity. Late-preterm infants are considered functionally mature (hence the widespread use of the “near term” label), and there is a relative lack of attention to neonatal considerations when delivery at these gestations is being contemplated. Although women in preterm labor at gestations 33 weeks and less are routinely considered for tocolysis and antenatal steroids, they are candidates for neither if gestation has advanced by a few days and crosses over to the magic 34-week mark. These decisions appear oblivious to the fact that inaccuracies in the estimation of gestational age abound, and up to 50% of infants at 34 weeks gestation may require intensive care.\(^{1}\)

What then will it take to drive a concerted effort to tackle this problem? A good starting point will be the availability of reliable data about short- and long-term outcome of late-preterm infants and documentation of serious morbidity that could dispel the myth of the “transient” nature of late-preterm woes. Recent reports about the occurrence of serious complications such as hypoxic respiratory failure and kernicterus are good first steps, and compilation of accurate mortality statistics would be another.\(^{2,7}\) In this issue of The Journal, Tomashek et al\(^{8}\) attempt to close the gap in our understanding of differences in mortality between late-preterm and term infants. Using period linked birth-infant death files from 1995 to 2002, the authors analyzed overall and cause-specific mortality rates for singleton late-preterm and term infants. The authors report that although significant declines in mortality were observed over the last decade for both groups of infants, the infant mortality rate for late-preterm infants was several-fold higher than that for term infants. Late-preterm infants were particularly more likely to die in the early neonatal period compared with term infants from causes such as respiratory compromise, maternal complications of pregnancy, and congenital anomalies.

The report by Tomashek et al is being highlighted for several reasons. First, although their data clearly demonstrate a higher mortality burden related to birth at late-preterm gestations, the magnitude of the reported difference is particularly striking. Problems associated with the use of large databases such as the one used by the authors notwithstanding, the low frequency of death in term and near-term infants precludes other methodological approaches including the use of smaller (but more detailed) local data sources for such analyses. This report underscores the need for prospective data collection to confirm the overall excess in mortality—information that is critical for affecting a change in allocation of resources and for an overall change in our approach to these neonates.

Second, this work sheds new light on the causes of death in late-preterm infants. For example, the reported high occurrence of congenital anomalies in late-preterm infants raises several questions that need to be addressed in future studies. Are fetuses with serious congenital anomalies more likely to be delivered early either spontaneously or electively, given the widespread practice of “controlled” delivery of an anomalous fetus? Does prematurity and...
lack of spontaneous labor add to the risk of death in infants with congenital anomalies? Are late-preterm infants at higher risk of death if infants with congenital anomalies are excluded? To address the last issue, the authors performed additional analysis of their data after excluding infants with any congenital malformation, deformation, or chromosomal abnormality (ICD-10Q00-99) as the underlying cause of death. The differences in infant mortality between late-preterm and term infants were found to persist even with these exclusions, underscoring the inherent vulnerability of the late-preterm infant to serious morbidity and death.

There are several limitations to the methodology used and, as such, to any conclusions drawn from data linked to death certificates.8 Death certificates lack information about contributing causes of death that could shed more light on diagnostic categories such as “atelectasis.” Autopsy findings were also not available to ascertain diagnoses such as sudden infant death syndrome (SIDS). Finally, data reported on gestational age may be subject to misclassification, although, as the authors argue, such errors should impact both subgroups included in the analysis. However, the hypothesis generated by these data that now needs further testing is straightforward: Are late-preterm infants at higher risk for death than their term counterparts, and, if so, why?

Overall, it should come as no surprise that the higher morbidity reported in late-preterm infants may be associated with an increase in mortality as well. What is surprising is the magnitude of the difference in death rates between late-preterm and term infants, given the perception of mild and transient nature of these problems. The findings should also foster debate around the rationale for preterm delivery, particularly when the decision to do so is based on soft indications. Although the data provide no direct link to the widespread practice of induction of labor and/or elective cesarean sections, it raises questions about the recent rise in such practices, particularly in the face of uncertainty in accurate estimation of gestational age. As such, future occurrences of serious morbidity/death in electively delivered late-preterm infants where a clear indication for early delivery is lacking should call for a thorough peer review of the circumstances around delivery and the subsequent care of the neonate. Finally, there is an urgent need to study the role of strategies to enhance maturity of the late-preterm fetus, such as the use of antenatal steroids. Given the large number of deliveries at late-preterm gestations, the public health impact of such preventive strategies could be enormous.

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Bronchodilator Response: Another Piece in the Asthma Mosaic

C onsidering that it is such a common disease, the diagnosis and severity classification of asthma is extraordinarily difficult. Gross put it well: “It’s like love, we all know what it is, but who would trust anybody else’s definition?”1 The National Asthma Education and Prevention Program (NAEPP) guidelines suggest the diagnosis of asthma should be in large part based upon the medical history and physical examination.2 However, these guidelines rightly go on to point out that “patients with asthma are heterogeneous and present signs and symptoms that vary widely from patient to patient as well as within each patient over time.” Subtle variations in the interpretation of an individual patient’s signs and symptoms may greatly influence not only whether the diagnosis of asthma is made, but also affect the aggressiveness of the ensuing treatment. Thus, we can think of asthma as a complex mosaic, with the history and exam as only two tiles in a much larger diagnostic picture.

Bronchodilator response
Forced expiratory volume in 1 second
National Asthma Education and Prevention Program
Peak expiratory flow rate

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In order to provide more objective diagnostic criteria, the NAEPB guidelines advise routine use of spirometry to aid in the diagnosis of asthma. Indeed, the three facets of history, exam and low baseline forced expiratory volume in 1 second (FEV1) remain the standard for diagnosing asthma in adults. However, in children there are convincing data showing that baseline FEV1 is not a good measure of the presence of asthma or its severity.

In the Childhood Asthma Management Program study, which evaluated 1041 children with mild to moderate asthma, more than 50% of the patients had moderate persistent asthma as defined by frequency of symptoms. Asthma was well documented in these patients over the 5-year life of the study, yet the prebronchodilator FEV1 at the start of the study was clearly normal at 94% of predicted.

A much quoted paper by Fuhlbrigge et al4 found those children with FEV1 values of <60% predicted had a 70% likelihood of having an asthma exacerbation in the following year. In those with FEV1 values >80%, the likelihood of experiencing an exacerbation was reduced to 25% to 30%. These data have been interpreted as showing that attacks can be predicted based on percent predicted FEV1. Yet it is perhaps more important to note that 94% of the FEV1 values in this population of asthmatic children were normal, meaning that 80% of asthma attacks occurred in children with a normal baseline FEV1. The limits of using FEV1 alone in the assessment of childhood asthma were also demonstrated by Bacharier et al5 who found a lack of association among asthma symptom severity, intensity of medication therapy, and percent predicted FEV1 in asthmatic children.

Bronchial lability may be a more useful measure in the diagnosis of childhood asthma. Proving the existence of airway hyperreactivity in the context of clinical symptoms begins to add more details to our asthma mosaic. This is not a new concept. Exaggerated bronchodilation followed by bronchoconstriction in response to exercise—the so-called “bronchial lability index”—was described in asthmatic children by Jones.6 This and other early studies observed that pediatric asthmatic airways are remarkably labile in both directions when appropriately stimulated.

The study by Gallant et al7 published in this issue of The Journal shows that detecting broncholability by measuring the response to an inhaled bronchodilator can aid in the diagnosis of asthma in children. The authors demonstrate that using 9% as a distinct cutoff value for improvement in FEV1 after inhaled albuterol (either 180 μg by metered dose inhaler or 2.5 mg by nebulizer) can distinguish a group of known asthmatic children from those who are normal by history.

The findings of Gallant et al support the earlier study by Dundas et al8 that determined that a 9% cutoff for the bronchodilator response (BDR) to 400 μg of salbutamol (albuterol) provided the greatest balance between sensitivity and specificity in separating wheezers from nonwheezers in a group of London schoolchildren (race not described). However as stated by Dundas et al, the diagnostic value of a 9% BDR cutoff will vary with the prevalence of wheezing in the study population. Gallant et al studied a group of clinically diagnosed asthmatic children with a presumed incidence of wheezing of 100%. This exaggerated the difference between this study group and the comparator group to some degree. As a diagnostic test, BDR will be used in populations in which the incidence of wheezing may be much lower and the distinction between asthmatics and nonasthmatics is less clear. Without a prospective assessment of the 9% BDR cutoff value in an unselected cohort of subjects, the findings of Gallant et al still leave us several steps away from implementing BDR as a diagnostic test for asthma.

Although the ethnic composition of Gallant et al’s population is described as primarily Hispanic, the racial composition is not fully described. As recognized by the authors, extrapolating the 9% BDR cutoff to similarly aged African-American, Caucasian, or mixed populations is difficult, especially in light of the fact that different genetic groups respond to bronchodilator medications differently.9 The diagnostic BDR cutoff point certainly may be lower in children with less sensitivity to beta-agonist medications than the general population.

The effect of baseline lung function on BDR measurement also must be considered, as Gallant et al acknowledge. This relationship was described by Sly10 who noted that the greatest percent increase in peak expiratory flow rate (PEFR) with treadmill exercise was seen in those asthmatic children with the lowest baseline PEFR. Where a child stands in relation to his or her maximum lung function on the day of testing will contribute to his or her ability to respond. A child already at his or her personal maximum for FEV1 would not exhibit a response to a bronchodilator even if he or she were asthmatic. In a disease as variable as asthma, this may prove a difficult hurdle to cross to use BDR as a diagnostic criterion.

The present study used 2 distinct methods of delivering the albuterol medication—some subjects used a metered dose inhaler, whereas others received the medication via wet nebulization. Although the quantitative difference in medication delivery between these 2 methods of medication administration may be small, the effect on BDR is not known. Using a single delivery method may have resulted in different outcomes. The dose and mode of delivery of beta-agonists are likely to play some role in the degree of observed bronchodilation and will need to be standardized to make this a clinically helpful test.

Gallant et al have presented a very sound idea for helping pediatric clinicians diagnose asthma. They have shown that BDR distinguishes between asthmatics and nonasthmatics better than baseline FEV1 alone, and that a combination of a high BDR and a low FEV1 is best for discriminating asthmatics from nonasthmatics (although these characteristics may be linked). Finally, and perhaps most importantly, they have demonstrated another way in which lung function testing can be helpful in the difficult process of diagnosing and managing asthma in children. Spirometric evaluation is relatively simple to perform in many preschool-age and nearly all school-age children.11 We believe that with further study, BDR testing will prove to be an important tool in our efforts to complete the asthma mosaic.
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Parenting Stress and Childhood Impairment

As neonatal intensive care has evolved, mortality and serious morbidity in survivors were the initial concerns and remain issues still today for those children born at borderline viability. It was also recognized that children who survive without major morbidities still have a wide variety of high frequency but less-severe impairments of cognitive, behavioral, and motor function. More recently, we have become equally concerned that simply measuring performance against normative data or comparison children born at term may give a fallacious view of outcome that is unnecessarily over-pessimistic. Recent studies have concerned outcomes for children and their families in functional terms that reflect the impact that these impairments have on day-to-day life. This in turn may affect our own perceptions of these conditions.

There is little doubt that taking home a child who has been through the whole panoply of neonatal intensive care after very preterm delivery is a daunting task, even to well-adapted mothers. The stress may be enhanced when there is evolving disability and will persist when there is serious childhood impairment. In this issue of The Journal, 2 groups report studies of parenting stress and wellbeing in children with or at high risk of childhood impairment and their families.

Majnemer et al report a study of the factors that determine quality of life in school age children with cerebral palsy. The risk of this condition is often used to guide intensive care decisions, and thus it is valuable to detail what impact the associated disability has on the child or family and which factors determine the extent of this impact. This group of children was thought to be representative of a complete population of children with cerebral palsy from the case list of 1 pediatric neurologist (and comprised a high proportion of preterm children), but the associated motor deficit was classed as mild (GMFCS level 1) in nearly half the children, half were attending mainstream school, and only 28% had IQ scores >2 SD below the mean. This is far from the commonly held outcome when a diagnosis of cerebral palsy is first broached with parents. The questionnaires used give a broad view of function in a wide range of dimensions for child and family. In particular, physical wellbeing might be easily predicted from the degree of limitation of activity (and is reassuringly well assessed with the simple gross motor function classification system), but psychosocial wellbeing was more dependent on associated behavioral problems, an area which might be amenable to modification and thus enhance quality of life.

Notable among the measures that they report is the observation that parenting stress was high in nearly half of the families. Alongside this paper is a report from a longitudinal study of maternal stress and coping for families after very low birthweight (VLBW) infants are born from Singer et al. They observed 3 groups of children from birth: “high risk” VLBW children with chronic lung disease, “low risk” VLBW children, and term comparators. This is an important study because it charts the evolution of family environment from birth. It presents a mixed picture—mothers of VLBW children reported fewer family strains than the comparator group and less parent-child conflict, but perceived more concern for their child’s health state and more
personal strain. The study was somewhat confounded by the additional stress of having multiple birth and the increase in parenting stress associated with a low IQ in the child, which was more common in the VLBW group and more so in the “high risk” group. The authors do not tell us how many of these children had cerebral palsy. Furthermore, the mothers of the “high-risk” VLBW children had made positive adaptation from the earlier assessment at 2 years postpartum.

We have recently attempted to support maternal coping strategies and relieve maternal stress in families with very preterm babies by using a targeted nurse-led intervention during the neonatal stay and during the period of transition to home. Sadly, and despite a moderately intensive intervention, we were unable to demonstrate significant benefit in parenting stress at 3 months post-term age. The stresses and stressors are maximal in the periods closest to birth when uncertainty is greatest, particularly as the parent adapts to the child’s homecoming, but are easily measurable at 3 years out, as Singer et al have shown. In this period, however, they demonstrated that adaptive mechanisms came into play; although stress scores remained high, coping strategies improved. In middle childhood, this period of adaptation continues.

Although a range of interventions are targeted at maternal stress during the period of intensive care, it is often difficult to know whether they produce lasting benefits after the period of intervention. It is clear that further studies are necessary to define what makes a good support strategy after preterm birth. A systematic review of studies that attempted to influence maternal sensitivity and attachment has arrived at the counter-intuitive conclusion that relatively infrequent interventions commencing later in the first year seem to be more effective than earlier, more intense interventions.

We still have a lot to learn about the key goal of relieving parenting stress—this could be 1 route by which we might enhance the outcome of this vulnerable group of children—but it is also clear from these papers that disability and non-optimal childhood outcomes, which are an ever present feature of outcome after very preterm birth, are important determinants of parenting stress despite the impressive adaptation that occurs during early childhood.

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REFERENCES

Differences in Mortality between Late-Preterm and Term Singleton Infants in the United States, 1995–2002

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Objective  To assess differences in mortality between late-preterm (34-36 weeks) and term (37-41 weeks) infants.

Study design  We used US period-linked birth/infant death files for 1995 to 2002 to compare overall and cause-specific early-neonatal, late-neonatal, postneonatal, and infant mortality rates between singleton late-preterm infants and term infants.

Results  Significant declines in mortality rates were observed for late-preterm and term infants at all age-at-death categories, except the late-neonatal period. Despite the decline in rates since 1995, infant mortality rates in 2002 were 3 times higher in late-preterm infants than term infants (7.9 versus 2.4 deaths per 1000 live births); early, late, and postneonatal rates were 6, 3, and 2 times higher, respectively. During infancy, late-preterm infants were approximately 4 times more likely than term infants to die of congenital malformations (leading cause), newborn bacterial sepsis, and complications of placenta, cord, and membranes. Early-neonatal cause-specific mortality rates were most disparate, especially deaths caused by atelectasis, maternal complications of pregnancy, and congenital malformations.

Conclusions  Late-preterm infants have higher mortality rates than term infants throughout infancy. Our findings may be used to guide obstetrical and pediatric decision-making. (J Pediatr 2007;151:450-6)

The rate of preterm birth (<37 weeks’ gestation) has increased >30% in the United States since the early 1980s. More recent increases in preterm birth may be explained in part by an increase in late-preterm births (34-36 completed weeks’ gestation). From 1990 to 2004, the percentage of all births that were late-preterm increased 22%, from 7.3% to 8.9% (Figure; available at www.jpeds.com). In 2004, late-preterm births accounted for 71% of all preterm births, up from 69% in 1990. Some of the increase in late-preterm births likely is caused by changes in obstetric practice, such as more frequent labor induction and use of cesarean delivery before 37 weeks gestation in women at high risk for adverse pregnancy outcomes. These practice decisions are made after considering the fetal, maternal, and infant risks associated with preterm delivery. Clinical decisions may be driven, in part, by the perception that late-preterm infants are at no greater risk for morbidity and mortality than are term infants (37-41 weeks’ gestation). Although this has not been proven, a detailed assessment of mortality comparing late-preterm infants with term infants could help inform clinical decision-making.

Late-preterm infants experience a higher incidence of respiratory distress syndrome, apnea, transient tachypnea of the newborn, hypoglycemia, hypothermia, hyperbilirubinemia, and feeding difficulties when compared with infants born at term. Studies have also found that late-preterm infants have longer hospital stays when admitted to the neonatal intensive care unit and higher hospital costs. Most of these studies were small hospital-based analyses that, because of their limited sample size, were unable to assess severe morbidity resulting in death. One US and 1 Canadian study examined the risk of mortality in late-preterm infants versus term infants using data from before 1995. Both studies demonstrated that late-preterm infants are at greater risk of dying before their first birthday than are term infants. Neither study, however, used the system for classifying leading causes of death used by the National Center for Health Statistics

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the affiliated agencies.

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ICD  International Classification of Diseases
LMP  Last normal menstrual period
NCHS  National Center for Health Statistics
SIDS  Sudden Infant Death Syndrome
(NCHS) to examine differences in the leading causes of mortality by age at time of death and the ranking of these causes. A more recent analysis of all infant deaths from Utah found similar results, but also demonstrated that the risk of infant death decreased significantly from 34 to 36 weeks gestation.

The objective of this study was to compare trends and differences in overall US mortality rates by age at time of death (ie, during infancy and the early-neonatal, late-neonatal, and postneonatal period) between late-preterm and term singleton infants. To gain a better understanding of the underlying causes of death for these 2 groups of infants, we used the National Center for Health Statistics’ (NCHS) leading cause of death classification system to examine differences in cause-specific mortality rates by age at death and the ranking of the leading causes of death.

METHODS

We used the US period-linked birth/infant death data for 1995 to 2002 to compare trends and differences in overall mortality rates by age at time of death between singleton late-preterm infants and term infants born to residents of the 50 states and the District of Columbia. We used aggregated 2000 to 2002 data to compare the differences in cause-specific mortality rates by age at time of death and the ranking of the leading causes of death in these groups. The period-linked data file, compiled by the NCHS, consists of all infants who died in a particular year regardless of whether their birth was in the same year or the preceding year. Infant death certificates are linked to the corresponding birth certificates with a >97% linkage rate during the study period. NCHS applies a weight to the data file to account for deaths that could not be linked.

Late-preterm infants were defined as infants born between 34-0/7 and 36-6/7 weeks gestation, and term infants were defined as infants born between 37-0/7 and 41-6/7 weeks gestation. Gestational age in the period-linked file was reported in completed weeks of gestation and was calculated by NCHS. For most infants, gestational age was calculated by using the interval between the first day of the mother’s last normal menstrual period (LMP) and the infant’s date of birth, as reported on the birth certificate. If only the month and year of the LMP were available, NCHS imputed gestational age by assigning the weeks of gestation of the previous completed record in the file with a similar race and birth weight. In cases in which the month, year, or entire LMP is missing or is inconsistent with reported birth weight, the clinical estimate of gestation is used. This occurred in approximately 5% of cases. When neither LMP nor the clinical estimate of gestation could be used, the gestational age was reported as missing. During the study years 1995 to 2002, only 3% of singleton infant deaths were missing gestational age data.

To calculate overall mortality rates by age at death, we used data from 1995 to 2002. During this period, there were 30,732,957 singleton live births in the United States; 30,419,290 infants (99.0%) had gestational age data reported. Of these infants, 2,221,545 (7.3%) were born late-preterm and 24,973,117 (82.1%) were born at term. Overall infant mortality rates were calculated by age at time of death and were defined as infant deaths in a given year divided by the live births in that same year, multiplied by 1000. Early-neonatal deaths were between 0 and 6 days of life; late-neonatal deaths were between 7 and 27 days; and postneonatal deaths were between 28 and 364 days. Infant deaths were all those between 0 and 364 days of life.

To calculate more stable estimates of cause-specific mortality rates, we aggregated 3 years of data, choosing 2000 to 2002 for this study. This period corresponded to the year after the change from International Classification of Diseases, Ninth Revision (ICD-9) to ICD-10 took place and 1 year before the introduction of the newly revised US birth certificate. During these years, there were 11,719,205 singleton live births in the United States, and 11,598,521 of these had gestational age data reported. Of the singleton births with reported gestational age, 871,608 (7.5%) were late-preterm and 9,573,950 (82.5%) were term.

Rates for specific causes of death were defined as the number of infant deaths in 2000 to 2002 divided by the number of live births in these years, multiplied by 100,000. Cause-of-death data were derived from the underlying cause-of-death reported by physicians, medical examiners, or coroners on the death certificate and as coded and defined by ICD-10. Final underlying cause-of-death data depends not only on the coding, but also on how conditions are reported by the certifier. Infant deaths were assigned 1 of 71 rankable causes as defined by NCHS. For the 10 leading causes of death in each age-at-death category, the ratio between late-preterm and term mortality rates was calculated.

All data analyses were conducted with SPSS software version 12.0.1 (SPSS, Chicago, IL). Statistical testing of differences in the rates with time was performed by applying the chi-squared test of linear trends in proportions by using StatCalc software from EpiInfo Version 6. Statistical significance was set a priori at a P value < .01.

RESULTS

Infant Mortality

Between 1995 and 2002, 187,830 singleton infants died before their first birthday; 18,484 (9.8%) were late-preterm infants, and 67,197 (35.8%) were term infants. Overall infant mortality rates for both late-preterm (by 16.8%, P < .01) and term infants (by 20.0%, P < .01) declined significantly from 1995 to 2002 (Table I). Throughout the study period, overall infant mortality rates were approximately 3 times higher in late-preterm infants than term infants.

From 2000 to 2002, there were 68,697 singleton infant deaths; 6840 (10%) were late-preterm infants, and 23,956 (34.9%) were term infants. Cause-specific infant mortality rates were 1.8 to 4.5 times higher in late-preterm infants than term infants during the 2000 to 2002 period (Table I). The 5 leading causes of infant mortality for late-preterm and term
infants were congenital malformations, sudden infant death syndrome (SIDS), accidents, diseases of the circulatory system, and intrauterine hypoxia and birth asphyxia (Table I). These 5 causes accounted for 66% of all deaths in late-preterm and term infants. Death caused by congenital malformations accounted for 42% and 31% of deaths for late-preterm infants and term infants, respectively. During infancy, late-preterm infants were approximately 4 times more likely than term infants to die of newborn bacterial sepsis (11.2 versus 2.6 deaths per 100,000 live births), congenital malformations (332.6 versus 77.1), and complications of placenta, cord, and membranes (10.7 versus 2.4).

Early-Neonatal Mortality

More than one-third (38%) of all infant deaths among late-preterm infants occurred during the early-neonatal period (the comparable result was 22% for term infants). Between 1995 and 2002, rates of overall early-neonatal mortality declined significantly in both late-preterm infants (by 22.2%, \( P < .01 \)) and term infants (by 28.6%, \( P < .01 \); Table II). Despite this decline, in 2002, late-preterm infants were still nearly 6 times more likely than term infants to die during their first week of life (2.8 versus 0.5 deaths per 100,000 live births), congenital malformations (332.6 versus 77.1), and complications of placenta, cord, and membranes (10.7 versus 2.4).

Late-Neonatal Mortality

The overall late-neonatal mortality rate for late-preterm infants did not change significantly between 1995 and 2002 (Table III). Although the change in the rate in term infants was statistically significant, the rate on the basis of 1 decimal place remained the same during the study period. The statistical difference is an artifact of the size of the database, and the finding is not meaningful. The overall late-neonatal mortality rates were 3 times higher in late-preterm infants than in term infants throughout the study period.

Cause-specific late-neonatal mortality rates were 1.5 to 9.6 times higher in late-preterm than term infants (Table III). From 7 to 27 days after birth, congenital malformations and SIDS were the 2 leading causes of death for both late-preterm and term infants. Late-preterm neonates were nearly 19 times more likely than term infants to die of atelectasis (9.4 versus 0.5 deaths per 100,000 live births), 10 times more likely to die of maternal pregnancy complications (6.2 versus 0.6), and 6 times more likely to die of congenital malformations (188.3 versus 29.5). Hydrops fetalis, disorders related to short gestation and low birth weight, and respiratory distress of the newborn were other important causes of early-neonatal death among late-preterm infants, but they were not leading causes in term infants.

<table>
<thead>
<tr>
<th>Cause of death at 0 to 364 days</th>
<th>ICD-10</th>
<th>Late-preterm infants</th>
<th>Term infants†</th>
<th>Ratio‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>Q00-99</td>
<td>2,899 332.6 1</td>
<td>7,386 77.1 1</td>
<td>4.3</td>
</tr>
<tr>
<td>SIDS</td>
<td>R95</td>
<td>865 99.2 2</td>
<td>4,716 49.3 2</td>
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<tr>
<td>Accidents (unintentional injuries)</td>
<td>V01-X59</td>
<td>327 37.6 3</td>
<td>1,958 20.5 3</td>
<td>1.8</td>
</tr>
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<td>Diseases of the circulatory system</td>
<td>I00-99</td>
<td>213 24.5 4</td>
<td>986 10.3 4</td>
<td>2.4</td>
</tr>
<tr>
<td>Intrauterine hypoxia and birth asphyxia</td>
<td>P20-21</td>
<td>147 16.8 5</td>
<td>682 7.1 5</td>
<td>2.4</td>
</tr>
<tr>
<td>Influenza and pneumonia</td>
<td>J10-18</td>
<td>107 12.2 6</td>
<td>431 4.5 7</td>
<td>2.7</td>
</tr>
<tr>
<td>Assault (homicide)</td>
<td>X85-Y09</td>
<td>100 11.5 7</td>
<td>600 6.3 6</td>
<td>1.8</td>
</tr>
<tr>
<td>Bacterial sepsis of newborn</td>
<td>P36</td>
<td>98 11.2 8</td>
<td>250 2.6 9</td>
<td>4.3</td>
</tr>
<tr>
<td>Newborn affected by complications of placenta, cord, and membranes</td>
<td>P02</td>
<td>93 10.7 9</td>
<td>234 2.4 10</td>
<td>4.5</td>
</tr>
<tr>
<td>Atelectasis</td>
<td>P28.0-28.1</td>
<td>88 10.1 10</td>
<td>68 0.7 24</td>
<td>14.4</td>
</tr>
</tbody>
</table>

Table I. Infant (0-364 days) mortality


<table>
<thead>
<tr>
<th></th>
<th>Late-preterm infants</th>
<th>Term infants†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>IMR</td>
</tr>
<tr>
<td>Late-preterm infants</td>
<td>2,899</td>
<td>332.6</td>
</tr>
<tr>
<td>Term infants</td>
<td>7,386</td>
<td>77.1</td>
</tr>
</tbody>
</table>

IMR, Infant mortality rate.

*Cause-specific infant mortality rates are the number of deaths in children aged 0 to 364 days per 100,000 live births for a specific cause of death. Leading causes were defined according to methodology used by the NCHS (see Methods section for more information).

†Septicemia (A40-41) was the eighth-leading cause of infant mortality in term infants.

‡Ratio is defined as the rate in late-preterm infants divided by the rate in term infants.
newborn (4.8 versus 0.5 deaths per 100,000 live births), 5 times more likely to die of bacterial sepsis of the newborn (6.0 versus 1.2 deaths per 100,000 live births), and 3 times more likely to die of congenital malformations (59.9 versus 17.5 deaths per 100,000 live births).

Postneonatal Mortality

Nearly half (47%) of all infant deaths among late-preterm infants and 63% of all infant deaths in term infants occurred during the postneonatal period. Overall postneonatal mortality rates declined significantly from 1995 to 2002 for late-preterm (by 19.6%, \( P < .01 \)) and term infants (by 15.8%, \( P < .01 \); Table IV). Even so, in 2002, late-preterm infants were still 2 times more likely to die during the postneonatal period than term infants (3.7 versus 1.6 deaths per 1000 live births).

Cause-specific postneonatal mortality rates were 1.7 to 3.3 times higher in late-preterm infants than in term infants (Table IV). The first 4 leading causes of postneonatal mortality were the same for late-preterm and term infants. Late-preterm infants were nearly 3 times more likely than term infants to die as a result of congenital malformations (84.4 versus 30.1 deaths per 100,000 live births), influenza and pneumonia (11.3 versus 4.0), and septicemia (7.1 versus 2.7).

DISCUSSION

In this national study, we observed significant declines in infant mortality rates for both late-preterm infants and term infants in all the age-at-death categories except the late-neonatal period. Even so, in 2002 late-preterm infants were 3 times more likely than term infants to die before their first birthday and 6 times more likely to die in their first week of life; this disparity has remained relatively unchanged since 1995. Clearly, these 2 groups of infants have distinctly different mortality outcomes, and combined with our knowledge of their increased risk for morbidity,\textsuperscript{7-19} clinicians should consider closer monitoring of late-preterm infants immediately after birth and throughout the first year of life. Obstetricians and other clinicians who attend deliveries can use this information in weighing the risks and benefits of preterm delivery.

For late-preterm infants, we found that the mortality rate during the first week of life was nearly 6 times higher than for term infants. Much of the disparity in early neonatal mortality rates between late-preterm infants and term infants was caused by higher rates of death from congenital malformations in late-preterm infants. For example, in late-preterm infants, more than half (57%) of the deaths caused by congenital malformations occurred in the first week of life, and >75% occurred by the end of the first month of life (data not
shown). For term infants, these proportions were 38% and 61%, respectively. It is possible that the detection of these conditions and recognition of their severity in utero may have led to a preterm delivery, or perhaps the condition caused a spontaneous preterm delivery. What is not known is whether these late-preterm deaths could have been averted with earlier obstetric intervention, or whether the late-preterm infant would have fared better if she or he had not been delivered preterm. However, we do know that differences in infant mortality between late-preterm infants and term infants persist even when infants with any congenital malformation (ICD-10 Q00-99) as the underlying cause of death are excluded from the analysis. In a subanalysis (data not shown), we found that infant mortality rates were 2.6 times higher in late-preterm infants than term infants (4.5 versus 1.7 deaths per 1000 live births); early, late, and postneonatal rates were 5.0, 3.5, and 2.2 times higher, respectively.

Our finding that late-preterm infants were also more likely to die in the first week of life of conditions associated with preterm birth confirm results of earlier studies, which found that late-preterm infants are at increased risk for neonatal morbidities associated with prematurity compared with term infants.7-16 For example, earlier studies have found that late-preterm infants are more likely than term infants to be diagnosed with respiratory distress10-12,15,16 and apnea12-14 and to require mechanical ventilation during their initial birth hospitalization.15 In our study, late-preterm infants were 19 times more likely than term infants to have atelectasis coded as the underlying cause of death in the early-neonatal period. “Primary atelectasis of newborn (P28.0)” is coded as the cause-of-death when the death certifier indicates on the death certificate that there was a primary failure to expand terminal respiratory units. This includes terms such as pulmonary hypoplasia associated with short gestation or pulmonary immaturity. This coding scheme may be problematic in the case of late-preterm infants with pulmonary hypoplasia caused by an underlying congenital malformation such as renal agenesis, because the case may be coded as the infant having atelectasis as the underlying cause-of-death instead of the congenital malformation because they are preterm infants with pulmonary hypoplasia. Despite these issues, late-preterm infants were also 8.5 times more likely to die with a diagnosis of respiratory distress of the newborn in the early neonatal period, a diagnosis which is not prone to misclassification due to coding error.

Late-preterm infants were 10 times more likely than term infants to die in the early neonatal period as a result of being affected by maternal complications of pregnancy. This category includes many different causes, such as incompetent cervix, premature rupture of membranes, and multiple pregnancies. This finding is concerning because a recent study reported a 10.4% increase (between 1992 and 2002) in the proportion of singleton live births with premature rupture of membranes delivered in the late-preterm period.1

Our finding that the proportion of infant deaths that occurred in the postneonatal period was higher for term births...
(63%) compared with late-preterm births (47%) was expected. However, it was unexpected that the risk of cause-specific postneonatal mortality are 2 to 3 times higher for late preterm infants than term infants, including potentially preventable causes such as accidents, influenza and pneumonia, and septicemia. In addition, late-preterm infants were 2 times more likely to die of Sudden Infant Death Syndrome (SIDS).

This study had several strengths, including the calculation of population-based estimates using a large multiyear dataset, with nearly all US birth and death certificates successfully linked. Also, the large sample allowed us to examine cause-specific infant mortality by age at time of death.

Our study also had several limitations. First, we were limited to the reported underlying cause of death on the death certificate and did not have any additional information about contributing causes that might be helpful in describing more fully why infants died. For example, atelectasis, a diagnosis typically based on autopsy findings, was the third leading cause of early-neonatal mortality and the tenth leading cause of infant mortality in late-preterm infants. Unfortunately, autopsy findings are not available in vital statistics data. Moreover, we did not have information about secondary clinical diagnoses that might have informed us what conditions lead to atelectasis (eg, a respiratory disease such as respiratory distress syndrome, meconium or amniotic fluid aspiration pneumonia, or transient tachypnea versus a congenital malformation). Second, the underlying cause of death data may be misclassified for both term and late-preterm deaths. For example, both term and late-preterm infants had high rates of SIDS in the first month of life. A recent study found that in the last decade there was an increase in the proportion of SIDS cases diagnosed in the first month of life. This recent shift in the age distribution of SIDS is thought to be caused by a change in cause-of-death reporting or the classification of SIDS rather than a true increase in the occurrence of SIDS. Third, the data provided on gestational age may be subject to misclassification. For example, we know that the gestational age derived from the LMP on birth certificates may not be accurate. However, this is not expected to impact late-preterm births and term births differentially.

In conclusion, late-preterm infants and term infants have different risks for death during their first year of life; late-preterm infants are 3 times more likely to die before their first birthday. Our study indicates that the greatest disparity in infant mortality rates occurs during the first week of life, and this may reflect the severity of the conditions that contribute to these untimely deaths. We found that many of these early deaths were reportedly caused by conditions such as life-threatening congenital malformations and complications of pregnancy that, when detected, may have led health care providers to deliver the infant before term. Future research should assess the rationale for preterm delivery for those infants delivered by cesarean delivery or induction, such as maternal or fetal medical conditions or even maternal request.

Analysis of linked antenatal records will be essential for assessing the extent to which these early-neonatal deaths can be prevented.

### Table IV. Postneonatal (28-364 days) mortality

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-preterm infants</td>
<td>4.6</td>
<td>4.2</td>
<td>4.2</td>
<td>4.0</td>
<td>3.6</td>
<td>3.8</td>
<td>3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Term infants</td>
<td>1.9</td>
<td>1.8</td>
<td>1.7</td>
<td>1.7</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
<td>1.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause of death at 28 to 364 days</th>
<th>ICD-10 Codes</th>
<th>Late-Preterm Infants</th>
<th>Term Infants†</th>
<th>Ratio‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDS</td>
<td>R95</td>
<td>784</td>
<td>4,332</td>
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</tr>
<tr>
<td>Congenital malformations, deformations, and chromosomal abnormalities</td>
<td>Q00-99</td>
<td>736</td>
<td>2,883</td>
<td>2.8</td>
</tr>
<tr>
<td>Accidents (unintentional injuries)</td>
<td>V01-X59</td>
<td>291</td>
<td>1,754</td>
<td>3.1</td>
</tr>
<tr>
<td>Diseases of the circulatory system</td>
<td>I00-99</td>
<td>126</td>
<td>690</td>
<td>2.7</td>
</tr>
<tr>
<td>Influenza and pneumonia</td>
<td>J10-18</td>
<td>99</td>
<td>379</td>
<td>2.6</td>
</tr>
<tr>
<td>Assault (homicide)</td>
<td>X85-Y09</td>
<td>87</td>
<td>553</td>
<td>5.2</td>
</tr>
<tr>
<td>Septicemia</td>
<td>A40-41</td>
<td>61</td>
<td>256</td>
<td>2.6</td>
</tr>
<tr>
<td>Gastritis, duodenitis, and non-infective enteritis and colitis</td>
<td>K29,K50-55</td>
<td>26</td>
<td>82</td>
<td>3.3</td>
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<tr>
<td>Malignant neoplasms</td>
<td>C00-97</td>
<td>25</td>
<td>143</td>
<td>1.9</td>
</tr>
<tr>
<td>Diseases of the blood and blood-forming organs and certain disorders</td>
<td>D50-89</td>
<td>21</td>
<td>112</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Total postneonatal deaths in 2000-2002: 3,192 vs. 15,167

PNMRR, Postneonatal mortality rate.

*Cause-specific postneonatal mortality rates are the number of deaths in children aged 28 to 364 days per 100,000 live births for a specific cause of death. Leading causes were defined according to methodology used by the NCHS (see Methods section for more information).
†Meningitis (G00, G03) was the tenth-leading cause of postneonatal mortality in term infants.
‡Ratio is defined as the rate in late-preterm infants divided by the rate in term infants.
REFERENCES


Figure. Late-preterm birth rates in the United States, 1981 to 2004.
Value of the Bronchodilator Response in Assessing Controller Naïve Asthmatic Children

STANLEY P. GALANT, MD, TRICIA MORPHEW, MS, SILVIA AMARO, RN, AND OTTO LIAO, MD

Objective To define the bronchodilator response (BDR) cutoff point that best identified asthma to determine the frequency of abnormal spirometry results across severity.

Study design Controller naïve children were evaluated with clinical criteria alone to establish a diagnosis of asthma and severity classification, then compared with the BDR, which was calculated as the percent change from the initial forced expiratory volume in 1 second. Receiver operator characteristic analysis determined the cutoff point for asthma diagnosis that gave the best combination of sensitivity and specificity.

Results Children with asthma (n = 346) and 51 children without asthma, aged 4 to 17 years, who met entry criteria for spirometry were identified. The mean BDR in asthmatics was 8.6% (95% CI, 7.5-9.8), compared with 2.2% (95% CI, 0.2-4.3) for non-asthmatics (P < .001). A BDR ≥9% best differentiated these populations with a sensitivity rate of 42.5% and a specificity rate of 86.3%. Abnormal spirometry results, defined as a BDR ≥9%, a forced expiratory volume in 1 second <80% predicted, or both, ranged from 44.4% for mild intermittent bronchial asthma to 57.0% for severe persistent bronchial asthma.

Conclusion Spirometric criteria that include BDR can potentially identify children who have clinically mild asthma and might benefit from controller therapy. (J Pediatr 2007;151:457-62)

According to the National Asthma Education and Prevention Program (NAEPP) guidelines spirometry, including baseline forced expiratory volume in 1 second (FEV₁) and the bronchodilator response (BDR) to short acting beta agonists (SABA), should be undertaken in children as objective measures to establish the diagnosis and severity of bronchial asthma (BA).¹ Spirometry is thought to be necessary because physician evaluation on a clinical basis alone may not adequately detect airway obstruction² and reliance on patient or parent-reported symptoms may not provide an accurate diagnosis of BA.³ Spirometry use in a pediatric clinic setting can lead to important changes in pharmacotherapy that were not initially indicated with clinical evaluation.⁴,⁵ However, serious questions have been raised about its value to pediatricians as a practical in-office tool.⁶ In addition, baseline FEV₁, the "gold standard" for evaluating airway obstruction,¹ is usually in the reference range (≥80% predicted) in children, regardless of BA severity,⁷ thus limiting its value for diagnosis and treatment strategy. Because of this limitation, several other objective measures have been suggested for diagnosis and treatment in children, including the BDR,⁸-¹³ which reflects not only airway reversibility, central to diagnosis, but also may represent a surrogate marker of airway inflammation.¹¹-¹⁴ The current definition of a positive BDR (≥12% reversibility and ≥200 mL increase in initial FEV₁) after SABA¹⁵ has been established primarily in adults. A recent report suggested that a ≥9% BDR cutoff point best distinguishes children with asthma from children without asthma.¹⁰

The purpose of this retrospective, observational study was to determine the BDR cutoff point that best differentiates children with asthma from children without asthma and establish the frequency of abnormal baseline FEV₁ and BDR values across symptom-based asthma severity in a cohort of children who are controller naïve.
METHODS

Patient Population

Children participating in a school-based, low-income asthma mobile van program, the Breathmobile (S.C. Johnson and Son, Inc., Racine, WI), were recruited from school nurses, community public health clinics, response to flyers, and an asthma screening questionnaire. Criteria for the diagnosis of asthma made by the asthma specialist included a history of recurrent coughing, wheezing, or shortness of breath at rest or with exercise, symptomatic improvement after bronchodilator use, and exclusion of other diagnoses. Patients who did not have these characteristics were classified as non-asthmatic control subjects. This distinction was made solely on clinical grounds without the results of spirometry.

Asthma severity was evaluated by using daytime/nighttime symptom frequency criteria as described in the NAEPPI guidelines. Patients not receiving controller medication in the 6 to 8 weeks before the initial evaluation were considered controller naïve. The patients were not excluded from the BDR evaluation on the basis of earlier albuterol use or recent upper respiratory tract infection.

Institutional review was waived by Children’s Hospital of Orange County’s institutional review board because data acquisition analysis was not directly linked to individual patient identities.

Spirometry

Pulmonary function testing was attempted in children aged ≥4 years in the standing position. Spirometric results were included in the analysis only when the child completed at least 3 baseline forced vital capacity (FVC) maneuvers that met American Thoracic Society criteria in a maximum of 6 attempts and was able to successfully complete post-bronchodilator (BD) spirometry. An observation of the flow expiratory curve was made to ensure that the forced expiratory time (FET) was >1 second in all age groups, particularly in the 4- to 7-year-old population. In addition, the software had a computer bell that sounded when the curve reached completion. The best spirometric measures of at least 3 attempts were recorded for analysis, including FVC, FEV₁, FEV₁/FVC ratio, and the forced expiratory flow (FEF₂₅-₇₅) predicted. Post-BD spirometry was evaluated 10 minutes after administering 2 puffs (180 mcg) from an albuterol metered dose inhaler with a spacer, or nebulized Albuterol pre-mix (.083%) at a dose equivalent to 2.5 mg of albuterol. The latter was used in younger patients or when the metered dose inhaler technique was not successful. Completed and acceptable spirometric measures were compared with the Knudson Intermountain Thoracic Society normal predicted values and adjusted for potential confounding effects of age, sex, ethnicity, and height on the relationship between severity and spirometric measures. The receiver operator characteristic (ROC) curve evaluated the diagnostic accuracy of the BDR expression to identify asthma. Sensitivity, specificity, and positive and negative predictive values on the basis of single cutoff values for the continuous BDR expression to positively identify asthma were calculated across a range of optimal points. Chi-square tests evaluated significance of association between abnormal spirometry results and asthma diagnosis and level of symptom severity in asthmatic patients.

RESULTS

Demographic characteristics of both the asthmatic and non-asthmatic populations that successfully completed both pre- and post-BD maneuvers are shown in Table I. There were 346 children with asthma and 51 children without asthma, with an age range of 4.5 to 17.8 years and 4.2 to 15.5 years, respectively. The mean height for each group was similar. None of the group differences was statistically significant. Evaluation of symptom-based classification of asthma severity revealed that 34% of children had mild intermittent (MI) disease, 12% of children had mild persistent (MIP) disease, 26% of children had moderate persistent (MOP) disease, and 27% of children had severe persistent (SP) disease (Table I). The 51 patients without asthma consisted primarily of children with recurrent upper respiratory tract problems, including allergic rhinitis, adenotonsillitis, or recurrent sinusitis.

Significant differences in the unadjusted (univariate) and adjusted (multivariate) models were observed in the pre-BD FEV₁ of 91% predicted for the children with asthma and 97% predicted FEV₁ for the children without asthma, (P = .005, P = .003, respectively; Table II). Comparing children without asthma with children with asthma of different severity, statistical significance was seen starting with those with MIP (P = .037). On average, younger children (4-7 years old) and older children (>10 years old) had higher pre- and post-bronchodilator values compared with children 8 to 10 years old across severity categories. There were no significant differences in the post-BD FEV₁ between the non-asthmatic group and asthmatic group regardless of severity.

FEV₁ mls post-BD

\[ \text{FEV₁ mls post-BD} = \frac{\text{FEV₁ mls pre-BD}}{\text{FEV₁ pre-BD}} \times 100\% \]

Statistical Analysis

Analysis of variance was conducted to assess significance of differences in mean FEV₁% predicted pre- and post-BD and BDR across asthma diagnosis and severity groups. Multivariate analysis of variance enabled examination of potential confounding effects of age, sex, ethnicity, and height on the relationship between severity and spirometric measures. The receiver operator characteristic (ROC) curve evaluated the diagnostic accuracy of the BDR expression to identify asthma. Sensitivity, specificity, and positive and negative predictive values on the basis of single cutoff values for the continuous BDR expression to positively identify asthma were calculated across a range of optimal points. Chi-square tests evaluated significance of association between abnormal spirometry results and asthma diagnosis and level of symptom severity in asthmatic patients.
Table I. Characteristics of this controller naïve pediatric asthma population described by means of asthma diagnosis

<table>
<thead>
<tr>
<th>Post-albuterol response measured</th>
<th>Significance of asthma Dx group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No asthma (n = 51)</strong></td>
<td><strong>Asthma (n = 346)</strong></td>
</tr>
<tr>
<td><strong>Age, mean (95% CI)</strong></td>
<td><strong>9.0 years (8-10)</strong>*</td>
</tr>
<tr>
<td>4-7 years</td>
<td>19 (37%)</td>
</tr>
<tr>
<td>8-10</td>
<td>22 (43%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>10 (20%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (61%)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (39%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>45 (88%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (12%)</td>
</tr>
<tr>
<td><strong>Height, mean (95% CI)</strong></td>
<td><strong>134 cm (129-138)</strong>*</td>
</tr>
<tr>
<td><strong>Symptom severity</strong></td>
<td></td>
</tr>
<tr>
<td>Mild intermittent</td>
<td>119 (34%)</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>42 (12%)</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>91 (26%)</td>
</tr>
<tr>
<td>Severe persistent</td>
<td>94 (27%)</td>
</tr>
</tbody>
</table>

Table II. Examination of asthma diagnosis and symptom severity group differences in average FEV1%-predicted

<table>
<thead>
<tr>
<th>Asthma Dx and symptom severity</th>
<th>Patients, n (%)</th>
<th>FEV1% pre pred, mean (95% CI)</th>
<th>FEV1% post-bronchodilator, mean (95% CI)</th>
<th>BDR-Δ FEV1% initial, mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No asthma group</td>
<td>51 (12.8%)</td>
<td>97 (93-100)</td>
<td>99 (95, 102)</td>
<td>2.2% (0.2, 4.3)</td>
</tr>
<tr>
<td>Asthma Dx—overall</td>
<td>346 (87.2%)</td>
<td>91 (89-92)</td>
<td>99 (97, 100)</td>
<td>8.6% (7.5, 9.8)</td>
</tr>
<tr>
<td>Mild Intermittent</td>
<td>119 (30.0%)</td>
<td>93 (91-96)</td>
<td>100 (97, 103)</td>
<td>7.6% (5.8, 9.5)</td>
</tr>
<tr>
<td>Mild Persistent</td>
<td>42 (10.6%)</td>
<td>91 (87-95)</td>
<td>98 (95, 102)</td>
<td>7.3% (4.2, 10.4)</td>
</tr>
<tr>
<td>Moderate Persistent</td>
<td>91 (22.9%)</td>
<td>90 (87-94)</td>
<td>99 (95, 102)</td>
<td>9.1% (6.9, 11.3)</td>
</tr>
<tr>
<td>Severe Persistent</td>
<td>94 (23.7%)</td>
<td>87 (84-91)</td>
<td>97 (94, 101)</td>
<td>10.1% (7.6, 12.6)</td>
</tr>
</tbody>
</table>

ANOVA

Asthma Dx and symptom severity

Group differences

| Unadjusted model* | F = 3.8 (P < .005) | F = 0.4 (P = .796) | F = 5.2 (P < .001) |
| Adjusted model† | F = 4.0 (P < .003) | F = 0.4 (P = .824) | F = 5.2 (P < .001) |

Contrast comparisons (adjusted models)

| No asthma versus asthma Dx | (P < .001) | (P < .001) | (P < .001) |
| No asthma versus intermittent symptoms | (P = .107) | (P = .818) | (P = .002) |
| No asthma versus mild persistent symptoms | (P = .037) | (P = .701) | (P = .019) |
| No asthma versus moderate persistent symptoms | (P = .014) | (P = .957) | (P = .001) |
| No asthma versus severe persistent symptoms | (P < .001) | (P < .001) | (P < .001) |

*Pred, Predicted.

Δ = change; analysis performed after removal of outliers for BDR (7 values ≥70.0%).
BDR-% change from initial FEV1mls: no factors significant in model that controls for asthma Dx and symptom severity.

*Variable Coding: no asthma, intermittent symptoms, mild persistent symptoms, moderate persistent symptoms, and severe persistent symptoms.
†Additional factors considered in adjusted (multivariate) models: age (4-7, 8-10, >10 years), ethnicity (Hispanic and other), sex, and height (cm). Significance of asthma diagnosis and symptom severity variable in each model adjusted for these significant demographic characteristics, described by outcome:

FEV1% pre: (Age, P < .001).

FEV1% post: (Age, P = .003).
The BDR was found to give a more highly significant differentiation between the asthmatic group and non-asthmatic group \((P < .001)\) than pre-BD FEV\(_1\) (Table II), with statistical significance noted even in the MI disease group \((P = .002)\). The BDR in the non-asthmatic group showed a mean of 2.2% (95% CI, 0.2–4.3) response compared with 8.6% (95% CI, 7.5–9.8) in the asthma group \((P < .001)\). The range seen was 7.6% (95% CI, 5.8–9.5) for MI asthma to 10.1% (95% CI, 7.6–12.6) in the SP group. In the multivariate analysis, the only variable that was significant was severity \((P < .001)\). Age, ethnicity, sex, and height did not impact the positive relationship of asthma diagnosis and increased severity to BDR. Some children, however, were unable to perform pre- and post-BD responses and were not included in this analysis. Less than 50% of children <6 years old were able to adequately perform both responses, 74% of children aged 6 to 7 years, 80% of children aged 8 to 10 years old, and 96% of children >10 years old.

ROC analysis to identify asthma by BDR was performed (Figure 1; available at www.jpeds.com). The area under the curve was 0.674 \((P < .001)\). The cutoff points closest to the left-hand border and the top border of the ROC space that provide the best possible tradeoff between sensitivity and specificity are presented below the plot. A cutoff point \(\geq 9%\) offered optimal balance with a sensitivity rate of 42.5% and a specificity rate of 86.3%, a positive predictive value of 95.5%, and a negative predictive value of 18.1%. Applying a cutoff point \(\geq 12%\) gave a better specificity rate of 94.1%, but the sensitivity rate was substantially reduced to only 30.4%, the positive predictive value was 97.2%, and the negative predictive value was 16.7%. The percentage of those with \(\geq 9%\) BDR increased with BA severity regardless of baseline FEV\(_1\) (data not shown).

In Figure 2A, we compare the percentage of abnormal spirometry results, either baseline FEV\(_1\) <80%, BDR \(\geq 9%\), or both, between the asthmatic group and the non-asthmatic group and across severity. The percentage of children with a FEV\(_1\) <80% either alone or in combination with BDR \(\geq 9%\) ranged from 19.7% to 24.7% in children with MI BA to children with SP BA \((P = .704)\). In the non-asthmatic group, the FEV\(_1\) <80% alone was 7.8%, and none had the combination criteria. In contrast, the BDR >9%, either alone or in combination with FEV\(_1\) <80%, ranged from 13.7% in the non-BA group to 51.1% in the group with SP BA \((P = .002)\). Using either/or criteria, children with asthma were significantly more likely to have abnormal spirometry results (49.3%, compared with 21.5% of the children without asthma; \(P = .001)\). Although non-significant, the percentage of abnormal spirometry results increased with severity, reaching 57.1% in the SP group \((P = .323)\). However, 44.4% of children with MI BA also had abnormal spirometry results. The BDR \(\geq 9%\) contributed to most of the abnormal findings across severity, most of which were seen when the baseline FEV\(_1\) was >80% (normal). In Figure 2B, with the BDR cutoff point \(\geq 12%\), we observed the same pattern, but abnormal spirometry results were found less often in the non-BA group (13.7% compared with 21.5%), reflecting greater BDR specificity, with decreased sensitivity particularly noted in the MI group in which abnormal spirometry results were seen in 34.2%, compared with 44.4%. This was mainly caused by decreased positive BDR from 35.9% to 21.3% comparing the \(\geq 9%\) with the \(\geq 12%\) cutoff point criteria.

**DISCUSSION**

We have shown in a controller naïve, inner city pediatric population that those in whom asthma is diagnosed on a clinical basis by an asthma specialist had significantly greater mean BDR, even at the mildest level, compared with those who were deemed non-asthmatic, regardless of age, sex, height, or ethnicity. This distinction was clearly better than that shown by means of baseline FEV\(_1\) (Table II; Figure 2A and B). Several reports have shown that the mean BDR can differentiate BA from non-BA by using impulse oscillom-
ery in young children\textsuperscript{20,21} and with conventional spirometry,\textsuperscript{10,22-24} even when baseline values were in the reference range.\textsuperscript{22,24}

However, the major usefulness of the BDR in clinical practice requires a cutoff point that best distinguishes children with asthma from children without asthma. This has previously been estimated by epidemiological data in healthy children\textsuperscript{25} and by evaluating variability limits on repeated measurements of baseline FEV\textsubscript{1}.\textsuperscript{26} The Dales study found that 99\% confidence limits of healthy children, aged 9 to 11 years.\textsuperscript{25} Strachan reported that the 95th percentile for variability of FEV\textsubscript{1} within the same day and between days in children 7 years old was 10.2\%.\textsuperscript{26} The most direct approach, however, was taken by Dundas et al, who, in the only earlier report we could find, compared several BDR cutoff points in healthy children and subjects suspected to have mild, step 1 asthma assessed clinically by a physician.\textsuperscript{10} Similar to our finding, a BDR of >9\% gave a better sum of sensitivity and specificity, 50\% and 86\%, respectively, than 12\%, which had a sensitivity rate of 35\% and a specificity rate of 98\%. In our step 1 asthmatics (MI), the sensitivity rate was 37\% at the >9\% cutoff point, perhaps because we used 180 mcg, which is a frequently used dose in children,\textsuperscript{11} compared with 400mcg in the other study. Dundas also observed that baseline FEV\textsubscript{1}, although reduced, was neither sensitive nor specific in identifying the child with asthma.\textsuperscript{10}

Perhaps the major value of the BDR for the clinician was shown in those with step 1 MI BA on the basis of symptom frequency criteria (Figure 2A,B). By using combination criteria of FEV1 \(\leq 80\%\), BDR \(\geq 9\%\), or both, we found that 44.4\% of the children classified as having MI BA had abnormal spirometry results and thus could be candidates for controller therapy. Although guidelines currently do not recommend controller therapy for MI BA, we recently reported that 24.3\% of those classified as having MI BA had significant exacerbations resulting in hospitalization or emergency outpatient visits in the previous year.\textsuperscript{27} Robertson et al found that as many children with clinical evidence of mild BA die as those who have more serious disease.\textsuperscript{28} Furthermore, children with mild disease experience far less morbidity when appropriately treated.\textsuperscript{29}

For diagnosis, a stepwise algorithm has been suggested in children characterized by a careful history of chronic cough, recurrent wheezing, and dyspnea relieved by bronchodilator and exclusion of alternative diagnosis.\textsuperscript{30} To confirm the diagnosis, an objective test of airway obstruction is recommended.\textsuperscript{1}\textsuperscript{30} Furthermore, when obstruction is demonstrated, a BDR \(\geq 12\%\) is suggested as more definitive evidence of BA diagnosis.\textsuperscript{1,15,30} We would argue that these spirometric assumptions may not be valid in the pediatric population. First, as seen in our data (Table II), most children have baseline FEV\textsubscript{1} in the reference range (\(\geq 80\%\)), with approximately 10\% to 20\% of children having levels <80\% regardless of severity.\textsuperscript{7} We found that a BDR >9\% or \(\geq 12\%\) can be present even with a baseline \(\geq 80\%\) (Figure 2A,B). In addition, a \(\geq 9\%\) BDR increases sensitivity by 35\% overall and by 68.5\% in those with MI disease in which sensitivity is needed most; 44.4\% of the MI group would have been under-treated if we assume that children with abnormal spirometry results should receive controller medications even if BA is clinically mild. To substantiate this assumption, several investigators have shown that patients with a low FEV\textsubscript{1} in childhood often continue to have more severe airway obstruction in adulthood\textsuperscript{31} and have an increased morbidity rate.\textsuperscript{32} In addition, an increased BDR has been shown to be associated with biomarkers of inflammation including exhaled nitric oxide\textsuperscript{11-13} and bronchial eosinophilia.\textsuperscript{14} Furthermore, the BDR is a predictor of future lung function\textsuperscript{33} and correlates significantly with responsiveness to inhaled corticosteroids.\textsuperscript{14,34} We have demonstrated that spirometry including the BDR can be successfully performed in most children \(\geq 6\) years of age. Although in many primary care settings the peak expiratory flow is used in place of spirometry to assess pulmonary function, it has been shown to correlate poorly with the FEV\textsubscript{1} and, therefore, it can be misleading in evaluating the child suspected of having BA.

Several limitations need to be addressed in this observational, retrospective study. Our pediatric population was predominantly Hispanic, from the inner city with poor access to medical care. Although we did not find any significant spirometric differences on the basis of ethnicity, one cannot necessarily generalize our findings to other populations. Furthermore, our non-asthmatic population did not consist of “normal” prescreened healthy control subjects because they were referred, usually by the school nurse on the basis of perceived respiratory problems. Approximately 8\% had a FEV\textsubscript{1} <80\%, and approximately 14\% had a positive BDR \(\geq 9\%\). In addition, we found that approximately 33\% of subjects were atopic on the basis of positive skin test results (data not shown). The atopic state itself has been associated with an increased BDR.\textsuperscript{35} One would expect that the differences between patients in whom BA is diagnosed and prescreened healthy non-atopic subjects might be even greater than reported here. Our cohorts might better reflect the “real world” situation faced by the clinician in practice, where the asthmatic child must be differentiated from a population of children with a variety of respiratory symptoms, not healthy children with no symptoms. We also did not account for albuterol use 4 to 6 hours before spirometry. None of the subjects had received long-acting beta agonists. However, those reporting albuterol use \(\geq 3\) times per week had lower baseline FEV\textsubscript{1} (\(P < .014\)) and greater BDR (\(P < .001\); data not shown). One could assume that our results would have been even better had we excluded children receiving albuterol 4 to 6 hours before spirometry. Patients were also not excluded on the basis of earlier upper respiratory infection within 2 weeks of spirometry. However, this would apply to both patients diagnosed with BA and the non-BA population. The standard we used to determine the value of spirometry was the diagnosis by the asthma specialist on the basis of recommended guideline clinical criteria alone,\textsuperscript{1} which has frequently been the standard against which more objective tests have been evaluated.\textsuperscript{10,13}
Our data suggest that spirometry including the BDR, although objective, provides only modest sensitivity in confirming the diagnosis of BA. Of greater potential is our observation that the BDR in combination with baseline FEV1 can detect a population of children with asthma with only mild clinical manifestations who might benefit from inhaled corticosteroid therapy. Although confirmation is needed, we suggest that a BDR ≥90% be considered a positive response in children. We recommend that the BDR be performed in all children ≥6 years old who are suspected of having BA as a practical tool that may help the physician decide which therapeutic strategy is most appropriate.

Thanks to Joseph Spahn, MD, and Leonard Bacharier, MD, for their advice on this manuscript, and to Rhonda Robles for manuscript preparation.

REFERENCES

Receiver Operator Characteristic (ROC) CURVES – Outcome: Asthma Diagnosis
Test Variable: BDR - Δ FEV1 % initial
(AUC=0.674, p<0.001)

<table>
<thead>
<tr>
<th>BDR - Δ FEV1 % initial</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PVP</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=6%</td>
<td>55.2%</td>
<td>66.7%</td>
<td>91.8%</td>
<td>18.0%</td>
</tr>
<tr>
<td>&gt;=9%</td>
<td>42.5%</td>
<td>86.3%</td>
<td>95.5%</td>
<td>18.1%</td>
</tr>
<tr>
<td>&gt;=12%</td>
<td>30.4%</td>
<td>94.1%</td>
<td>97.2%</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

Figure 1. ROC analysis to identify patients with asthma from FEV1 BDR. AUC, Area under the curve; PVP, positive predictive value; NPV, negative predictive value. The triangle denotes change.
Parenting Very Low Birth Weight Children at School Age: Maternal Stress and Coping

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Objective To compare severity and determinants of stress and coping in mothers of 8-year-old very low birth weight (VLBW) and term children varying in medical and developmental risk.

Study design Three groups of mothers/infants were prospectively compared in a longitudinal study from birth to 8 years (110 high-risk VLBW, 80 low-risk VLBW, and 112 term). Maternal psychological distress, coping, parenting/marital stress, child health, and family impact were measured in the children at age 8 years.

Results Mothers of VLBW children differed from term mothers, reporting less consensus with partners, more concern for their children’s health, less parent–child conflict, and fewer years of education attained. Mothers of high-risk VLBW children experienced the greatest family and personal strains and used less denial and disengagement coping. The groups exhibited no differences in the sense of parenting competence, divorce rate, parenting/marital satisfaction, family cohesion, and psychological distress symptoms. Multiple birth, low socioeconomic status, and lower child IQ added to maternal stress.

Conclusions VLBW birth has long-term negative and positive impacts on maternal/family outcomes related to the infant’s medical risk. (J Pediatr 2007;151:463-9)

Survival rates are increasing in the 59,000 very low birthweight (VLBW) and extremely low birthweight (ELBW) infants born annually.1 Although a wide range of outcomes has been studied,2-4 little attention has been paid to parental adaptation to VLBW birth beyond the neonatal period. Addressing the psychological impact of VLBW birth on parents is increasingly important, because parental involvement is now expected in decisions about life-sustaining treatment for critically ill infants.5 Physicians need to be apprised of parental perspectives, because treatment decisions should be informed by facts.6 In addition, the relationship of children’s cognitive and behavioral outcomes to family stress7,8 may be more salient for preterm, medically ill infants.9 Understanding the nature, scope, and determinants of stress and coping in families of VLBW children can lead to interventions to reduce stress and improve child outcomes.

A convergent literature acknowledges the strong, immediate psychological distress of mothers of VLBW infants neonatally.10,11 A longitudinal, controlled, prospective study of parenting VLBW infants found that the severity of medical risk, child’s age, and developmental delay influenced maternal psychological distress and parenting stress during the 3 years after birth.12 Three studies examined later parental experiences in families of VLBW children and found persistent negative maternal and family sequelae, but methodological flaws, including lack of prospective designs, low statistical power, and failure to control for confounding factors, led to conflicting findings.13-15 None of these 3 studies recruited control families prospectively from birth, preventing longitudinal comparisons. They also did not screen for substance exposure; thus, adverse sequelae could

See editorial, p 448 and related article, p 470

From the Departments of Pediatrics (L.S., S.F., L.K., S.E., B.L., M.M., C.K., J.B.) and General Medical Sciences (L.S.), School of Medicine, and Department of Psychology, College of Arts and Sciences (L.S., E.S.), Case Western Reserve University, Cleveland, OH.

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10.1016/j.jpeds.2007.04.012
be due to maternal drug or alcohol use rather than VLBW birth.\textsuperscript{13-16} They also focused only on stress and did not address the role of coping.\textsuperscript{17,18}

The present study improved the methodology through prospective recruitment of regionally representative VLBW cohorts and controls from birth; assessment of a wider range of outcomes, including coping; exclusion of drug/heavy alcohol-exposed children; and enrollment of an adequate sample size to allow evaluation of the moderating effects of socioeconomic status (SES). The conceptual model (Double ABCX Model of Family Adjustment)\textsuperscript{9} views VLBW birth as a stressful life event that may negatively impact families across multiple biopsychosocial domains. This model is transactional and recognizes that stressors and resources may change over time. Race, SES, maternal education, and other stressful life events were considered confounding factors that did not differ among groups at birth. Multiple birth was also considered a confounding variable, and its effects were examined statistically. Based on our previous findings,\textsuperscript{12} we hypothesized that the negative impact of VLBW birth would continue to school age and would be related to poorer child functional outcomes and risk status.

**METHODS**

Mothers were interviewed in a longitudinal study of the outcomes of infants with bronchopulmonary dysplasia (BPD), a chronic lung disease of prematurity,\textsuperscript{19,20} and VLBW.\textsuperscript{4,9,12,21} Children with VLBW admitted to all neonatal intensive care units in a Midwest region were prospectively enrolled between 1989 and 1991 at birth, with current follow-up at 8 years.

High-risk children with VLBW (high-risk VLBW; \(n = 110\)) had a diagnosis of BPD, birth weight <1500 g, supplementary oxygen requirement for more than 28 days, and radiographic evidence of chronic lung disease.\textsuperscript{22} A partial stratification sampling approach\textsuperscript{21} was adopted to enroll adequate numbers of subjects without socioeconomic disadvantage or severe neurologic risk, to assess the impact of social class and medical risk factors on outcomes. Infants with BPD free of neurologic problems other than grade I or II intraventricular hemorrhage and not socially disadvantaged (ie, Hollingshead classification IV or V)\textsuperscript{23} were exhaustively recruited. The remainder were recruited by approaching the family of the next infant with BPD that could be accommodated in the schedule.

Low-risk children with VLBW (low-risk VLBW; \(n = 80\)) did not have BPD, weighed <1500 g at birth, and required oxygen supplementation for <25 days.

Term children (\(n = 112\)), recruited from neonatal nurseries, had no diagnosed medical illnesses or abnormalities at birth; were more than 36 weeks gestation, and, for singletons, weighed more than 2500 g at birth. Infants with major congenital malformations, drug or heavy alcohol exposure, maternal major psychiatric/physical illness as noted in the medical history, human immunodeficiency virus, or mental retardation, or who lived more than 2 hours driving distance from the study center, were excluded. Further details regarding recruitment and attrition have been reported previously.\textsuperscript{4,9,12,21} Follow-up rates were 90% for the high-risk VLBW group, 90% for the low-risk VLBW group, and 80% for the term group.

**Procedures**

Mothers completed the following standardized, self-report measures at the 8-year visit. Several areas of stress were examined, assessing specific maternal psychological symptoms, stress related to parenting, family impact, marital stress, and child health concerns.

**Stress Outcomes**

The Brief Symptom Inventory (BSI)\textsuperscript{24} measures psychiatric symptom patterns (eg, somatic complaints, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, phobic anxiety, paranoid ideation, hostility, psychosis) with consensually valid clinical significance. A summary score, the General Severity Index (GSI), measures overall psychological distress. Cutoff scores identify subjects whose symptoms reach severity levels higher than the 84th percentile compared with same-sex nonpatient norms.

The Parenting Stress Index (PSI)\textsuperscript{25} assesses parental perceptions of the degree of stress related to dimensions of the parenting role. The parent domain measures 6 dimensions of stress: reinforcement of parent, depression, role restriction, sense of competence, social isolation, and spousal/partner support. Under the child domain, child characteristics of adaptability, acceptability, distractibility-hyperactivity, mood, and attachment and reinforcement to parent are rated.

The Impact on Family Scale\textsuperscript{26} measures maternal perceptions of the child’s impact on the family. Although this scale was designed to assess the impact of a child with a chronic illness/disability, statements were modified to apply to healthy children as well. The scale includes 1 factor assessing total impact and 1 set of items assessing financial impact. A mastery (coping) set was also retained from the original test.

The Dyadic Adjustment Scale (DAS),\textsuperscript{27} a 32-item self-report measuring the quality of marital adjustment, yields an overall relationship adjustment score and 4 subscale scores: Consensus, Affection, Satisfaction, and Cohesion.

Questions from the Child Health Questionnaire (CHQ),\textsuperscript{28} Parent Form 50 (PF50) allows mothers to describe the child’s physical health and limitations. Global Health provides a global parental health rating; Physical Health (6 questions) rates how health problems have limited specific activities in the last 4 weeks; Pain (2 questions) assesses the amount of pain that the child experienced in the last 4 weeks; and Your Child’s Health (7 questions) assesses the child’s health in general. In addition, questions 11 and 12 (Everyday Activities) rate restrictions on schoolwork and activities.
Coping Outcomes

The COPE Questionnaire of 60 items yields 15 subscales that assess 4 distinct, theoretically derived dimensions of coping in a 4-point Likert-type scale.29,30 Factors include Adaptive Internal (Active, Planning, Suppression of Competing Activities), Adaptive External (Focus on and Venting of Emotion, Seeking Social Support for Emotional Reasons/for Instrumental Reasons), Avoidant (Behavioral Disengagement, Denial, Mental Disengagement), Acceptance (Positive Reinterpretation and Growth, Restraint), and Alcohol/Drug Use, Humor, and Turning to Religion.

Life Events

The Family Inventory of Life Events and Changes (FILE)31 assesses family experience of stressful life changes in the previous year in 9 categories: intrafamily strains, marital strains, pregnancy and childbearing strains, finance/business strains, work-family transitions, illness, losses, transitions, and legal violations. At birth enrollment, FILE identified whether group differences in life stressors other than infant illness/prematurity could account for maternal psychological or parenting stress.

Social Support

The Multidimensional Scale of Perceived Social Support (MSPSS)32 assesses perceived social support from family, friends, and significant other in 12 items on a 7-point Likert-type scale. At birth, families did not differ on these measures,12 providing a baseline to assess changes in stressful life events.

At follow-up, all children were administered the Wechsler Intelligence Scale for Children III (WISC-III)13 to obtain an IQ score. Demographic information was updated, including number of years of maternal education attained, number of children born, and marital status.

This study design was approved by the institutional review boards of the participating hospitals. Informed consent/assent was obtained from parents and children. A stipend of $100 was provided to each family.

Data Analyses

Before the analyses, positively skewed outcome variables were transformed with the natural logarithm function to achieve an approximately normal distribution. Negatively skewed outcome variables were log-transformed after reverse scoring (ie, loge [(maximum – x + 1)]. Means/standard deviations are reported from the original distribution, with transformations used in the analyses.

Group differences were assessed in terms of sample characteristics and the FILE using analysis of variance (ANOVA) and Kruskal-Wallis tests for continuous data and Pearson and Mantel-Haenszel χ² tests for categorical data. The original study design controlled for SES and maternal education, which are known to be related to various dimensions of stress at birth. Stressful life events and social supports were also examined, because we were interested in assessing the impact of VLBW birth apart from other life events. The groups did not differ in either dimension.12 Multiple birth was controlled statistically when related to outcome.

To assess overall group differences, multivariate analysis of covariance (MANCOVA) was conducted on the outcome variables controlling for maternal education at 8 years, multiple birth, and total intrafamily strains, covariates related to birth group, and known to relate to the outcomes. To reduce chance findings, summary scores were evaluated first and followed with MANCOVA only if total composite score differences were significant at P < .10. For child health, generalized estimating equations (GEEs) were used. Follow-up analyses of covariance (ANCOVA) identified differences by birth group. In the event of a significant group effect, Tukey’s multiple comparison technique assessed pairwise differences, controlling for the number of comparisons. Due to skewness, BSI scores were dichotomized using the clinical cutoff (t score > 63) and analyzed using logistic regressions.

A change in maternal educational level was calculated by deducting the number of years attained by each mother at birth from the number of years at the 8-year visit. T tests were used to determine the mean group difference. The interaction effect of birth group and SES was examined using ANOVA, with follow-up pairwise tests using a modified Bonferroni procedure. Because some mothers had multiple births, the Impact on Family Scale, CHQ, and PSI were assessed based on each child, whereas other variables were based on each mother. The power estimated under a general MANCOVA model, controlling for covariates, ranged from 84% to >99% to detect birth group effects, assuming a 2.5% significance level to account for multiple testing.

RESULTS

Sample Characteristics

Demographic and medical characteristics of the high-risk and low-risk VLBW groups at 8 years reflect the research design (Table). The high-risk VLBW children had lower birth weights, gestational ages, more neurologic and medical risk at birth, and lower IQ at 8 years compared with the low-risk VLBW and term children (Table). IQ scores were in the range of mental retardation (IQ < 70) for 19% of the high-risk VLBW children, 9% of the low-risk VLBW children, and <2% for the term children (χ² = 13.4; P < .001). The groups did not differ in terms of sex, race, social class, or maternal marital status.

Educational Attainment

At birth, mothers in the 3 groups had not differed in achieved years of education, but at child age 8 years, the mothers of both high-risk and low-risk VLBW children had attained significantly fewer years of additional education than the mothers of term children (term, 14.2 ± 2 years; high-risk and low-risk VLBW, 13.5 ± 2 years; t = 2.5; P < .01). On average, educational level increased by 9.1 months in the
mothers of term children and by 5.6 months in the mothers of high-risk and low-risk VLBW children (t = 2.2; P = .03).

Stressful Family Events During the Past Year

The total score of the FILE differed by birth group (χ² = 5.9; degrees of freedom [df] = 2; P < .052), reflecting differences in the Intrafamily Strains subscale. Surprisingly, the mothers of both high-risk and low-risk VLBW children reported fewer family strains than the mothers of term children at 8 years (mean, 2.5 ± 2.8 for the high-risk VLBW group, 2.8 ± 2.6 for the low-risk VLBW group, and 3.5 ± 2.8 for the term group (F = 7.5; P < .02). The mothers of high-risk and low-risk VLBW children reported less parent-child conflict, and the mothers of high-risk VLBW children reported that their children were engaged in fewer outside activities and were less difficult to manage compared with the low-risk VLBW and term mothers. There was no significant difference in parental divorce rate in the 3 groups, with divorce reported in 14 (16%) families of high-risk VLBW children, 4 (7%) families of low-risk VLBW children, and 11 (12%) families of term children (χ² = 1.1; P < .33).

Because in this study there were no differences among the 3 groups in maternal education or the incidence of stressful life events at birth, and because these factors had been considered confounding factors in the study design, they were controlled for in the remaining analyses.

Partner Relationship and Social Support

The MANCOVA was marginally significant (F = 1.72; P < .09). There were no differences on the DAS in Affection, Satisfaction, and Cohesion, but the mothers of both high-risk and low-risk VLBW children reported a lower level of Consensus With Partner/Spouse compared with the mothers of term children (F = 5.26; P < .006).

Perception of Child Health

Mothers perceived their child’s health differently at school age related to the child’s birth risk status. Only 66% of the mothers of high-risk VLBW children reported that their child was in excellent health, in contrast to 82.5% of the mothers of low-risk VLBW and term children (Figure 1). Likewise, the mothers of high-risk VLBW children described their children as being more limited in daily physical activities than term children, whereas the mothers of low-risk VLBW children did not. Nevertheless, the mothers of both high-risk and low-risk VLBW children were more likely to express concern for their child’s health than were the mothers of term children. Limitations in everyday activities, pain, and family cohesion did not differ among the 3 groups.

Psychological Distress

In contrast to earlier ages, there were no differences on the Summary Score (F = .61; P < .55) or any subscale on the BSI.
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risk (significantly from the term mothers. 

those of high-risk VLBW children, but neither group differed 

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perceived their children to be more stressful, demanding, 

reflecting that the mothers of high-risk VLBW children 

Impact On Family 

Perceived family impact of the child differed by group (Figure 2). The mothers of high-risk VLBW children reported greater family and social impact, greater personal strain, and greater financial strain compared with the mothers of term children. Mastery scale scores did not differ.

Parenting Stress 

Child Domain scores differed by group (Figure 3), reflecting that the mothers of high-risk VLBW children perceived their children to be more stressful, demanding, distractable, and hyperactive, and less acceptable and adaptable compared with the mothers of low-risk VLBW and term children. Parent Domain scores also differed among the 3 groups (mean, 112.5 ± 22, 106.7 ± 27, and 110.1 ± 23, respectively; F = 3.1; P < .05), indicating that the mothers of low-risk VLBW children had lower parenting stress than those of high-risk VLBW children, but neither group differed significantly from the term mothers.

Coping Mechanisms 

The MANCOVA was marginally significant (Wilks’ λ = .94 [F = 1.85; df = 8,440; P < .07]). The mothers of high-risk VLBW children were less likely to use withdrawal/avoidant coping, including denial, mental disengagement, and behavioral disengagement than the mothers of term children (mean, 17.7 ± 3.85 vs 19.55 ± 5.00; F = 5.3; P < .01).

Moderating Effects of Social Class 

SES did not differentially affect family stress relative to birth risk on any outcome. Social class was related to general family stress (total PSI Stress Score [r = .15; P < .02]), in that higher stress was related to lower social class, but the relationship did not differ by birth risk.

Other Factors Affecting Stress and Coping 

In addition to high-risk VLBW, other factors were related to maternal stress and coping. Multiple birth was related to greater maternal social isolation (β = -.12; P < .05). There were also trends toward greater negative family impact (β = .12; P < .07), lower feelings of mastery (β = -.12, P < .08), less child acceptability (β = .11; P < .07) and attachment (β = .13; P < .06), and to less use of humor (β = -.11; P < .09).

Lower IQ had low to moderate correlations with greater parenting stress in various areas, including less child acceptability (r = .38; P < .001), lower parent sense of competence (r = −17; P < .01), and greater role restriction and social isolation (r = −.15; P < .05). Financial and total family impacts also were related to lower child IQ (r = −.20, −.30, P < .002).

Higher maternal education was related to lower parenting stress in both the Child Domain (β = −0.19; P < .003) and the Parent Domain (β = −0.18; P < .002) of the PSI, as well as to all coping factors, including more active (β = .25, P < .0002), more adaptive (β = .25; P < .0002), less avoidant (β = −.21, P < .0001), and more acceptance (β = .16; P < .02) coping.

DISCUSSION 

At child age 8 years, the pattern of maternal adaptation to VLBW birth was similar to that noted at the 3-year follow-up,12 indicating significant stress in mothers of high-risk VLBW children but largely equivalent experiences between the mothers of low-risk VLBW children and those of term children. However, there were several areas in which the mothers of both high-risk and low-risk VLBW children differed from term mothers. The mothers of VLBW children did not advance in educational attainment at the same rate that mothers of term children did over the 8-year period, indicating a significant and long-lasting impact of the VLBW

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birth. Both groups reported greater concern than mothers of term children for the health of their child, even though mothers of low-risk VLBW children perceived their child’s health to be generally excellent. Surprisingly, although they also reported less parent-child conflict with their school-age children than mothers of term children, they reported less consensus in their marital/partner relationship.

As occurred at 3 years, at 8 years some effects of VLBW birth were found only for mothers of high-risk VLBW children, whose children at school age had lower IQ scores and higher rates of mental retardation. These mothers continued to report more negative family, social, and financial impacts and more personal strain from parenting compared with the mothers of low-risk VLBW and term children. As at 3 years, mothers in the 3 groups did not differ in terms of psychological distress symptoms, divorce rate, perception of family cohesion, or sense of mastery in parenting. Although the findings of fewer intrafamily strains, such as parent-child and sibling conflict, were unexpected, they are consistent with our other findings of greater parental concern for their child’s health, more child physical limitations, and fewer child activities outside the home, all of which may lead to increased parental monitoring and more child dependency and compliance, perhaps reducing or delaying some stressors of parenting school age children.

Earlier studies of this sample revealed no differences in maternal use of coping strategies 2 years postpartum in the mothers of high-risk VLBW children, who at that time had greater psychological distress symptoms than the mothers of low-risk VLBW and term children. At age 8 years, however, the mothers of high-risk VLBW children were less likely to use denial and mental disengagement in coping than the mothers of low-risk VLBW and term children, but no differences in maternal psychological symptoms were found among the 3 groups. Greater use of such avoidant coping has been associated with maternal psychological distress in mothers of VLBW and medically fragile children. The findings from the present study may demonstrate a positive adaptation over time in the mothers of high-risk VLBW children. The decrease in clinical symptoms of depression and anxiety, which had been prominent at birth and 2 years postpartum, and the general similarity of psychological symptoms with the mothers of low-risk VLBW and term mothers at child age 8 years suggest that these mothers have adopted less avoidant coping strategies to manage the significant stressors (eg, greater care giving demands, higher financial burdens, and poorer child outcomes) associated with parenting.

Although these findings may be unexpected, other studies support such positive outcomes in mothers of high-risk VLBW infants. In families with children with disabilities, mothers with greater caregiving demands also reported more personal growth and maturity. Parenting a child with disability may provide mothers with more opportunities to deal successfully with challenges and increase feelings of efficacy. Alternatively, positive perceptions may be a mechanism for coping with the stressors of caring for a child with disabilities. Keep in mind, however, that mothers may deny negative feelings because of social desirability bias. Multiple birth added to negative family impact and parenting stress. Mothers with multiple births felt more parenting stress and social isolation, consistent with previous studies. This is the first prospective study to assess the impact of multiple births within a VLBW cohort. Because negative effects were not apparent in this cohort at earlier ages, these findings indicate that the stressors for multiple birth families may increase with child age.

Higher maternal education was associated with lower stress, possibly through its association with greater use of coping mechanisms. In mothers of term children, higher maternal education has been found to enhance self-efficacy. Thus, lower maternal educational attainment, one outcome of VLBW birth, may be an additional mechanism by which VLBW birth contributes to parenting stress.

Finally, lower child IQ and SES predicted higher stress across all domains for all mothers. Although the effects of SES were not different by VLBW or risk status, these findings support the notion that SES is a risk factor for greater parenting stress for all families.

Limitations of the present study include an absence of data on fathers, who could not be reliably recruited despite attempts to do so. Thus, parental sex differences were not explored. In addition, measures of family impact were based on self-reports rather than objective measurement, and the interval between the 3-year and 8-year follow-ups did not allow us to make inferences about factors that may have altered maternal symptoms or coping strategies.

The increased survival rate of VLBW infants may be accompanied by important improvements in their medical care. However, survival of VLBW infants often results in child disability and family stress. Corresponding advances are needed to address maternal and family issues to ensure the long-term optimal outcome for VLBW infants and their families. Physicians and educators must be aware of burdens experienced by these families over time, so that appropriate advice and/or referrals can be provided to help ensure optimal family function and support for the long-term care of VLBW infants.

We thank the participating families and hospitals, Terri Lotz-Ganley for manuscript preparation, and Nancy Klein, PhD, George Asaad, and Elizabeth H. Lottig for assistance with data collection, coding, and analysis.

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Parenting Very Low Birth Weight Children at School Age: Maternal Stress and Coping

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Determinants of Life Quality in School-Age Children with Cerebral Palsy

Annette Majnemer, PhD, OT, Michael Shevell, MD, CM, Peter Rosenbaum, MD, CM, Mary Law, PhD, OT, and Chantal Poulin, MD

Objective To characterize the quality of life of children with cerebral palsy from the parents’ and children’s perspectives.

Study design Ninety-five children were recruited: a parent, and when feasible, the child also completed the Child Health Questionnaire and Pediatric Quality of Life Inventory. A range of predictor variables was measured relating to impairments, activity limitations, personal and environmental factors.

Results Mean age was 9.3 ± 2.1 years; 63.2% were male, and almost half had mild motor impairment (47% Gross Motor Function Classification System level I). Mean physical well-being (Child Health Questionnaire) was 39.6 ± 16.9 with 50% < 40; and mean psychosocial well-being was 43.0 ± 11.3 with 53.8% < 40. Similarly, with the Pediatric Quality of Life Inventory, 61% had summary scores < 1 SD. Scores of parents and their children were significantly correlated (physical: r = .59, P < .0001; psychosocial: r = .39, P = .01); however, children rated themselves higher.

Conclusions Results indicate that quality of life is highly variable in children with cerebral palsy, with about half experiencing a life quality similar to typically developing children. Motor and other activity limitations are indicators of physical but not psychosocial well-being. Family functioning, behavioral difficulties, and motivation are important predictors of social-emotional adaptation. Determinants of life quality may guide resource allocation and health promotion initiatives to optimize health of the child and family. (J Pediatr 2007;151:470-5)

Children with cerebral palsy (CP) experience difficulties associated with limitations in everyday activities. Children with CP are at risk for lower participation in social and leisure activities.1,2 Nonetheless, few studies have described their quality of life (QOL)—defined as a person’s perception of their well-being and satisfaction with life.3,4 This multidimensional construct includes elements about general functioning, as well as the person’s appraisal of their life experiences and social/emotional well-being. Use of generic QOL measures provides information that is not specific to the disease process and enables one to compare perceived QOL with universal values.5 Liptak et al6 described the QOL of children and youth with moderate to severe CP with the Child Health Questionnaire (CHQ). Mean scores were not provided, and no predictor variables were identified. Z scores above the normative mean occurred for Behavior and Mental Health subscales, whereas Physical Summary score and Impact on Parents–Time subscale were below −1 Z score. In a study by Wake et al,8 mean CHQ scores were significantly lower than the mean of 50 ± 10. Severity of CP was predictive of physical well-being only. Cognitive level and epilepsy were not predictive of CHQ scores. Houlihan et al9 assessed children and youth with Gross Motor Function Classification System (GMFCS) levels III-V also with the CHQ; however, scores were not described. There was a modest association between pain and the Parental Impact–Emotional subscale (r = .38, P < .001). Another study of children with CP also identified lower CHQ scores, with better psychosocial scores compared with physical well-being scores. Consistent with previous studies, level of motor function was associated with physical well-being and parent impact domains.10 Kennes et al11 evaluated children with CP using the Health Utilities Index (HUI-3). Severity of CP was variably associated with most components of the HUI but not with pain or emotion. One study

<table>
<thead>
<tr>
<th>CHQ</th>
<th>Child Health Questionnaire</th>
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<tr>
<td>CP</td>
<td>Cerebral palsy</td>
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<tr>
<td>DMQ</td>
<td>Dimensions of Mastery Questionnaire</td>
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<tr>
<td>GMFCS</td>
<td>Gross Motor Function Classification System</td>
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<tr>
<td>GMFM</td>
<td>Gross Motor Function Measure</td>
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</table>

HUI-3 Health Utilities Index
PedsQL Pediatric Quality of Life Inventory
QOL Quality of life
SD Standard deviation
VABS Vineland Adaptive Behavior Scale
sought the perspective of children and youth with CP. QOL scores were lower than typically developing peers but similar to children with other chronic health conditions. More than half of individuals with disabilities report a good to excellent life quality, whereas outside observers assume such lives to be undesirable. Clarification is needed with respect to the perceived QOL of children with CP. Reported studies had samples with a wide age range (eg, 5-18 years); however, it may be important to differentiate children from adolescents. With one exception, studies to date have exclusively used parents as proxy respondents. The objectives of this study were to (1) characterize QOL of school-aged children with CP from the perspectives of the parents and the children themselves, and (2) evaluate biomedical, functional, and contextual factors as possible determinants of QOL. We hypothesized that contextual factors would be significantly positively associated with quality of life, whereas impairments and activity limitations would be less predictive, particularly of psychosocial well-being.

METHODS

Design
In this historical cohort study, a sample of children diagnosed with CP by a single pediatric neurologist was recruited at school age (6-12 years) to ascertain health-related QOL. In this community, all children suspected of having CP are referred to a neurologist for diagnostic confirmation, etiologic determination, and medical management. Therefore this sample is believed to be representative of the population of children with CP. All files in the neurologist’s database within July 1991-June 2001 with a diagnosis of CP were reviewed. Files that met the selection criteria were sent a letter and consent form, outlining the study aims and procedures. Families who did not respond were called by the project coordinator to clarify procedures and determine whether they wished to participate. Once consent was obtained, an appointment was made for an evaluation at the Montreal Children’s Hospital. A neurologist examined all children to verify the diagnosis of cerebral palsy. An occupational therapist interviewed the families using the Vineland Adaptive Behavior Scale and carried out the Gross Motor Function Measure. A psychologist performed the Leiter Intelligence Test. While the child was assessed, parents completed questionnaires (see below). When feasible (determined by parent and interviewer, based on the child’s cognitive abilities and concentration), children also completed the QOL measures. Parents completed a brief questionnaire on demographic data, type of schooling (segregated, integrated), and current rehabilitation services provided to their child. All evaluators were blinded to medical history and each other’s findings. The study took 2.5 to 3 hours to complete, and rest periods were provided as needed. All measures selected were age-appropriate, standardized, with very good reliability and validity. Questionnaires were available in English and in French.

Subjects
The initial cohort in the database included 217 children with CP, and those who were school age during recruitment (2003-2005) were approached. Progressive disorders and disorders of non-cerebral origin were not included as per the definition of CP. Disorders not traditionally categorized as CP in spite of clinical presentation were excluded.

Measures of QOL
A parent served as a proxy respondent for their child’s perception of QOL using self-administered questionnaires. One tool was the Child Health Questionnaire (CHQ), a generic health-related QOL measure that quantifies the physical and psychosocial well-being of children >5 years. It provides detailed information on 14 multidimensional health concepts. This scale was rigorously developed and has excellent internal consistency and discriminant validity. The CHQ-PF50 (Parent Form–50 item) was used, which has a reliability of 0.93 (.66-.94 for subscales). Scores were transformed to T-scores (mean 50 ± 10) for the physical and psychosocial well-being summary scores, with higher scores indicating better QOL. The Pediatric Quality of Life Inventory (PedsQL 4.0) is another health-related QOL measure. It is a brief, generic scale with child self-reports (>5 years) and parent proxy-reports. The advantage of including this additional QOL measure was that it is more likely to be completed by the children themselves, given that it’s short and the forms are developmentally appropriate. Therefore only the PedsQL was completed by the children, if feasible. The PedsQL evaluates physical, emotional, social, and school domains. It has excellent validity, responsiveness, and reliability. This user-friendly generic measure was selected as a summary assessment of overall well-being. A 5-point scale is used per item, and items are reverse-scored and transformed (0-100 scale), with higher scores indicating a better QOL. Two summary scores may be derived (physical and psychosocial). Normative means are available for total and subscale scores.

Determinants of Quality of Life

Body Structures and Functions. We examined whether certain biomedical exposures documented at diagnosis were associated with worse outcomes. Type of CP was noted on neurologic examination, and the larger subgroups (hemiplegia, diplegia, and quadriplegia) were compared. A history of neonatal difficulties (necessitating neonatal intensive care) was examined as a predictor variable. Gestational age and presence of microcephaly (<2nd percentile) were also evaluated as risk factors. Behavior and cognition may influence QOL; therefore behavioral difficulties were measured with the Strengths & Difficulties Questionnaire, completed by parents. The psychologist evaluated intelligence with the Leiter Intelligence Scale, suitable for children with motor impairments.
**Activity Limitations.** Motor function was determined with the Gross Motor Function Measure (GMFM) by a trained evaluator. This criterion-referenced measure was developed for children with CP. An interval score (0-100) was derived.\(^22\) Severity of motor function was classified with the Gross Motor Function Classification System (GMFCS).\(^27\) The Vineland Adaptive Behavior Scale is a norm-referenced measure of functional status in communication, daily living skills, socialization, and adaptive behavior.\(^21\) With a semi-structured interview format, typical functional performance (what the child does do) is documented. The measure has a normative mean of 100 ± 15.

**Personal Factors.** Child’s age and sex at assessment may influence QOL. Child’s mastery motivation behaviors were measured as a possible determinant with the Dimensions of Mastery Questionnaire (DMQ).\(^28\) This parent-completed questionnaire evaluates the child’s persistence at object-oriented tasks, gross motor tasks, social persistence with adults and with other children, and also measures mastery pleasure and general competence. Normative data are available per subscale.

**Environmental Factors.** Family functioning was believed to be an important modifier of QOL. Therefore a parent completed 2 questionnaires that assess parents’ stress level and impact of the child’s condition on the family. The Parenting Stress Index—short form\(^29\) measures magnitude of stress in the parent-child system. Scores >85th percentile indicate high stress and <15th percentile indicate a defensive response. The Impact on Family Scale\(^30\) evaluates financial impact, disruption of planning, and caregiver and familial burden. An overall impact score is derived. We also examined whether school setting (segregated/integrated) and current involvement in rehabilitation services were associated with QOL. Family income was used as a marker of socioeconomic status.

**Statistical Analyses**

Descriptive statistics were used to characterize the sample and the outcomes. Univariate analyses determined which variables were significantly associated with QOL summary scores (parent ratings). Pearson correlations were used for continuous predictor variables, and simple linear regressions were used for categorical variables. Associations with \(P < .15\) were entered into stepwise selection models. Variables identified from these models were then entered into multiple linear regression models to derive the best predictive models. Given the sample size limitations, a maximum of 5 independent variables was included in each model.

**RESULTS**

**Group Characteristics**

Of the original 217 children in the database, 153 met criteria, but 25 were lost to follow-up. Of 128 approached, 33 (25.8%) refused to participate. Thus 95 subjects were recruited. Forty-three of 95 subjects (45.3%) were born prematurely with a mean gestational age of 30.8 ± 4.1 weeks, and 63.2% were male. At initial assessment by the neurologist, 82% had a suspected cause (28% asphyxia, 14% periventricular leukomalacia, 13% cerebral dysgenesis, 12% intracranial hemorrhage, 8% vascular event, 6% infection, 3% toxins), and 31% had microcephaly. Almost half had minimal mobility restrictions, and one quarter had severe limitations (GMFCS I, 47%; II, 16%; III, 2%; IV, 9%; V, 26%). In terms of spastic pattern, 36% had quadriplegia, 26% had hemiplegia, and 20% had diplegia; the remainder had other patterns. More than half were integrated into regular schools, although 44% were in schools for children with disabilities. Most (84%) were receiving rehabilitation services. Mean age at assessment was 9.3 ± 2.1 years (5.8–12.9). Table I provides scores on motor, cognitive, functional, and mastery motivation measures and performance on family functioning measures. Cognitive deficits, behavioral concerns, and activity limitations across domains were common. More than one third of parents indicated high levels of stress.

**Performance on Quality of Life Measures**

The CHQ provided information on 14 attributes contributing to QOL, whereas the PedsQL was shorter, allowing us to compare scores between parents and their children. In our sample, 55/95 (58%) children were able to complete this questionnaire independently (Table I). CHQ scores were 1 SD below the normative mean for physical well-being, with scores somewhat higher for psychosocial well-being. About half had scores <40 on both domains. Table II (available at www.jpeds.com) shows the proportion with scores <1 SD for the attributes that comprise the CHQ. For the PedsQL, more than half of parents rated their child’s well-being as <1 SD compared with norms. Children were less likely to rate themselves low for psychosocial well-being. Physical well-being correlated between parents and children (\(r = .59, P < .0001\)), but associations were weaker for psychosocial well-being (\(r = .39, P = .01\)).

**Determinants of Physical Well-Being**

Similar determinants of physical well-being were identified by the CHQ and the PedsQL (Table III; available at www.jpeds.com). The strongest predictor of physical functioning was the GMFM. Activity limitations (VABS scales) and higher GMFCS levels were also associated with diminished physical well-being, as was attendance at a segregated school. Children with spastic quadriplegia had lower physical functioning scores than those with hemiplegia. Families who were experiencing difficulties coping had lower ratings. The child’s persistence in performing tasks (motivation) correlated with better physical functioning (PedsQL). Parental stress was negatively associated with physical well-being. Children were more likely to be receiving rehabilitation (94% vs 69%) if their physical well-being (PedsQL) was low (with services: 44.7 ± 29.9, without: 76.0 ± 24.3). GMFM score, GMFCS
Table I. Performance on developmental, family function and quality of life measures

<table>
<thead>
<tr>
<th>Measures</th>
<th>Mean ± SD (range)</th>
<th>% beyond cut-off</th>
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<tbody>
<tr>
<td>Developmental measures</td>
<td></td>
<td></td>
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<tr>
<td>Gross Motor Function Measure</td>
<td>70.9 ± 28.1 (41-100.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Leiter&lt;sup&gt;a&lt;/sup&gt; Fluid Reasoning</td>
<td>81.9 ± 19.1 (50-126)</td>
<td>28.3% &lt;70</td>
</tr>
<tr>
<td>Leiter&lt;sup&gt;a&lt;/sup&gt; Brief IQ</td>
<td>81.0 ± 21.7 (38-143)</td>
<td>28.3% &lt;70</td>
</tr>
<tr>
<td>Strengths and Difficulties Questionnaire (total score)</td>
<td>11.9 ± 6.0 (0-28)</td>
<td>12.2% borderline</td>
</tr>
<tr>
<td>SD (range) % beyond cut-off</td>
<td></td>
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<tr>
<td>VABS Communication</td>
<td>64.1 ± 30.2 (11-123)</td>
<td>63.4% &lt;78</td>
</tr>
<tr>
<td>VABS Daily Living Skills</td>
<td>59.5 ± 30.3 (20-112)</td>
<td>64.6% &lt;78</td>
</tr>
<tr>
<td>VABS Socialization</td>
<td>73.3 ± 26.0 (20-117)</td>
<td>48.1% &lt;78</td>
</tr>
<tr>
<td>VABS Adaptive Behavior</td>
<td>61.9 ± 28.1 (20-116)</td>
<td>65.4% &lt;78</td>
</tr>
<tr>
<td>Dimensions of Mastery Questionnaire-Total Persistence</td>
<td>3.0 ± 0.7 (1.5-4.4)</td>
<td>N/A</td>
</tr>
<tr>
<td>Dimensions of Mastery Questionnaire-Total Mastery Motivation</td>
<td>3.2 ± 0.6 (1.6-4.5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Family functioning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impact on Family-Total Impact</td>
<td>30.4 ± 10.7 (15-55)</td>
<td>N/A</td>
</tr>
<tr>
<td>Parenting Stress Index-Total Stress</td>
<td>66.7 ± 32.0 (1-99)</td>
<td>43.8% high stress &gt;85&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Child Health Questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical summary score</td>
<td>39.6 ± 16.9</td>
<td>50.0% &lt;40</td>
</tr>
<tr>
<td>Psychosocial summary score</td>
<td>43.0 ± 11.3</td>
<td>53.8% &lt;40</td>
</tr>
<tr>
<td>PedSQL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical summary score</td>
<td>Parent: 50.4 ± 31.2</td>
<td>Parent: 60.9% &lt;1 SD</td>
</tr>
<tr>
<td>Psychosocial summary score</td>
<td>Child: 62.7 ± 21.1</td>
<td>Child: 65.5% &lt;1 SD</td>
</tr>
<tr>
<td></td>
<td>Parent: 61.7 ± 16.7</td>
<td>Parent: 61.2% &lt;1 SD</td>
</tr>
<tr>
<td></td>
<td>Child: 65.6 ± 15.3</td>
<td>Child: 49.1% &lt;1 SD</td>
</tr>
</tbody>
</table>

SD, Standard deviation; IQ, intelligence quotient; VABS, Vineland Adaptive Behavior Scale; N/A, not applicable.

<sup>a</sup>Plus additional 25.3% not testable because of cognitive limitations.

level, segregated school setting and rehabilitation services were highly correlated (ie, co-vary), therefore the GMFM was used for multivariate analyses because it was a continuous variable and had the strongest associations. The best predictive model for physical well-being indicated that the GMFM was highly associated with both QOL measures. Together with mastery motivation, these variables explained 65% of the variance of the PedsQL physical summary score (Table IV).

**Determinants of Psychosocial Well-Being**

Few variables, including biomedical factors, were associated with psychosocial well-being. Behavioral difficulties and poor socialization skills in the child were correlated with lower social-emotional well-being. Several aspects of mastery motivation, including object persistence ($r = .33$, $P = .006$) and persistence in motor tasks ($r = .31$, $P = .009$), in addition to subscales on **Table V** (available at www.jpeds.com) were also correlated. Higher levels of parental stress were strongly associated with child’s psychosocial well-being as well. Children with poor psychosocial scores were more likely to be receiving rehabilitation services (92% vs 71%; with services: mean = 58.4 ± 15.4; without: 75.8 ± 15.6). On multivariate analysis, behavioral difficulties and their impact on family life were highly associated with poor psychosocial well-being. Socialization skills and impact on the family were predictive with the CHQ whereas receipt of rehabilitation was associated with this summary score on the PedsQL. These factors together explained 55% to 60% of the variance of psychosocial well-being (Table IV).

**DISCUSSION**

Measurement of QOL, in addition to other developmental attributes, provides a more holistic view of overall functioning. These subjective perspectives are better indicators of social-emotional adaptation and a well-balanced life than objective measures. Individuals with disabilities have satisfactory well-being in spite of significant deficits, suggesting that individuals can adapt well to their activity limitations. Results of our study indicate that almost half of school-age children with CP experience a life quality similar to typically developing peers in spite of important functional limitations, thus confirming the disability paradox. Scores for physical well-being were lower than for psychosocial well-being, validating 2 recent studies. Examination of the attributes of the CHQ indicates that low scores are often associated with an impact on the parents’ emotional state, time constraints, and interruption of family activities, but not family cohesion. Diminished QOL was often associated with the child’s limitations in social roles (at school, with friends) because of emotional or behavioral difficulties. Children rated their QOL similarly to their parents; however, they were less likely to rate themselves low on psychosocial well-being, suggesting a more optimistic view of their social-emotional health. Mean ratings were similar to a recent study reporting
less important. Similarly, factors important for achieving a determinants of QOL, with disability characteristics being and individual adaptability (eg, motivation, hardiness) as key environments (eg, positive family coping, strong support network) nature on adults with disability has identified supportive envi-
ronments (eg, positive family coping, strong support network) to greater personal satisfaction with life.

It is increasingly appreciated in individuals with disabilities that contextual factors are important determinants of QOL. Nonetheless, available evidence in children with CP has not examined the importance of personal and environmental factors as mediators or modifiers of QOL. Demographic characteristics were not predictive in this study. Our sample was limited to children of school-age and differences by age and sex were not found within this particular stage. We would expect that families with higher income might have access to more resources and supports; however, we did not find a correlation between family income and QOL. It is conceivable that family expectations and knowledge of potential resources may mediate this relationship. A high mastery motivation, known to be associated with self-efficacy and pride in accomplishment, was related to a child's subjective well-being and satisfaction with life. This highlights the importance of child-centered rehabilitation approaches, whereby therapists capitalize on intrinsically motivating activities to promote health and functioning.

Family functioning is a vital environmental factor that can stabilize or disrupt a child's well-being. Parents of children with disabilities are at risk for experiencing ongoing stress, undermining family stability, and coping abilities. Factors contributing to parental stress are variable but do not appear to be related to the severity of their child's health condition. Rather, parental stress appears closely associated with their child's behavior and psychosocial adjustment. Children with similar disability levels may adapt differentially to their deficits, and families may use different coping strategies. Positive adaptation to disability by families encourages more effective adaptive responses in the child, whereas poor family adaptation may diminish their child's

Table IV. Best predictive models (multiple linear regressions with \( P < .0001 \) for the model) for physical and psychosocial well-being with the PedsQL and the CHQ

<table>
<thead>
<tr>
<th>Quality of life outcomes</th>
<th>Independent variables in the model</th>
<th>% variance explained by model (r²)</th>
<th>( \beta ) (parameter estimate)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical well-being</strong></td>
<td><strong>PedsQL</strong></td>
<td>65% (0.6546)</td>
<td>0.83</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>1. GMFM score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. DMQ-gross motor persistence</td>
<td></td>
<td>6.72</td>
<td>.0299</td>
</tr>
<tr>
<td></td>
<td>3. DMQ-social persistence with adults</td>
<td></td>
<td>−7.93</td>
<td>.0058</td>
</tr>
<tr>
<td></td>
<td><strong>CHQ</strong></td>
<td>32% (0.3206)</td>
<td>0.34</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>1. GMFM score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychosocial well-being</strong></td>
<td><strong>PedsQL</strong></td>
<td>55% (0.5460)</td>
<td>−1.36</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>1. SDQ-total score</td>
<td></td>
<td>−13.52</td>
<td>.0012</td>
</tr>
<tr>
<td></td>
<td>2. Rehabilitation services</td>
<td></td>
<td>−1.38</td>
<td>.0341</td>
</tr>
<tr>
<td></td>
<td>3. SDQ-impact scale</td>
<td></td>
<td>−1.12</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td><strong>CHQ</strong></td>
<td>60% (0.5998)</td>
<td>−0.22</td>
<td>.0072</td>
</tr>
<tr>
<td></td>
<td>1. VABS-socialization</td>
<td></td>
<td>−1.48</td>
<td>.0019</td>
</tr>
<tr>
<td></td>
<td>2. SDQ-total score</td>
<td></td>
<td>−1.48</td>
<td>.0019</td>
</tr>
<tr>
<td></td>
<td>3. SDQ-impact score</td>
<td></td>
<td>−0.55</td>
<td>.0007</td>
</tr>
<tr>
<td></td>
<td>4. IOF-total impact</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*IOF: Impact on family scale; SDQ: Strengths and Difficulties Questionnaire.*
subjective well-being. Our results indicate that high parental stress and poor family coping negatively impact on a child’s QOL. Resources and supports to enhance family coping and minimize stress are therefore critical to improve child and family well-being. Therefore future studies are needed to validate these findings and test the causal relationship between predictor variables and QOL, so effective health promotion initiatives may be developed to enhance the life quality of children with CP. Furthermore, longitudinal studies would be helpful in determining the stability of quality of life over time.

We wish to acknowledge the efforts of our research coordinator, Nicholas Hall. We are especially grateful to the children and families for their participation in this study. Special thanks to occupational therapists Rena Birnbaum, Cynthia Perlman, and Amy Brownstein, and psychologists Lisa Steinbach, Nancy Margret, Mafalda Porporino, Terry Viola, and Chantalle Martel for their assistance in testing.

REFERENCES

5. Guyatt GH, Naylor CD, Juniper E, Helyard DK, Jaszczuk R, Cook DJ, for the Evidence-based medicine working group. Users’ guides to the medical literature. XII. How to use articles about health-related quality of life. JAMA 1997;277:1232-7.  
Table II. The percentage of children with scores <1 SD of the normative mean on each of the 12 attributes that contribute to the subscales of the CHQ

<table>
<thead>
<tr>
<th>Attributes</th>
<th>CP sample % &lt;1 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent impact-emotional</td>
<td>59.5</td>
</tr>
<tr>
<td>Social role limitations because of emotional/behavioral issues</td>
<td>56.1</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>48.8</td>
</tr>
<tr>
<td>Parent impact-time</td>
<td>48.8</td>
</tr>
<tr>
<td>Family activities</td>
<td>48.2</td>
</tr>
<tr>
<td>Social role limitations due to physical issues</td>
<td>39.5</td>
</tr>
<tr>
<td>Mental health</td>
<td>38.6</td>
</tr>
<tr>
<td>Self esteem</td>
<td>38.5</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>35.7</td>
</tr>
<tr>
<td>General health perceptions</td>
<td>34.5</td>
</tr>
<tr>
<td>Behavior</td>
<td>31.7</td>
</tr>
<tr>
<td>Family cohesion</td>
<td>11.9</td>
</tr>
</tbody>
</table>
Table III. Predictors of physical well-being (parent’s rating) in children with cerebral palsy

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>PedsQL: Physical summary score</th>
<th>CHQ: Physical summary score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body structure and function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of CP</td>
<td>$r^2 = .25, P &lt; .0001$</td>
<td>$r^2 = .16, P = .005$</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>$r^2 = .06, P = .04$</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cognitive deficits (Leiter IQ)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Behavioral difficulties (SDQ)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Activity limitations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor function (GMFM)</td>
<td>$r = .79, P &lt; .0001$</td>
<td>$r = .57, P &lt; .0001$</td>
</tr>
<tr>
<td>Severity (GMFCS)</td>
<td>$r^2 = .57, P &lt; .0001$</td>
<td>$r^2 = .39, P &lt; .0001$</td>
</tr>
<tr>
<td>Communication (VABS)</td>
<td>$r = .61, P &lt; .0001$</td>
<td>$r = .40, P &lt; .0001$</td>
</tr>
<tr>
<td>Daily living skills (VABS)</td>
<td>$r = .71, P &lt; .0001$</td>
<td>$r = .52, P &lt; .001$</td>
</tr>
<tr>
<td>Socialization (VABS)</td>
<td>$r = .62, P &lt; .0001$</td>
<td>$r = .41, P &lt; .001$</td>
</tr>
<tr>
<td>Adaptive behavior (VABS)</td>
<td>$r = .66, P &lt; .0001$</td>
<td>$r = .45, P &lt; .001$</td>
</tr>
<tr>
<td><strong>Personal factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at assessment</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Family income</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total persistence (DMQ)</td>
<td>$r = .35, P = .0026$</td>
<td>NS</td>
</tr>
<tr>
<td>Total mastery motivation (DMQ)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>General competence (DMQ)</td>
<td>$r = .45, P &lt; .0001$</td>
<td>$r = .25, P = .04$</td>
</tr>
<tr>
<td>Negative reaction to failure (DMQ)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Environmental factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>School setting (segregated/integrated)</td>
<td>$r^2 = .22, P &lt; .0001$</td>
<td>$r^2 = .21, P &lt; .0001$</td>
</tr>
<tr>
<td>Rehabilitation services (yes/no)</td>
<td>$r^2 = .13, P = .0006$</td>
<td>$r^2 = .07, P = .0251$</td>
</tr>
<tr>
<td>Impact on family</td>
<td>$r = -.45, P &lt; .0001$</td>
<td>$r = -.43, P &lt; .0001$</td>
</tr>
<tr>
<td>Parental stress</td>
<td>$r = -.28, P = .01$</td>
<td>NS</td>
</tr>
</tbody>
</table>

Correlations ($r$ value) reported for continuous variables; simple linear regressions reported for categorical variables ($r^2$ value).

IQ, Intelligence Quotient; SDQ, Strengths and Difficulties Questionnaire; NS, not significant ($P > .05$).
Table V. Predictors of psychosocial well-being (parent’s rating) in children with CP

<table>
<thead>
<tr>
<th>Predictor variables</th>
<th>PedsQL: Psychosocial summary score</th>
<th>CHQ: Psychosocial summary score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body structure and function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of CP</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>$r^2 = .06, P = .03$</td>
<td>NS</td>
</tr>
<tr>
<td>Gestational age</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Cognitive deficits (Leiter IQ)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Behavioral difficulties (SDQ)</td>
<td>$r = -.62, P &lt; .0001$</td>
<td>$r = -.60, P &lt; .0001$</td>
</tr>
<tr>
<td>Activity limitations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor function (GMFM)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Severity (GMFCS)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Communication (VABS)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Daily living skills (VABS)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Socialization (VABS)</td>
<td>$r = .27, P = .02$</td>
<td>$r = .24, P = .04$</td>
</tr>
<tr>
<td>Adaptive behavior (VABS)</td>
<td>$r = .24, P = .02$</td>
<td>NS</td>
</tr>
<tr>
<td>Personal factors</td>
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<td></td>
</tr>
<tr>
<td>Age at assessment</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Family income</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total persistence (DMQ)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Total mastery motivation (DMQ)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>General competence (DMQ)</td>
<td>$r = .34, P = .005$</td>
<td>$r = .41, P = .0005$</td>
</tr>
<tr>
<td>Negative reaction to failure (DMQ)</td>
<td>$r = -.31, P = .009$</td>
<td>$r = -.37, P = .0018$</td>
</tr>
<tr>
<td>Environmental factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>School setting</td>
<td>$r^2 = .05, P = .05$</td>
<td>NS</td>
</tr>
<tr>
<td>Rehabilitation services (yes/no)</td>
<td>$r^2 = .14, P = .0004$</td>
<td>NS</td>
</tr>
<tr>
<td>Impact on family</td>
<td>NS</td>
<td>$r = -.24, P &lt; .05$</td>
</tr>
<tr>
<td>Parental stress</td>
<td>$r = -.43, P = .0002$</td>
<td>$r = -.49, P &lt; .0001$</td>
</tr>
</tbody>
</table>

Correlations ($r$ value) reported for continuous variables; simple linear regressions reported for categorical variables ($r^2$ value). IQ, Intelligence Quotient; SDQ, Strengths and Difficulties Questionnaire; NS, not significant ($P > .05$).
Long-Term Impact of Adolescent Dating Violence on the Behavioral and Psychological Health of Male and Female Youth

DIANN M. ACKARD, PHD, MARLA E. EISENBERG, SCD, MPH, AND DIANNE NEUMARK-SZTAINER, PHD, MPH, RD

Objective  To evaluate the long-term impact of adolescent dating violence (ADV) on behavioral and psychological health.

Study design  From a diverse sample of older adolescents who completed Project EAT in 1999 (wave 1) and 2004 (wave 2; mean age 20.4), 23 male and 102 female adolescents reporting ADV were compared with 671 male and 720 female adolescents reporting no ADV.

Results  ADV was positively associated with cigarette smoking and suicide attempts for both sexes, binge-eating and suicidal ideation in male adolescents, and smoking marijuana and high depressive symptoms in female adolescents in analyses unadjusted for wave 1 outcomes. In analyses adjusted for wave 1, in female adolescents, ADV was significantly associated with smoking cigarettes, marijuana use, and high depressive symptoms and marginally associated with suicide attempts; in male adolescents, ADV was significantly associated with smoking cigarettes and marginally associated with binge-eating and suicidal ideation. ADV was significantly associated with an overall high-risk profile (presence ≥3 health outcomes) for both sexes; results remained significant in female adolescents after adjusting for wave 1.

Conclusions  ADV is associated with greater likelihood of problematic health factors and increases nonspecific risk toward behavioral and psychological impairment in youth, particularly female adolescents. (J Pediatr 2007;151:476-81)

Approximately 2% to 9% of male1-5 and 4% to 20% of female1-3,5-8 adolescents in the United States have experienced physical or sexual abuse by their dating partner. Adolescent dating violence (ADV; physical violence, sexual violence, or both perpetrated by a dating partner) has been shown to be associated with compromised health. Specifically, it has been associated with alcohol use, drug use, or both,2,3,5-7 cigarette smoking,2 disordered eating behaviors,1,2,7,8 poorer self-esteem,1,2 depression and anxiety,1,2,4,6 sexual health risks and pregnancy among female adolescents,3-7 and suicidal thoughts and attempts1,2,4-7 in large, demographically diverse cross-sectional studies of youth. However, these studies are limited because they cannot determine a causal association or establish temporality.

Only a few studies have investigated the long-term impact of ADV. Two studies of college women identified that sexual victimization on a date during adolescence increased the risk for sexual victimization in college.10,11 However, these studies did not assess physical violence and did not include men. To address one of these limitations, 1500 college women were asked about physical victimization by a partner retrospectively across 2 periods (childhood and adolescence) and prospectively 3 times across 4 years of college.12 Women who reported ADV but not childhood physical or sexual abuse were more likely to report physical victimization, sexual victimization, or both by the fourth year of college than women who experienced no earlier violence (30.8% versus 15.6%). However, the study did not address the long-term impact on behavioral and psychological health for individuals who experience dating violence in adolescence.

A longitudinal study on the health consequences of violence reported on a national probability sample of >3000 adult women across a 2-year period.13 A new assault between the first and the last assessment, administered 2 years later, increased the odds of alcohol abuse by nearly 3-fold and drug use nearly 2-fold. A search for longitudinal studies on the impact of ADV on health risk behaviors in youth, men, or both yielded no findings.
Consolidating results from cross-sectional and longitudinal studies indicates that ADV is associated with a diverse set of health concerns and has been implicated as a cause for re-victimization or the uptake or worsening of substance use. It is possible that ADV is a nonspecific risk factor, meaning that ADV is significantly likely to increase the odds of health problems, but no one problem or set of problems is more prominent than others for all who have experienced dating violence. Other types of trauma, such as childhood sexual abuse, are nonspecific risk factors toward psychopathology.14-16

This study sought to investigate the associations between adolescent dating violence and subsequent health risks in a large population-based sample of teens. Specifically, we examined associations between ADV and extreme weight control behaviors, binge eating, suicidal ideation, suicide attempts, cigarette smoking, marijuana use, alcohol consumption, depressive symptoms, body dissatisfaction, and self-esteem, hypothesizing that ADV would be associated with higher risk profiles for outcomes.

METHODS

Design, Setting, and Participants

Data were drawn from Project EAT, an epidemiologic study of adolescent eating behaviors and weight-related issues with 2 waves of data collection 5 years apart (wave 1 in 1999 and wave 2 in 2004; mean age, 20.4 years; SD = 0.8).17,18 Project EAT participants were from 31 public middle and high schools in urban and suburban school districts in the greater St. Paul/Minneapolis, Minnesota, area; participants were diverse by age, race, body mass index, and socioeconomic status. In wave 1, participants completed Project EAT surveys and anthropometric measures of height and weight. After a complete description of the study was given, written informed consent was obtained. Approval for the study was granted by the University of Minnesota’s Institutional Review Board Human Subjects Committee and by the research boards of the participating school districts. The response rate for student participation in wave 1 was 81.5%.

The Project EAT wave 1 survey was revised for use in wave 2. Several new items were added to the wave 2 survey to explore issues of interest in older adolescents, including violence by a dating partner. The study team reviewed the literature and existing surveys to identify appropriate measures for use where available. Several items were added to make the demographic measures appropriate for young adults (eg, housing, employment status). A draft of the survey was pilot tested with 20 young adults, after which minor changes were made on the basis of feedback. Wave 2 surveys were sent by mail to the address provided by the participants during wave 1. Data collection ran from April 2003 to June 2004.

Of the original wave 1 cohort, 561 participants (18.2%) were lost to follow-up for various reasons, primarily missing contact information at wave 1 and no address found at follow-up. Of the remaining 2513 participants contacted, 1710 completed surveys, representing 55.6% of the original cohort and 68.0% of participants who were contacted for wave 2. The final wave 2 sample consisted of 764 male (44.7%) and 946 female (55.3%) participants.

For this study, participants included 1516 youth (46% male; 54% female) who completed Project EAT surveys at both wave 1 and wave 2, who completed questions on ADV, and who did not report ADV in the past year. They averaged 20.4 years of age at wave 2. The sample was reasonably distributed by socioeconomic status, with 12.2% in the lower quintile, 16.0% in the lower middle quintile, 23.7% in the middle quintile, 31.7% in the upper middle quintile, and 16.4% in the upper quintile. Participants described themselves as white (70.6%), Asian (14.8%), black (8.0%), Hispanic (3.6%), or other (3.1%) ethnicity. Self-reported ethnic background was assessed because the prevalence of some outcomes of interest (eg, weight-control behaviors, binge-eating) varies by ethnicity.

Measures

Adolescent dating violence was assessed with 2 questions: 1 for physical violence (“Have you ever been hit, shoved, held down or had some other physical force used against you by someone you were dating?”) and another for sexual violence (“In a dating relationship, have you ever been forced to touch your date sexually or have they forced some type of sexual behavior on you?”). The participant could mark as many answers that applied for each question: no; yes, in the past year; or yes, more than a year ago. Physical violence and sexual violence were combined for use in the current sample because some cells were too small for separate data analysis. Individuals in the ADV group answered, “yes, more than a year ago” to either or both physical and sexual dating violence. Individuals (n = 5) who answered “yes, in the past year” to either or both physical and sexual dating violence were excluded from further analyses to ascertain that the ADV occurred before the wave 2 dependent variables.

Participants were asked whether they used extreme weight-control behaviors with the question, “Have you done any of the following things in order to lose weight or keep from gaining weight during the past year?” followed by: took diet pills, made myself vomit (throw up), used laxatives, and used diuretics (water pills). Those reporting at least 1 of these are considered users of extreme weight control behaviors. To assess binge eating, participants were asked to answer (yes/no) the question, “In the past year, have you ever eaten so much food in a short period of time that you would be embarrassed if others saw you (binge-eating)?”

Thoughts about suicide (suicidal ideation) were measured with the question, “Have you ever thought about killing yourself?” (no; yes, more than a year ago; yes, during the past year). The presence of suicide attempts was measured by asking, “Have you ever tried to kill yourself?” (no; yes, more than a year ago; yes, during the past year). Those reporting ideation or attempts within the past year were considered to have these outcomes at wave 2.
Substance use was measured with a 5-point scale (never, a few times, monthly, weekly, daily) asking participants to mark “how often have you used the following during the past year (12 months)?”: cigarette smoking (monthly or more often versus a few times or less); alcohol consumption (weekly/daily versus monthly or less), and marijuana smoking (monthly or more versus a few times or less).

Body dissatisfaction, assessed with a modified version of Pingitore’s scale, included evaluations of 10 body parts, combined as an average composite score. Higher scores indicate greater body satisfaction. Internal reliability estimates (Cronbach’s alpha) for the current sample were .93 (male respondents) and .91 (female respondents) for the wave 2 composite scores. For this study, we used a “high body dissatisfaction” category to capture those scores in the highest quartile of dissatisfaction.

A scale by Kandel and Davies evaluated these depressive symptoms (not at all, somewhat, very much): fatigue; sleep disturbance; dysthymic mood; hopelessness; feeling tense/nervous; and worry. The summed scale ranged from 6 to 18; higher values indicate more severe depressive mood. We stratified the sample into quartiles and categorized those in the highest quartile as “high depressive symptoms.” Cronbach’s alpha reliability estimates for the current sample are .80 (male respondents) and .81 (female respondents).

Self-esteem was measured with 6 items from the Rosenberg Self-Esteem Scale, including items such as, “On the whole, I am satisfied with myself.” This scale had an internal reliability estimate of .83 (male and female respondents) at wave 2 and ranged from 6 to 24; higher scores indicate greater self-esteem. The “low self-esteem” category captured scores in the lowest quartile.

To assess nonspecific risk, a composite risk index was created. An individual reporting any 3 or more of these behaviors or conditions was considered to be high risk: extreme weight control; binge-eating; suicidal ideation; suicide attempt; smoking cigarettes at least monthly; drinking alcohol at least weekly; smoking marijuana at least monthly; high body dissatisfaction; high depressive symptoms; or low self-esteem.

### Data Analysis

Chi-square tests of association were used to compare the prevalence of wave 2 behavioral and psychological risks for young people reporting ADV and youth with no ADV history. Logistic regression models estimated the odds of each behavior for youth with ADV (versus youth with no ADV), controlling for the relevant behavior reported at wave 1, to predict the uptake or worsening of behaviors after the ADV experience. All analyses were stratified by sex and conducted with SAS software version 8.2 (SAS Institute, Cary, NC).

### RESULTS

Overall, 23 male and 102 female respondents reported ADV greater than 1 year ago. There were no significant differences in ADV by race or socioeconomic status.

#### Analyses Unadjusted for Wave 1 Outcomes

More males and females who reported ADV reported frequent cigarette smoking at wave 2 and suicide attempts within the past year than those who did not report ADV (Table I). Furthermore, ADV was significantly associated with binge eating and suicidal ideation among males and smoking marijuana at least monthly and high depressive symptoms among females.

#### Analyses Adjusted for Wave 1 Outcomes

In analyses adjusted for wave 1 scores on the same outcomes (Table II), ADV was significantly associated with smoking cigarettes, using marijuana, and high depressive symptoms in female respondents; results for the association between ADV and suicide attempts in female respondents approached significance. In male respondents, results from analyses adjusted for wave 1 outcomes indicated that ADV...
Table II. Odds of behavioral and psychological health outcomes and high-risk status: multiple logistic regressions adjusted for wave 1

<table>
<thead>
<tr>
<th>Health outcome</th>
<th>Males only (n = 694)</th>
<th>Females only (n = 822)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Behavioral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme weight control</td>
<td>0.69</td>
<td>0.59-0.80</td>
</tr>
<tr>
<td>Binge eating</td>
<td>3.60</td>
<td>2.99-4.34</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>3.05</td>
<td>2.26-4.04</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>7.55</td>
<td>5.87-9.59</td>
</tr>
<tr>
<td>Cigarettes (≥ monthly)</td>
<td>3.04</td>
<td>2.21-4.17</td>
</tr>
<tr>
<td>Alcohol (≥ weekly)</td>
<td>0.64</td>
<td>0.41-1.02</td>
</tr>
<tr>
<td>Marijuana (≥ monthly)</td>
<td>1.69</td>
<td>1.19-2.39</td>
</tr>
<tr>
<td><strong>Psychological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High body dissatisfaction</td>
<td>2.33</td>
<td>1.84-2.96</td>
</tr>
<tr>
<td>High depressive symptoms</td>
<td>2.08</td>
<td>1.48-2.85</td>
</tr>
<tr>
<td>Low self-esteem</td>
<td>0.83</td>
<td>0.52-1.34</td>
</tr>
<tr>
<td><strong>Risk index†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (≥ 3 outcomes)</td>
<td>1.83</td>
<td>1.42-2.38</td>
</tr>
</tbody>
</table>

*Analyses adjusted for the same behavioral or psychological outcome measure at wave 1.
†Analyses adjusted for high-risk status (≥3 behavioral or psychological outcomes at wave 1).

was significantly associated with smoking cigarettes and marginally associated with binge-eating and suicidal ideation.

In the entire sample, 14.7% of male and 31.6% of female respondents were categorized as high risk by virtue of reporting ≥3 of the 10 behaviors or conditions examined. In bivariate analyses, ADV was associated with high-risk status for male and female respondents; 30.4% of male and 50.0% of female respondents who reported ADV had ≥3 health risk factors, compared with only 13.1% of male and 27.4% of female respondents without ADV (male respondents: χ² = 5.65, P = .018; female respondents: χ² = 21.73%, P < .001). After adjusting for wave 1 high-risk status, associations between ADV and high risk at wave 2 remained statistically significant in female respondents, but not male respondents (Table II).

**DISCUSSION**

In this study, adolescent dating violence was found to be a nonspecific risk factor for behavioral and psychological health concerns, primarily among female youth. The lack of significant findings for male youth may be due to the small number of males affected by ADV, yielding low power to detect associations in sex-stratified analyses. Our findings are consistent with the many cross-sectional studies that have found that those who report ADV also report a myriad of health concerns.\(^1\)\(^-\)\(^9\)

However, this investigation builds on the extant cross-sectional literature by using data from a 2-wave longitudinal study, thereby allowing us to adjust for our outcome measure at wave 1 to determine whether ADV preceded the initiation or worsening of the health risks included in the survey. In part, the question of whether ADV or other problematic behaviors comes first arises from similar directionality concerns with longitudinal research on violence and risk behaviors among adults. For example, Kilpatrick and colleagues studied >3000 women in 3 assessment waves across 2 years to ascertain whether substance use contributes to later assault or assault contributes to substance use.\(^1\)\(^3\) Study results supported both directions of influence, thus illustrating a vicious perpetuation of violence and psychopathology that may reciprocally maintain itself; no matter which event comes first, the subsequent events maintain an ongoing cycle of violence and substance use.

Furthermore, this study adds to the extant literature with the development of an index to calculate the nonspecific risk that ADV places on youth. This index increases the clinical usefulness of the findings because it provides the opportunity for those who have experienced ADV not to be “typecast” as likely to develop a particular problem, and for those who are struggling with a specific problem not to have others assume they have a history of abuse.

**Implications**

It is concerning that ADV was found to increase subsequent health risk. Individuals in caring roles for youth (eg, parents, school personnel, healthcare providers, coaches) should screen for detrimental dating situations. Other authors have made recommendations for how to screen for abusive dating situations in adolescents,\(^2\)\(^2\) and screening practices should be designed for the highest level of disclosure while ensuring safety, security, and confidentiality. Discussions on sensitive topics can be uncomfortable, yet are associated with lower rates of health risks.\(^2\)\(^3\) However, only 32% of male adolescents and 44% of female adolescents who report dating violence seek help.\(^2\)\(^4\) Although most youth turn to peers or trusted adults to discuss sensitive topics, more than one-third of male adolescents and nearly half of female adolescents believe that a healthcare provider should discuss the topic of physical or sexual abuse.\(^2\)\(^5\) There is ample opportunity to
provide favorable occasions for youth to discuss sensitive
matters.

Primary intervention efforts are critical to reducing the
consequences of ADV. Peer focus groups are essential for
collecting important information about the culture of roman-
tic and sexual interactions. Today’s youth may be less inclined
to establish a romantic relationship with a single partner and
more likely to engage in brief sexual interludes or to incor-
porate occasional sexual activity into a platonic friendship.
Concerned adults can discuss guidelines for appropriate social
interactions and options for handling high-risk situations.
Intervention programs show promise and may need to be
tailored to better address higher-risk populations, as imple-
mented by colleagues in Canada.26-28 A 5-wave longitudinal
study on the Safe Dates program found the school-based
program to be significantly effective in reducing violence
perpetration and marginally effective in reducing sexual vio-
JOURNAL OF PEDIATRICS
lence victimization.29 Continued longitudinal research on the
study on the Safe Dates program found the school-based
program to be significantly effective in reducing violence
perpetration and marginally effective in reducing sexual vio-
JOURNAL OF PEDIATRICS
lence victimization.29 Continued longitudinal research on the
primary outcome constructs. Finally, some cells of interest
were too small (eg, male sex, ethnicities, sexual versus physical
dating violence) for robust analyses, thus may be inappropri-
ate for drawing conclusions and be statistically nonsignificant
but clinically significant.

Findings from this study indicate that ADV is associ-
ated with a diverse set of problematic behaviors and condi-
tions and is a significant but nonspecific risk factor for the
behavioral and psychological health of youth, particularly
female adolescents. Findings from this study and earlier stud-
ies4-9 point to a need for addressing ADV with youth. There
is ample opportunity for primary and secondary intervention
to reduce the likelihood of ADV and to lessen the impact of
ADV among affected individuals.

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COMPARISON OF OCULAR REACTIONS USING PENICILLIN AND BACITRACIN OINTMENTS IN OPHTHALMIA NEONATORUM PROPHYLAXIS

Margileth AM. J Pediatr 1957;51:646-51

In 1880, ophthalmia neonatorum was the leading cause of blindness in children in Europe and was responsible for the majority of children in institutions for the blind. This changed in 1882, when Crede reported that a single drop of 2% silver nitrate solution instilled in the eyes of newborns markedly reduced the incidence of gonococcal ophthalmia. Subsequently, many state legislators in the United States passed laws requiring the instillation of silver nitrate eye drops in newborns.

It became apparent, however, that silver nitrate instillation was often associated with a marked chemical conjunctivitis. Some authors asserted that a chemical conjunctivitis was necessary for adequate ophthalmia neonatorum prophylaxis. The mechanism of action of silver nitrate involves almost instantaneous binding of silver ions to the protein walls of the gonococcal bacteria and conjunctival epithelial cells, resulting in death of the bacterial and conjunctival epithelial cells and an acute neutrophilic reaction.

With the advent of antibiotic therapy, clinicians searched for an alternative prophylactic therapy for ophthalmia neonatorum with fewer side effects. In the above-referenced study, Margileth studied penicillin drops and ointment and bacitracin ointment for ophthalmia neonatorum prophylaxis. No severe ocular reactions occurred in a total of 7,774 infants studied. The incidence of mild to moderate ocular reactions was approximately 1% with both medications. The infection rate appeared to be low in both groups.

Neither penicillin nor bacitracin is presently used for ophthalmia neonatorum prophylaxis. The most commonly used medication today in the United States is erythromycin ophthalmic ointment instilled once at birth. Tetracycline ophthalmic ointment also may be used. Silver nitrate solutions are still used in developing countries with limited economic resources.

Presently, the most common cause of ophthalmia neonatorum in the United States is chlamydia. The topical ocular medications used for gonococcal prophylaxis are not effective in preventing chlamydia ophthalmia neonatorum. Of interest, the germicidal agent povidone-iodine has been studied for ophthalmia neonatorum prophylaxis. More studies on the efficacy of this agent are needed. Another concern relates to the emergence of resistant gonorhea, such that in the United States, penicillin and fluoroquinolones are no longer recommended for treating such conditions as cervicitis, urethritis, and pelvic inflammatory disease. Whether current ophthalmic preparations will remain effective against resistant gonococcal strains is uncertain. It is heartening that Crede’s creativity allowed so many infants to have normal vision and to develop with no opthalmologic sequelae.

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Long-Term Impact of Adolescent Dating Violence on the Behavioral and Psychological Health of Male and Female Youth

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Protective Factors and Suicide Risk in Adolescents with a History of Sexual Abuse

MARLA E. EISENBERG, ScD, MPH, DIANN M. ACKARD, PhD, and MICHAEL D. RESNICK, PhD

Objective To test the hypothesis that certain protective factors will reduce the risk of suicide behaviors in youth who are sexually abused.

Study design Survey data come from 83,731 students in the 6th, 9th, and 12th grades in Minnesota. Four childhood sexual abuse groups were created: a) no history of sexual abuse; b) abuse by non-family member; c) abuse by family member; and d) abuse by both. Dependent variables included suicidal ideation and attempts. Four protective factors included: family connectedness, teacher caring, other adult caring, and school safety. Logistic regression was used in detecting differences in suicide behaviors across the 4 childhood sexual abuse categories.

Results Four percent of students reported sexual abuse by a non-family member, 1.3% by a family member, and 1.4% by both. Although youth with a history of childhood sexual abuse were at increased risk for suicide behaviors compared with other youth, when protective factors were accounted for, the predicted probabilities of suicide behaviors for childhood sexual abuse youth were substantially reduced. Family connectedness was the strongest of the 4 protective factors.

Conclusion Modifying select protective factors, particularly family connectedness, may reduce suicide risk in adolescents with childhood sexual abuse. (J Pediatr 2007;151:482-7)

Recent reports have estimated that approximately 1 in 12 children have experienced sexual abuse. A meta-analysis of studies conducted in North America between 1969 and 1991 found that 22.3% of women and 8.5% of men reported experiencing childhood sexual abuse. A history of sexual abuse is a significant risk factor for a wide array of health-jeopardizing behaviors, including suicidal ideation and attempts in adults and adolescents. Molnar et al, for example, found the odds of suicide attempts 2 to 4 times higher in women and 4 to 11 times higher in men with a history of childhood sexual abuse than in individuals without such a history. Other studies have found the relationship between childhood sexual abuse and suicide to be fully mediated by other adversities or personal factors.

The pathway by which childhood sexual abuse influences suicide risk is not clear.

Factors such as connection to family and the presence of a caring adult have been shown to have a strong protective effect against a variety of health outcomes in a general population of adolescents and in adolescents who are in particularly vulnerable subgroups. Using a resiliency paradigm, Chandy et al noted that certain factors were protective against adverse outcomes in adolescents with a history of sexual abuse, including personal perceptions of health, a sense of spirituality, living with both biological parents, maternal education, perceived parent caring, and caring from school personnel. Greater satisfaction with support from caregivers around the abuse incident was associated with resiliency—manifested as less depression, better self-esteem, and better adjustment—1 year later.

Much of the research into protective factors in youth with a history of sexual abuse has focused largely on factors not amenable to change through intervention, such as maternal education. Although earlier findings provide important insights into factors that may contribute to a vulnerable young person’s success, additional information is needed to identify modifiable protective factors in a variety of domains. This study examines 4 factors that may be modifiable through intervention and their associations with both a
Methods

The 2004 Minnesota Student Survey (MSS) data were used for this study. This statewide survey assesses a wide variety of health behaviors and related factors in students enrolled in the 6th, 9th, and 12th grades every 3 years. Surveys were administered in schools during class time; no identifying information was collected. Passive parental consent procedures were used in most districts; active parental consent was used when required by school or district research protocols. The University of Minnesota’s institutional review board approved this secondary data analysis project with the MSS.

Eighty-eight percent of school districts in Minnesota participated, and student participation rates within school districts varied widely. Statewide, 76% of students in the 6th grade, 75% of students in the 9th grade, and 55% of students in the 12th grade participated. A small percentage of surveys (approximately 3%) was eliminated from analyses because designation of sex was missing (1.7%), responses were highly inconsistent (eg, age >2 years outside of expected range for grade, <1%), or there was a pattern of likely exaggeration (eg, reported using at least 3 hard drugs ≥40 times each in the past year, <1%). The sample consisted of 131,862 students (65,278 male and 66,584 female). The grade level distribution was as follows: 36.5% in 6th grade, 37.3% in 9th grade, and 26.2% in 12th grade. The sample was predominantly white (76.9%); the largest minority group included students who reported >1 racial or ethnic group (5.2%), followed by Asian American (4.8%), and African American (4.4%). Almost 2 of 3 students (64.3%) lived in their original 2-parent family. Demographic characteristics of the final sample are shown by sex in the “total” columns of Table I.

Measures

Two survey items were used to detect a history of sexual abuse: 1) “Has any adult or older person outside the family ever touched you sexually against your wishes or forced you to touch them sexually?” and 2) “Has any or stronger member of your family ever touched you sexually or had you touch them sexually?” Responses for both items were yes or no. A 4-category variable was created to classify respondents reporting no abuse, abuse by a non-family member, abuse by a family member, and abuse both by a family member and non-family member. A total of 6981 respondents (5.3%) were missing data on both sexual abuse items and were therefore excluded from analysis. Dependent variables were measured with the items “Have you ever thought about killing yourself?” and “Have you ever tried to kill yourself?” Response options for each were “no,” “yes, during the last year,” and “yes, more than a year ago.” The “yes” options were combined for each to assess past suicidal ideation and attempts.

Four protective factors were measured by using multiple items from different sections of the survey. Family connectedness included 7 items: “Can you talk to your [father/mother] about problems you are having” (“yes, most of the time” = 1; “my father/mother is not around” = 5); “How much do you feel . . . a) your parents care about you; b) your family cares about your feelings; c) your family understands you; d) your family has lots of fun together; e) your family respects your privacy” (“not at all” = 1, “very much” = 5; Cronbach’s alpha for family connectedness = .87). Teacher caring included 3 items: “How much do you feel . . . teachers or other adults at school care about you” (“not at all” = 1, “very much” = 5), “How many of your teachers . . . a) are interested in you as a person; b) show respect for the students” (“all” = 1, “none” = 5; Cronbach’s alpha for teacher caring = .77). Other adult caring included 3 items: “How much do you feel . . . a) church or spiritual leaders care about you; b) other adults in your community care about you; c) other adult relatives care about you” (“not at all” = 1, “very much” = 5; Cronbach’s alpha for adult caring = .67). School safety included: “I feel safe going to and from school,” “I feel safe at school,” and “Bathrooms in this school are a safe place to be” (“strongly agree” = 1, “strongly disagree” = 4; Cronbach’s alpha for school safety = .84). For each factor, certain items were re-coded so all were in a uniform direction, by which higher scores indicate more of the protective factor. The mean of the included items constituted the score for that factor.11

Participants were asked to describe themselves by checking ≥1 of 6 racial/ethnic groups. A dichotomous family structure variable was also included in analysis; all respondents who lived with 2 biological or adoptive parents were compared with respondents in other family living situations.

Data Analysis

Chi-square tests of association and general linear modeling were used to detect differences in suicide involvement and each protective factor across the 4 categories of sexual abuse history. Multiple logistic regression, controlling for grade level, family structure, and race, was used to examine the associations between sexual abuse and suicidal ideation and attempts (dichotomous dependent variables) and between 4 protective factors and suicidal ideation and attempts (odds ratios and 95% CIs are presented). Sexual abuse and protective factors were entered in separate models (model 1). Additionally, both sexual abuse and the 4 protective factors were entered together (model 2). A substantial attenuation of the odds ratios for each sexual abuse group from model 1 to model 2 was interpreted as evidence of protection conferred by the 4 protective factors. All analyses were stratified by sex. A criterion level of .01 was selected to minimize type I error, because of the very large size of the MSS sample. SAS software version 9.1 was used for statistical analyses.
Table I. Demographic characteristics, total and by sexual abuse category, percent (n)

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n)</td>
<td>None (n)</td>
</tr>
<tr>
<td>Sexual abuse category</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total 96.0 (58,652)</td>
<td>2.2 (1344)</td>
</tr>
<tr>
<td>Grade</td>
<td>Grade 6, df = 6,</td>
<td></td>
</tr>
<tr>
<td>6th</td>
<td>37.1</td>
<td>96.3</td>
</tr>
<tr>
<td>9th</td>
<td>36.8</td>
<td>95.8</td>
</tr>
<tr>
<td>12th</td>
<td>26.1</td>
<td>96.0</td>
</tr>
<tr>
<td>Race</td>
<td>Race 465.6, df = 18,</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>76.3</td>
<td>96.9</td>
</tr>
<tr>
<td>African American</td>
<td>4.7</td>
<td>91.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.0</td>
<td>94.1</td>
</tr>
<tr>
<td>Asian</td>
<td>4.8</td>
<td>94.6</td>
</tr>
<tr>
<td>Native American</td>
<td>1.6</td>
<td>92.6</td>
</tr>
<tr>
<td>Mixed</td>
<td>4.6</td>
<td>93.0</td>
</tr>
<tr>
<td>“Don’t know”</td>
<td>5.0</td>
<td>93.2</td>
</tr>
<tr>
<td>Original family (yes)</td>
<td>63.9</td>
<td>97.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Suicidal ideation (yes) | Total | None | Non-family | Family | Both | $\chi^2$ | Total | None | Non-family | Family | Both | $\chi^2$
---|---|---|---|---|---|---|---|---|---|---|---|---|---
Suicidal ideation (yes) | 24.5 | 22.9 | 57.1 | 56.7 | 72.7 | 1870.2, df = 3, $P < .001$ | 34.1 | 30.5 | 66.2 | 64.2 | 76.8 | 3442.4, df = 3, $P < .001$
Suicide attempt (yes) | 7.4 | 5.9 | 33.3 | 34.0 | 61.8 | 4712.7, df = 3, $P < .001$ | 11.9 | 9.2 | 35.7 | 29.1 | 53.2 | 4610.3, df = 3, $P < .001$

RESULTS

Characteristics of the Sample
In the whole sample, 93.1% of students reported no history of sexual abuse, including 96.0% of male students and 90.3% of female students. Four percent of students reported sexual abuse by a non-family member, 1.3% by a family member, and 1.4% by both a family and non-family perpetrator. Demographic characteristics differed significantly across sexual abuse categories (Table I).

Across the sample, 24.5% of male and 34.1% of female students reported thinking about suicide, and 7.4% of male and 11.9% of female students reported attempting suicide (Table II). As expected, suicidal ideation and attempts varied significantly across abuse categories. Whereas 22.9% of non-abused male students reported contemplating suicide, 57.1% and 56.7% of male students abused by non-family and family members, respectively, reported suicidal ideation, as did 72.7% of male students with both family and non-family abuse ($\chi^2 = 1870.2; P < .001$). More than half of the male (61.8%) and female students (53.2%) with both family and non-family abuse reported an earlier suicide attempt.

The means of all 4 protective factors also varied according to sexual abuse category, for both male and female students. Students reporting either family or non-family sexual abuse had significantly lower levels of each factor than students with no history of sexual abuse, and students with both family and non-family abuse had significantly lower levels of protection than students with a single source of abuse (Table III).

Sexual Abuse, Protective Factors, and Suicide Involvement
In logistic regression models controlling for grade, race, and family structure, students with a history of sexual abuse had significantly greater odds of thinking about and attempting suicide compared with students who had no sexual abuse history (Table IV, model 1). For example, male students reporting sexual abuse by a non-family member had odds of suicide attempts that were 7.19 times higher than the odds for male students with no history of abuse (CI, 6.35-8.13); male students reporting both sources of abuse had odds of suicide attempts that were 21.8 times higher than those for the comparison group (CI, 18.40-25.80).

When modeled together, family connectedness, teacher caring, other adult caring, and school safety had significant protective associations with suicidal ideation and suicide attempts, for both male and female students, as shown in Table IV, model 1. Each unit of family connectedness, for example, was associated with approximately half the odds of suicide attempts for female students (odds ratio, 0.49; CI, 0.48-0.51), meaning that for each 1-point difference in family connectedness, a girl's risk for a suicide attempt differed by approximately 50%.

In model 2, sexual abuse and all 4 protective factors were included simultaneously. The addition of protective factors significantly reduced the association between sexual abuse and suicide involvement (for male students: $\chi^2_{\text{ideation}} = 5070.3, P < .001$; $\chi^2_{\text{attempt}} = 2580.6, P < .001$; for female students: $\chi^2_{\text{ideation}} = 7149.2, P < .001$; $\chi^2_{\text{attempt}} = 3774.2, P < .001$). For example, the previous odds ratio of 21.80 for male students with both types of sexual abuse became 10.80 (CI, 8.90-13.10) in the fully adjusted model. Although the odds of suicide involvement in students with a history of sexual abuse remained statistically significant, this attenuation suggests a buffering of the association by the protective factors included here.

DISCUSSION
Results suggest that specific protective effects operate in the lives of young people who are at increased risk for suicide attempt because of a history of sexual abuse. Family connectedness, teacher caring, other adult caring, and school safety were associated with lower levels of suicidal ideation and attempts for both male and female adolescents. Family connectedness appeared to have a particularly strong protective association with the outcomes. This finding suggests that if levels of protective factors could be raised in adolescents with a history of sexual abuse to the levels reported by adolescents with no such history, suicidal ideation and attempts could be substantially reduced across the adolescent population.

An important point for further examination is the potential relationship between family connectedness and sexual abuse by a family member. Although family connectedness was lower, on average, for students reporting intrafamilial abuse compared with students with no abuse history, some respondents with this type of abuse also reported high levels of family connectedness. This finding raises questions about...
how “family” was interpreted by respondents, both vis-à-vis connectedness and abuse perpetration. It is possible, for example, that a respondent reported abuse by a distant uncle as abuse by a family member, but considered only their immediate family when rating their level of family connectedness. Likewise, among students experiencing abuse from members of the immediate family, questions about family connectedness may have been answered in terms of close, nurturing relations among others in the family, not including the perpetrator(s) of abuse. Adding to this complexity are reports of perceived family caring by victims of abuse even when referring to perpetrating family members. Further research with more specific measures of family abuse and connectedness is needed to explicate these complicated dynamics.

A strength of this study is the large sample size, because it allowed for meaningful analysis of relatively small groups of youth who have experienced different types of sexual abuse. The anonymous nature of data collection may make youth more comfortable reporting adverse events, which may have led to a more accurate classification of young people than seen previously. The population-based sampling frame permits for generalization to a broader population of young people, which complements sexual abuse research using clinical samples. In addition, the response rate at the school level is fairly high (88%), and participation rates are comparable with earlier administrations of the MSS and the Youth Risk Behavior Survey. However, student participation rates are somewhat lower. Differences between responders and non-responders could not be assessed and may have biased the analysis, particularly in light of potential exclusion of adolescents at highest risk for adverse outcomes that would co-occur with absence from school during survey administration. The measures of sexual abuse are also a limitation of this study, because sexual abuse was not objectively defined and not behaviorally specific. In addition, sexual abuse measures specified perpetration by those who were “older or stronger,” which may have excluded some cases and did not include information on the age of onset of abuse, duration and frequency or severity of force, which may be important considerations for this research. However, the definition of sexual abuse used here was similar to questions used in other large surveys of adolescents to assess prevalence of sexual abuse. The survey also did not include measures of other potentially important protective factors, such as neighborhood safety. Finally, because this analysis relies on cross-sectional data, a causal association between protective factors and suicide behaviors cannot be inferred.

Our findings are consistent with earlier literature that has demonstrated characteristics such as family connectedness and the presence of caring adults to be protective against emotional distress in adolescents, including in youth in other populations at increased risk for suicidal behaviors. As a corollary to earlier research suggesting that the suicide risk associated with sexual abuse may be attributable in part to other adverse experiences (e.g., interpersonal conflict or work stress), this study’s findings indicate that this suicide risk may

<table>
<thead>
<tr>
<th>Table III. Protective factors,* by sexual abuse category, least square mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual abuse category†</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Family connectedness (1-5)</td>
</tr>
<tr>
<td>Teacher caring (1-5)</td>
</tr>
<tr>
<td>Adult caring (1-5)</td>
</tr>
<tr>
<td>School safety (1-4)</td>
</tr>
</tbody>
</table>

*High score indicates more of the factor.
†Within sex, LS means differ at \( p < .01 \) between each sexual abuse category, unless otherwise noted.
‡LS means with the same superscript (within each row) are not significantly different at \( p < .01 \) level.
be ameliorated in part by the protective factors examined here. Taken together, this work further supports both a resiliency paradigm20 and a life course perspective9 as frameworks for considering the role of sexual abuse in emotional distress: although the experience of sexual abuse may be very damaging, numerous other influences contribute to each young person's life trajectory and well-being. This study therefore suggests that increasing protective factors may be a means of reducing suicide risk in the population of young people reporting a history of sexual abuse.

REFERENCES


Advanced Pubertal Status at Age 11 and Lower Physical Activity in Adolescent Girls

BIRGITTA L. BAKER, MS, LEANN L. BIRCH, PhD, STEWART G. TROST, PhD, AND KIRSTEN KRAHNSTOEVER DAVISON, PhD

Objective  To examine the relationship between pubertal timing and physical activity.

Study design  A longitudinal sample of 143 adolescent girls was assessed at ages 11 and 13 years. Girls’ pubertal development was assessed at age 11 with blood estradiol levels, Tanner breast staging criteria, and parental report of pubertal development. Girls were classified as early matures (n = 41) or later matures (n = 102) on the basis of their scores on the 3 pubertal development measures. Dependent variables measured at age 13 were average minutes/day of moderate to vigorous and vigorous physical activity as measured by the ActiGraph accelerometer.

Results  Early-maturing girls had significantly lower self-reported physical activity and accumulated fewer minutes of moderate to vigorous and vigorous physical activity and accelerometer counts per day at age 13 than later maturing girls. These effects were independent of differences in percentage body fat and self-reported physical activity at age 11.

Conclusion  Girls experiencing early pubertal maturation at age 11 reported lower subsequent physical activity at age 13 than their later maturing peers. Pubertal maturation, in particular early maturation relative to peers, may lead to declines in physical activity among adolescent girls. (J Pediatr 2007;151:488-93)

Although the health benefits of physical activity are widely promoted, many youth do not meet physical activity recommendations. In 2005, only 59.9% of adolescent girls in the United States participated in at least 30 minutes of moderate physical activity or 20 minutes of vigorous activity on 3 or more days per week. Furthermore, both males and females evidence a decline in physical activity across adolescence. Adolescent girls report lower levels of physical activity than boys from middle childhood onward and exhibit greater rates of decline in physical activity across adolescence.

Few studies have examined factors that predict or explain the noted decline in physical activity among adolescent girls. One particular factor leading to low physical activity among girls may be the psychological experience of puberty and in particular the timing of pubertal maturation. Although links between pubertal maturation and physical activity have been examined in a number of studies, the vast majority of studies to date have examined physical activity as a predictor, rather than a consequence, of pubertal maturation. In general, these studies found that competitive female athletes reported later menarche than nonathletes. Later menarche among athletes was hypothesized to be the result of differences in percentage body fat and energy balance. More recent studies indicate that much of the difference in pubertal timing between athletes and nonathletes is the result of self, coach, or parent selection of girls into sports in response to their physical stature, suggesting that pubertal maturation may be the initiating factor in the link between pubertal timing and physical activity. To the authors’ knowledge, pubertal timing has not been examined as a precursor to low physical activity among adolescent girls. Therefore, with a longitudinal sample of girls examined at ages 11 and 13 years, this study tests the hypothesis that girls who experience early pubertal maturation at age 11 will exhibit lower subsequent levels of physical activity at age 13 compared with later-maturing girls.
METHODS

Participants
Participants were 143 adolescent non-Hispanic white girls who were part of a longitudinal study examining girls’ nutrition, dieting, physical activity, and health. Approval for research involving human participants was obtained from the Institutional Review Board at the Pennsylvania State University. Participants were assessed at ages 11 (mean = 11.33, SD = .29) and 13 (mean = 13.32, SD = .28) years. Parents and the participants provided written informed consent for all procedures. Only girls (n = 143) who had measures of both pubertal development and physical activity were included in this study. No differences in girls’ body mass index (BMI), girls’ self-reported physical activity, girls’ breast development, fathers’ education, or family income were noted for girls who were and were not included in the final sample.

Measures
Girls’ BMI, percent body fat, and self-reported physical activity were measured at ages 11 and 13 years. Data regarding pubertal status, parental education, and family income were collected at age 11. An objective assessment of girls’ physical activity (with accelerometers) was obtained at age 13.

Measures of Body Composition
BMI AND OVERWEIGHT STATUS. Girls’ height and weight were measured in triplicate and were used to calculate their BMI (weight (kg)/height (m)²). Age and sex-specific BMI percentiles and z-scores were calculated by use of the 2000 growth charts from the Centers for Disease Control and Prevention. Girls with a BMI percentile ≥85 and <95 were defined as “at risk of overweight” and girls with a BMI percentile of ≥95 were defined as overweight.13

PERCENT BODY FAT. Dual-energy X-ray absorptiometry was used to measure girls’ percent body fat. Whole body scans were done with the Hologic QDR 4500W (S/N 47261; Hologic Inc, Bedford, MA) in the array scan mode and analyzed with whole body software, QDR4500 Whole Body Analysis (Hologic Inc). Dual-energy X-ray absorptiometry has received widespread use and is the preferred method of assessing body composition among children, because it provides an accurate, reliable, and noninvasive means of quantifying bone mineral content and body mass content, including fat and lean mass, while minimizing radiation exposure during measurement.14-17

Measures of Pubertal Development
ESTRADIOL. Blood samples collected on filter paper were used to measure levels of estradiol (pg/mL). Girls arrived at the laboratory at 7:45 A.M. after an overnight fast. All blood samples were collected between 8 A.M. and 9 A.M. The samples were air dried and then frozen until assayed as outlined in Shirtcliff et al.18 The estradiol assay has been validated against serum samples in both adults and children, and its sensitivity is sufficient for the detection of prepubertal levels of estradiol in girls. Specifically, the minimum concentration at which estradiol could be distinguished from 0 was 2 pg/mL. The intraassay coefficient of variation was 16%, and the interassay coefficient was 8.9%.

BREAST DEVELOPMENT. Girls’ breast development was assessed by use of Tanner’s criteria for pubertal breast stages.19 Stages range from 1 (no development) to 5 (mature development). Visual inspection of each breast was made unobtrusively by a trained nurse and a nurse’s assistant while using a stethoscope to check heart rate. In cases where ratings of the 2 breasts were not equal, the lower stage was used because the girl had not fully attained the higher stage.

PUBERTAL DEVELOPMENT SCALE. Mothers provided information on their daughter’s pubertal development by completing the pubertal development scale (PDS).20 The PDS is a noninvasive measure of pubertal development and consists of 6 items assessing growth or change in height, the presence of body hair (including underarm and pubic hair), skin changes, especially the presence of pimples, breast development, and menstruation. Previous research supports the reliability and validity of this scale.20,21

Classification of Timing of Puberty
Each measure of pubertal development outlined above has strengths and weaknesses. The estradiol assay provides an objective measure of a hormone associated with pubertal development. There is, however, substantial between-individual variation in the level of estrogen at any stage of pubertal development and within-individual variation throughout the menstrual cycle, making it difficult to determine a specific cutoff to define early maturation. The assessment of breast development can also be problematic. Although we were able to obtain a visual assessment of breast development, rather than relying on self-reports from girls, fat tissue can be mistaken for breast tissue in cases where the breast is not palpated. A key advantage of this method, however, is that it is widely used by researchers and clinicians, thereby increasing its applicability. Finally, the advantage of the PDS is that it is simple and inexpensive to administer. It is, however, based on the assumption that mothers are knowledgeable about daughters’ pubertal status. Because of the strengths and weaknesses described above, information from these 3 measures were combined into an overall index of pubertal status, which categorized girls as having either earlier or later timing of puberty at age 11 relative to the sample. Earlier developers were girls who fulfilled 2 of the following 3 criteria: (a) highest tertile for estradiol; (b) Tanner stage 3 or higher for breast development; and (c) highest tertile for the PDS. With these criteria, 41 girls were classified as earlier developers, and 102 were classified as later developers (Table I). The aforementioned criteria were chosen to identify a select group of girls who were clearly more physically mature than girls.
of the same age. Consequently, these groups indicate timing of puberty relative to same age peers in the sample and are not intended as clinical indexes of either precocious or delayed puberty.

### Measures of Physical Activity

**Self-reported physical activity.** The Children’s Physical Activity scale (CPA) was used to measure girls’ self-reported physical activity at age 11. In a self-administered survey, girls responded to 15 questions such as “I participate in sports almost every day” with a 4-point scale ranging from 1 (completely false) to 4 (completely true). Scores on the 15 items were averaged to create a score ranging from 1 (low activity) to 4 (high activity). In previous studies, scores on the CPA have been correlated in the expected direction with total daily counts, with multiple regression analysis. Specifically, pubertal timing and subsequent physical activity was assessed between earlier-maturing and later-maturing girls at ages 11 and 13 were assessed with t tests. The relationship between pubertal timing and subsequent physical activity was assessed with multiple regression analysis. Specifically, pubertal timing and subsequent physical activity at age 13, controlling for physical activity and percentage body fat at age 11. A composite measure of family socioeconomic status (SES) created with principal components analysis of mother’s education, father’s education, and family income was also entered as a covariate in analyses. Outcome variables at age 13 included minutes of MVPA, VPA, and raw accelerometer counts; a separate regression model was run for each outcome variable. Self-reported physical activity at age 11 was entered as a covariate to account for the likely scenario that girls who are more physically active at age 11 are also more physically active at age 13. Percent body fat at age 11 was entered as a covariate to account for the possibility that girls with higher body fat percentages had both earlier pubertal timing and lower levels of physical activity and that body fatness, rather than pubertal timing, was responsible for differences in physical activity at age 13. Pubertal status was entered as a dichotomous variable.

### Table I. Measures of pubertal status at age 11 for girls classified as earlier or later maturing

<table>
<thead>
<tr>
<th>Measure</th>
<th>Earlier maturation (n = 41)</th>
<th>Later maturation (n = 102)</th>
<th>T value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean estradiol (pg/mL)</td>
<td>12.51 (7.42)</td>
<td>4.21 (3.74)</td>
<td>3.89</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean PDS</td>
<td>2.51 (0.36)</td>
<td>1.77 (0.37)</td>
<td>4.66</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean breast development stage</td>
<td>2.83 (0.74)</td>
<td>2.00 (0.61)</td>
<td>2.96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>0%</td>
<td>15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>34%</td>
<td>73%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 3 (%)</td>
<td>51%</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 4 (%)</td>
<td>12%</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 5 (%)</td>
<td>3%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Of the same age. Consequently, these groups indicate timing of puberty relative to same age peers in the sample and are not intended as clinical indexes of either precocious or delayed puberty.

### Measures of Physical Activity

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RESULTS

The percentage of girls who lived in households with reported incomes of less than $35,000, $35,001 to $49,999, or $50,000 or more per year was 16%, 24%, and 60%, respectively. The average years of education for mothers was 14.42 years and for fathers was 14.89 years. On the basis of the composite pubertal development variable, 30% (n = 11005/41) of the girls were classified as earlier maturers, and 70% (n = 11005/102) of the girls were classified as later maturers (Table I). With respect to weight status, at age 11, 31% of girls were at risk of overweight, and 13% were overweight. At age 13, 28% of the girls were at risk of overweight, and 12% were overweight.

At age 11, earlier-maturing girls had significantly higher height, weight, percent body fat, and BMI scores than later-maturing girls (Table II). No significant group differences in self-reported physical activity were noted at age 11. At age 13, earlier-maturing girls continued to have significantly higher weight and BMI scores and had significantly higher percent body fat than later-maturing girls. There was no height difference between early- and late-maturing girls. Significant differences were noted in both accelerometer and self-report measures of physical activity at age 13, with early-maturing girls being less physically active.

As shown in Table III, pubertal timing at age 11 was a significant predictor of objectively measured physical activity at age 13. After controlling for age 11 physical activity (CPA), percent body fat, and SES, earlier-maturing girls engaged in significantly fewer minutes per day of MVPA and VPA at age 13 than later developers. In comparison to later-maturing girls, earlier-maturing girls engaged on average in 6.07 fewer minutes per day, or 42.5 fewer minutes per week, of MVPA and 2.17 per day, or 15 minutes per week, of VPA. Similarly, early pubertal maturation at age 11 was associated with significantly lower total accelerometer counts per day at age 13 after controlling for covariates. Adding age and height as covariates did not affect the results of the analysis.

DISCUSSION

Results from this study indicate that earlier timing of pubertal development at age 11 is associated with lower levels of physical activity at age 13. This relationship remained after controlling for body fatness, self-reported physical activity, and family SES at age 11. Consequently, the identified associations are not driven by preestablished levels of physical activity (ie, low-active girls maturing more quickly than high-active girls) or body fat (ie, girls who are more overweight and more sedentary going through puberty earlier than their leaner peers). These findings indicate that early-maturing girls are at an increased risk of physical inactivity during adolescence and that additional research on possible factors explaining this association is warranted.

Early pubertal timing combined with low levels of physical activity may place girls at particular risk of negative health outcomes. Previous research indicates that early pubertal maturation is linked with negative mental and physical health outcomes such as poor body image, eating disorders, and increased breast cancer risk. Physical inactivity is also a risk factor for negative health outcomes such as obesity, cardiovascular disease, diabetes, depression, ovarian cancer, and lower levels of social functioning. Drawing together these 2 bodies of research suggests that early-maturing girls who are inactive may experience compounded risk for negative health outcomes. The possibility of increased risk among early-matur-
ing girls provides further justification for research on mechanisms linking early maturation and physical inactivity and ways to promote physical activity in this high-risk group.

Early pubertal maturation may lead to low physical activity for a variety of reasons including both intrapersonal factors (eg, body esteem, depression, and perceived skill) and interpersonal factors (eg, parent and peer support). With regard to intrapersonal factors, early-maturing girls have been found to have poorer body image than their later-maturing peers, which has been identified as a constraint to both participation in and enjoyment of leisure activities. Earlier-maturing girls may be reluctant to participate in physical activity in settings they believe draw attention to their bodies. Higher levels of depression exhibited by early-maturing girls may also decrease girls’ motivation for engaging in physical activity. In addition to decreasing girls’ motivation for physical activity, the physical changes of puberty may impact girls’ ability to participate in physical activity. For example, breast development may directly reduce spontaneous physical activity because of the need for appropriate clothing. Furthermore, puberty-related changes put girls at a performance disadvantage in some sports. As a result, earlier-maturing girls may select out of sports because they are less skilled than their later-maturing peers.

Early-maturing girls may also decrease their physical activity during adolescence as a result of changes in interpersonal factors such as interactions with parents and peers. Parent-daughter relationships change significantly during puberty. Parents, particularly fathers, may be uncomfortable with the changes in their daughter’s body. Along similar lines, early-maturing girls report that adults expect them to behave more maturely. This combination of parental discomfort regarding their daughter’s more mature body and their tendency to encourage more adult behaviors may result in parents providing less support for “childlike” activities such as playing outdoors and more encouragement for less physically strenuous activities that are perceived as more feminine. Although parental support is important throughout childhood and into adolescence, peers become increasingly influential during this developmental period. Research shows that earlier-maturing girls tend to associate with an older peer group. Given the general decline in physical activity with age in adolescence, earlier-maturing girls are likely to belong to a peer group that is less active than their age cohort. In sum, there is a broad range of factors that may explain the link between pubertal timing and physical activity, including intrapersonal and interpersonal factors that warrant future investigation.

This study has a number of strengths. The longitudinal design of the study allowed the examination of the effect of pubertal timing among young adolescent girls (at age 11) on their physical activity levels 2 years later (at age 13) controlling for physical activity levels at age 11. Additional strengths include the use of multiple measures of pubertal development to classify pubertal timing and the use of an objective measure of physical activity. There were also several limitations. Participants in the study were primarily white girls residing in central Pennsylvania. Therefore results may not generalize across geographic areas or ethnicities. It is possible that very different associations would be identified between pubertal timing and physical activity among other ethnic groups given ethnic differences in pubertal timing, ideal body shape, and baseline physical activity. An additional limitation is the use of a self-report measure of physical activity at age 11 (objective monitoring was not available at age 11) for which relatively little measurement work has been done. Differences in physical activity between earlier- and later-maturing girls may have existed at age 11, but the self-report physical activity measure may not have been sensitive enough to detect them. Finally, the measurement of pubertal development resulted in limitations. Because of the limited age span that was assessed, it was not possible to separate the effects of early

### Table III. Results from regression analyses with pubertal timing at age 11 to predict physical activity at age 13 controlling for physical activity, percent body fat, and SES at age 11

<table>
<thead>
<tr>
<th>Outcome at age 13</th>
<th>Independent variable and covariates at age 11</th>
<th>b</th>
<th>β</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to Vigorous PA</td>
<td>Intercept</td>
<td>22.22</td>
<td>.134</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Self-reported PA (cov)</td>
<td>6.46</td>
<td>.108</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage body fat (cov)</td>
<td>−0.11</td>
<td>.049</td>
<td>.607</td>
</tr>
<tr>
<td></td>
<td>SES (cov)</td>
<td>−1.5</td>
<td>.014</td>
<td>.875</td>
</tr>
<tr>
<td></td>
<td>Early pubertal timing (IV)</td>
<td>−6.07</td>
<td>.202</td>
<td>.025</td>
</tr>
<tr>
<td>Vigorous PA</td>
<td>Intercept</td>
<td>−2.85</td>
<td>.492</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Self-reported PA (cov)</td>
<td>3.01</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Percentage body fat (cov)</td>
<td>−0.03</td>
<td>.055</td>
<td>.556</td>
</tr>
<tr>
<td></td>
<td>SES (cov)</td>
<td>.26</td>
<td>.338</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Early pubertal timing (IV)</td>
<td>−2.17</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>Accelerometer counts/d</td>
<td>Intercept</td>
<td>226,636</td>
<td>.018</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Self-reported PA (cov)</td>
<td>51,249</td>
<td>.018</td>
<td>.487</td>
</tr>
<tr>
<td></td>
<td>Percentage body fat (cov)</td>
<td>−61</td>
<td>.004</td>
<td>.964</td>
</tr>
<tr>
<td></td>
<td>SES (cov)</td>
<td>−211</td>
<td>.014</td>
<td>.727</td>
</tr>
<tr>
<td></td>
<td>Early pubertal timing (IV)</td>
<td>−45440</td>
<td>.016</td>
<td></td>
</tr>
</tbody>
</table>

*IV: Independent variable; Cov, covariates; b, unstandardized beta weight; β, standardized beta weight; PA, physical activity.*
pubertal timing from pubertal development per se. In addition, because 2 of the 3 variables used to measure pubertal status were not assessed at age 13, potential relationships between tempo of pubertal timing and physical activity could not be explored.

Although results from this study do not directly speak to the mechanisms that may lead early-maturing girls to disengage from physical activity, they highlight that early-maturing girls are at risk of low physical activity. Individuals interacting with adolescent girls such as doctors, teachers, parents, and coaches should be aware of this fact and seek ways to maintain girls’ interest in physical activity as they transition through puberty.

We would like to thank Dorothy Schmalz for her valuable assistance in collecting the data and the families who have participated in this study since the girls were 5 years old.

REFERENCES


Fetal Growth Restriction in Preterm Infants and Cardiovascular Function at Five Years of Age

KAIJA MIKKOLA, MD, JAANA LEIPÄLÄ, MD, PHD, TALVIKKI BOLDT, MD, PHD, AND VINETA FELLMAN, MD, PHD

Objectives We have previously reported an increased cardiac workload in newborn preterm small (SGA) infants, but not in infants appropriate for gestational age (AGA). We hypothesized that these cardiovascular changes will persist at follow-up at 5 years of age.

Study design We assessed blood pressure, echocardiography, and skin perfusion with laser Doppler flowmetry in 22 SGA (821 ± 248 g, 28.5 ± 2.5 gestational weeks) and in 25 AGA (1065 ± 241 g, 27.6 ± 0.8 weeks) preterm children at age 5 years. Laser Doppler flowmetry also was used in 13 control children (3982 ± 425 g, 40.4 ± 1.8 weeks).

Results The preterm children in both the SGA and AGA groups had similar higher systolic blood pressures, increased interventricular septum thicknesses, and smaller left ventricular end-diastolic diameters compared with population reference values. Maximal endothelium-independent perfusion to sodium nitroprusside was higher and maximal endothelium-dependent perfusion to acetylcholine reached a plateau earlier in the AGA preterm group than in the control group.

Conclusions Prematurity may impair cardiovascular function independently of intrauterine growth restriction. Altered cardiac dimensions and differences in perfusion responses may reflect increased cardiac afterload.

Being small size at birth, especially when combined with accelerated weight gain in childhood, is associated with an increased risk for cardiovascular morbidity.1,2 Further, low gestational age is associated with increased systolic blood pressure (BP) in early adulthood,3 and low birth weight with impaired endothelial function.4 Endothelial function is modulated by vasoactive substances, but the endothelium also regulates vascular tone, permeability, cellular transmigration, smooth muscle cell proliferation, and platelet aggregation.5 Endothelial dysfunction in childhood leads to cardiovascular diseases,6,7 but the pathophysiological mechanisms remain unidentified. Whether intrauterine growth restriction in prematurely born children causes an increased risk for cardiovascular morbidity is unknown.

In this prospective cohort study of small (SGA) and appropriate for gestational age (AGA) very low birth weight (<1500 g) preterm infants, SGA infants had cardiac hypertrophy and elevated initial left ventricular output during the first week of life as signs of increased cardiac workload and compromised capacity for hemodynamic adaptation.8 Similarly, increased aortic wall thickness, suggesting an increased intrauterine cardiac workload, has been reported in full-term growth-restricted infants at birth.9 We hypothesized that SGA children with increased cardiac workload perinatally would show persisting workload and signs of endothelial dysfunction at age 5 years. Furthermore, we studied the relationship of perinatal risk factors and postnatal growth to cardiovascular and endothelial function.

We assessed the macrocirculation with echocardiography and BP, and cutaneous microvascular blood flux with non-invasive laser Doppler flowmetry (LDF). In LDF, the reflection of Doppler shift in the illuminated area of the superficial microcirculation is proportionate to the number of blood cells and their perfusion velocity expressed as arbitrary perfusion units (PU).10 LDF combined with iontophoresis can be used to assess the skin perfusion response to a charged drug delivered locally through the skin by a direct low-intensity electric current.11 Cholinergic endothelium-dependent skin perfusion has been assessed with acetylcholine (ACh), which induces endothelial vasoactive production, and endothelium-independent perfusion with sodium nitroprusside (SNP), a nitric oxide donor.
The study was approved by the Ethics Committee for Pediatrics, Adolescent Medicine, and Psychiatry, Hospital District of Helsinki and Uusimaa.

**Echocardiography and Blood Pressure**

Echocardiography (Acuson Sequoia C 512, transducers 4 and 5 MHz, Acuson, US, Mountain View, CA) was performed by 1 cardiologist (T.B.) with a within-observer variability of 5.8%. The left and right ventricular dimensions, thickness and motion of the ventricular walls, left ventricular ejection fraction, and fractional shortening were measured. The dimensions were adjusted to body surface area.

The internal diameter of the aortic annulus and the flow velocity integral of the ascending aorta were measured for the calculation of left ventricular output. The same pediatric cardiologist (T.B.) performed all echocardiographic measurements with a within-observer variability of 5.8%. BP was measured after echocardiography (20-minute rest) from the right upper arm with a Dinamap Critikon (model 1846SX/P, Critikon Inc., Tampa, FL) in a recumbent position. Healthy control subjects were not recruited for echocardiography and BP measurements, because well-described age-adjusted normal values were calculated with published data.

**Laser Doppler Flowmetry**

The LDF recordings were performed at a temperature of 22° to 23°C. The child was sitting with 1 arm at a time immobilized with pillows listening to a fairy tale. The right forearm was used for physiological provocations, thereafter the left for acetylcholine (ACh, Sigma-Aldrich Ab, Stockholm, Sweden), and finally the right forearm for sodium nitroprusside (SNP, Sigma-Aldrich Ab) provocations. After cleaning with 70% alcohol, skin perfusion was measured on the proximal volar side of the forearm where no large veins were seen. The illuminated skin area was 1 mm², the probe temperature was 32°C, and a single spot laser-Doppler ultrasound scanner with a wavelength of 780 nm was used (Periflux 5000 Perimed AB, Järffalla, Sweden). The same investigator (K.M.) performed all LDF recordings with coefficient of variation of 17% for basal perfusion on different forearm sites and 20% for the maximal ACh and SNP perfusion.

After a baseline measurement at 32°C for 2 minutes (probe PF 457, Perimed AB), arterial occlusion was applied for 2 minutes, inducing a suprasystolic pressure with a pneumatic cuff. The peak perfusion during the post-occlusive hyperemia, the time-to-peak after cuff release, and the relative perfusion change during the reactive hyperemia (percent-age of the peak-baseline difference in relation to baseline) were measured. After the original baseline perfusion was achieved, the perfusion change to local warming from 32° to 44°C was assessed.

Iontophoretical transdermal drug provocations were performed at 32°C with 2% ACh, using anodal current of 0.1 mA for 20 seconds 6 times at 40-second intervals (drug delivery probe PF 481, drug delivery electrode PF 383, dispersive electrode PF 384, Perimed AB). Endothelium-inde-
Table II. Echocardiographic measurements (mean ± SD) of preterm small and appropriate for gestational age children at the age of 5 years

<table>
<thead>
<tr>
<th></th>
<th>SGA (n = 21)</th>
<th>AGA (n = 24)</th>
<th>Reference values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventricular septum</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
<td></td>
</tr>
<tr>
<td>(mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventricular septum</td>
<td>0.6 ± 1.2*</td>
<td>0.7 ± 1.3*</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>diameter (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle end-diastolic</td>
<td>32 ± 4</td>
<td>32 ± 2</td>
<td></td>
</tr>
<tr>
<td>diameter (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle end-diastolic</td>
<td>−0.6 ± 1.0*</td>
<td>−0.9 ± 0.7*</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>diameter (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle systolic</td>
<td>21 ± 3</td>
<td>21 ± 2</td>
<td></td>
</tr>
<tr>
<td>diameter (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle systolic</td>
<td>−0.2 ± 1.0</td>
<td>−0.4 ± 0.9</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>diameter (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle posterior</td>
<td>5 ± 1</td>
<td>6 ± 1</td>
<td></td>
</tr>
<tr>
<td>wall diameter (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle posterior</td>
<td>0.1 ± 1.1</td>
<td>0.2 ± 1.1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>wall diameter (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle fractional</td>
<td>35 ± 6</td>
<td>37 ± 5</td>
<td>28-40</td>
</tr>
<tr>
<td>shortening (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle ejection</td>
<td>66 ± 7</td>
<td>66 ± 7</td>
<td>50-70</td>
</tr>
<tr>
<td>fraction (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle stroke</td>
<td>55 ± 11</td>
<td>52 ± 10</td>
<td>40-60</td>
</tr>
<tr>
<td>index (mL/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle cardiac</td>
<td>5.2 ± 1.3</td>
<td>5.4 ± 1.7</td>
<td>2-5</td>
</tr>
<tr>
<td>index (L/min x m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < .05 as compared with values calculated from references.15,16

Table III. Microvascular perfusion response (mean ± SD) to arterial occlusion in preterm small and appropriate for gestational age and term control children at the age of 5 years

<table>
<thead>
<tr>
<th></th>
<th>SGA (n = 20)</th>
<th>AGA (n = 25)</th>
<th>Control (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal perfusion (PU)</td>
<td>15 ± 5*</td>
<td>19 ± 8†</td>
<td>14 ± 5</td>
</tr>
<tr>
<td>Biological zero perfusion (PU)</td>
<td>4 ± 2</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
</tr>
<tr>
<td>Postocclusive peak perfusion (PU)</td>
<td>78 ± 38</td>
<td>85 ± 34</td>
<td>68 ± 33</td>
</tr>
<tr>
<td>Relative postocclusive perfusion change (%)</td>
<td>459 ± 301</td>
<td>385 ± 157</td>
<td>393 ± 236</td>
</tr>
<tr>
<td>Time to peak (seconds)</td>
<td>9 ± 4</td>
<td>9 ± 3</td>
<td>9 ± 3</td>
</tr>
<tr>
<td>Duration of hyperemia</td>
<td>43 ± 22</td>
<td>44 ± 18</td>
<td>45 ± 11</td>
</tr>
<tr>
<td>(seconds)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perfusion at 32°C (PU)</td>
<td>14 ± 5</td>
<td>19 ± 9</td>
<td>15 ± 10</td>
</tr>
<tr>
<td>Perfusion at 44°C (PU)</td>
<td>232 ± 91</td>
<td>327 ± 125‡</td>
<td>244 ± 79</td>
</tr>
<tr>
<td>Perfusion change, 32°C</td>
<td>1694 ± 862</td>
<td>1860 ± 875</td>
<td>1716 ± 697</td>
</tr>
<tr>
<td>to 44°C (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p = .06, SGA versus AGA.
†p = .08, AGA versus control.
‡p < .05, AGA versus SGA and control.

**RESULTS**

Systolic BP preterm children in the SGA group (110 ± 15 mm Hg, *P = .20, N = 21) and AGA group (109 ± 7 mm Hg, *P = .056, N = 21) did not differ from a reference of 106 ± 8 mm Hg, nor did the diastolic BP (SGA, 63 ± 13 mm Hg, *P = .52; AGA, 63 ± 9 mm Hg, *P = .43) differ from the reference of 65 ± 9 mm Hg.22 When both preterm groups were pooled (N = 42), systolic BP was slightly higher than the population reference (110 ± 11 mm Hg, *P = .040). In the preterm children, BP did not correlate with birth weight, 5-year weight, or body mass index.

In echocardiography, the thickness of the IVS was increased and the left ventricular end-diastolic diameter was decreased in preterm children compared with the reference values; no differences were found between preterm children in the SGA group and those in the AGA group (Table II). With stepwise linear regression, perinatal risk factors (Table I) were not associated with IVS thickness at age 5 years, nor was the neonatal IVS or left ventricular end-diastolic diameter with values at 5 years. The IVS correlated with the left ventricular end-diastolic (*r = −0.43, *P = .003) and systolic (*r = −0.31, *P = .038) diameters, and posterior wall (*r = 0.45, *P = .002), when adjusted to body surface area (Figure 1; available at www.jpeds.com).

LDF physiological measurements are shown in Table III. When the results for all preterm children were pooled, the post-octclusive relative perfusion change was lower in girls.

Statistical Analysis

Statistical analysis was performed with SPSS software version 12.0.1 for Windows with analysis of variance (Tukey HSD post hoc), Student *t* test, and Mann-Whitney *U* test for group differences. The associations of perinatal risk factors and neonatal echocardiography with the 5-year findings were assessed with multiple linear regression analysis. The multivariate general linear model for repeated measurements with log-transformed perfusion values, and with perfusion baseline as a covariant, was used to analyze drug provocation responses. Area under the curve (AUC) was calculated by summarizing the AUC slices between each pair of consecutive observations. During arterial occlusion, the mean cutaneous biological zero was similar in all study groups; it was not subtracted from the raw data. Perfusion responses are reported in perfusion units and not as percentage of baseline, because even small baseline variations may lead to major differences in percentage.5 The strength and direction of relationships between variables is expressed with the Pearson correlation (*r*). The number of subjects with reliable measurements is shown in every table and figure. A *P* value < .05 was statistically significant.
Cardiac Afterload in Preterm Children

In regression analyses, an increase of 1 SD in IVS thickness was associated with 0.17 SD (95% CI, 0.04-0.3) decrease in left ventricular end-diastolic diameter, with 0.14 SD (95% CI, 0.004-0.28) decrease in left ventricular systolic diameter, with 0.23-second (95% CI, 0.14-0.3) longer post-occlusive time to peak perfusion, and with 0.05 mm Hg (95% CI, 0.01-0.1) higher systolic BP. A 1-mm Hg increase in systolic BP was associated with lower relative post-occlusive perfusion change by 149% (95% CI, 19%-278%).

Growth

At age 5 years, children in both preterm groups had lower height SD, head SD, and weight than control subjects (Table IV; available at www.jpeds.com). Preterm children with postnatal dexamethasone treatment had smaller height SD, weight to height percentage, and body mass index than preterm children without postnatal dexamethasone treatment (P < .05). In the preterm children, birth weight SD correlated significantly with weight-to-height percentage (r = 0.38, P = 0.008) and with head circumference SD (r = 0.47, P = 0.002). Family histories of diabetes mellitus, hypercholesterolemia, hypertension, or obesity were unrelated to growth variables at age 5 years.

DISCUSSION

Our main findings were an increased thickness of the IVS and a decreased left ventricular end-diastolic diameter SD in both preterm groups. Systolic BP of the preterm children was higher than the population reference. No differences appeared between the SGA and AGA groups in echocardiography or in BP. The endothelium-dependent perfusion response reached a plateau earlier in the AGA
group than in the control children. Furthermore, both maximal endothelium-independent perfusion response and response to temperature provocation were higher in the AGA group than the control children. The growth of the preterm children was suboptimal at age 5 years.

**Blood Pressure**

Reports of BP after prematurity are contradictory. A study of adolescents showed no difference in BP among preterm SGA, AGA, and term control groups, whereas other studies have shown elevated BP in preterm children compared with term-born children with normal birth weight, especially in girls. Fetal growth restriction has not, however, been associated with elevated BP in adolescents born prematurely. We found that an increase in systolic BP was associated with a decrease in endothelial reactivity assessed as a relative post-occlusive perfusion change.

**Echocardiography**

During the first 2 postnatal weeks, the preterm infants in the SGA group had cardiac hypertrophy compared with infants in the AGA group. At age 5 years, both showed increased IVS thickness and decreased left ventricular end-diastolic diameter, which may lead to impaired left ventricular diastolic relaxation and decreased left ventricular systolic diameter. Because there were no significant associations with perinatal echocardiographic measurements, our results at the age 5 years suggest that the effect of prenatally increased cardiac workload caused by fetal growth restriction may be transient, whereas prematurity per se may have an independent, more permanent effect on cardiac diameters, despite normal cardiac function. Almost one third of the preterm children had been treated with early postnatal dexamethasone, which may cause transient left ventricular hypertrophy and hypertension. In our study, dexamethasone was not associated with hypertension. When children treated with dexamethasone were excluded, the results for blood pressure and LDF remained.

LDF was rather challenging to perform on 5-year-old children. Some measurements had to be discarded because of movement artefacts caused by tickling of iontophoresis and loss of cooperation of the preterm children during the almost 1-hour procedure. Thus, the success rate in the ACh and in SNP provocations were only 72% and 62%, respectively, leaving a possibility of beta error. Several factors affect LDF recordings. Iontophoresis may induce sensory nociceptive C fibres (axon reflex) to produce vasodilative substances, and the vehicle itself may cause non-specific vasodilatation. The voltages of the anodal and cathodal currents were low, in accordance with recommendations for iontophoresis, and iontophoresis with sodium chloride with the same magnitude of anodal current as in our study produced no skin perfusion change. Application of local anesthetic cream and antihistamine before recordings would reduce involvement of sensory nerves and histamine-related reactions, but these agents may have other confounding effects. A methodological limitation is the rather high variability in repeated LDF measurements.

Neonatal LDF studies of endothelium-dependent perfusion response have shown an impaired relative response to ACh-induced perfusion in full-term infants who are growth retarded, but not in preterm infants who are growth-restricted and preterm or term control infants. Endothelial function in adolescents studied with flow-mediated vasodilation did not differ between preterm infants with growth restriction and term-born control infants. In this study, the endothelium-dependent response reached plateau earlier in the preterm children in the AGA group than the children in the control group. Whether this reflects an altered physiological response is unclear.

The endothelium-independent, SNP-induced maximal perfusion response was higher in children in the AGA group than in children in the control group. A study on vascular smooth muscle function in children showed that the smooth muscle response induced by glyceryl trinitrate correlated inversely with vessel diameter. Female adolescents who were prematurely born and adolescents who were term-born with intrauterine growth restriction had diminished abdominal aortic diameters compared with those of control subjects. In this study, the vessel diameter was not measured. Our finding of the enhanced SNP-induced perfusion combined with higher systolic BP and increased IVS thickness in the children in the AGA group may indicate a compensatory smooth muscle function to probably diminished blood vessel diameters. The preterm children in this study had no signs of metabolic disorders such as obesity or diabetes mellitus, and no associations appeared between endothelial dysfunction and family history.

In conclusion, we found no differences in cardiovascular function between SGA and AGA preterm children at age 5 years, and our hypothesis of persistent cardiac workload only in SGA preterm children was not confirmed. Increased systolic BP and a thickened IVS in the preterm children may be a result of a reduced vessel diameter, because reduced arterial distensibility leads to an increase in left ventricular afterload and in systolic BP. Thus, prematurity per se may lead to increased cardiac afterload and an increased systemic vascular resistance. We found differences in LDF perfusion responses, especially between the children in the AGA group and those in the control group that may indicate altered function at a microvascular smooth muscle level. However, long-term follow-up studies of echocardiography and endothelial function in preterm children are needed to evaluate the persistence of the changes.

**REFERENCES**

Figure 1. In 5-year-old preterm children (N = 45), interventricular septum thickness correlated inversely with left ventricular end-diastolic ($r = -0.43$, $P = .003$) and systolic diameter ($r = -0.31$, $P = .038$), and positively with left ventricular posterior wall ($r = 0.45$, $P = .002$), when adjusted to body surface area (SD score).
Table IV. Growth data at age 5 years and family history of preterm small and appropriate for gestational age and term-born control children

<table>
<thead>
<tr>
<th></th>
<th>SGA (n = 22)</th>
<th>AGA (n = 25)</th>
<th>Control (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>16.2 ± 2.3*†</td>
<td>18.3 ± 3.5‡</td>
<td>21.5 ± 3.0</td>
</tr>
<tr>
<td>Weight to height</td>
<td>−9 ± 11*†</td>
<td>0 ± 14</td>
<td>1 ± 7</td>
</tr>
<tr>
<td>(kg/cm, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.06 ± 0.04†</td>
<td>1.08 ± 0.06‡</td>
<td>1.17 ± 0.06</td>
</tr>
<tr>
<td>Height SD</td>
<td>−1.0 ± 0.9†</td>
<td>−0.6 ± 1.2‡</td>
<td>0.9 ± 1.1</td>
</tr>
<tr>
<td>Head circumference</td>
<td>49.6 ± 1.8*‡</td>
<td>50.8 ± 2.0</td>
<td>52 ± 1.3</td>
</tr>
<tr>
<td>(cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head SD</td>
<td>−1.5 ± 1.5*†</td>
<td>−0.6 ± 1.5‡</td>
<td>0.3 ± 0.8</td>
</tr>
<tr>
<td>Body mass index</td>
<td>14.2 ± 1.7*†</td>
<td>15.6 ± 2.1</td>
<td>15.7 ± 1.1</td>
</tr>
<tr>
<td>(kg/m², %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area</td>
<td>0.69 ± 0.06*†</td>
<td>0.74 ± 0.09‡</td>
<td>0.84 ± 0.08</td>
</tr>
<tr>
<td>(m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midparental target</td>
<td>0.2 ± 0.7</td>
<td>0.2 ± 0.7</td>
<td>0.2 ± 0.6</td>
</tr>
<tr>
<td>height SD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Maternal body mass</td>
<td>25.2 ± 5.2</td>
<td>25.2 ± 4.8</td>
<td>23.17 ± 2.8</td>
</tr>
<tr>
<td>index (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paternal body mass</td>
<td>27.0 ± 3.6†</td>
<td>26.9 ± 3.6‡</td>
<td>24.3 ± 2.5</td>
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<td>index (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 or 2 diabetes</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>mellits in 1° relative, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Hypercholesterolemia</td>
<td>4 (18)</td>
<td>4 (16)</td>
<td>1 (8)</td>
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<td>in 1° relative, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension in 1°</td>
<td>4 (18)</td>
<td>6 (24)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>relative, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index &gt;25</td>
<td>9 (41)</td>
<td>10 (40)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>% in 1° relative, n (%)</td>
<td></td>
<td></td>
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</tbody>
</table>

SD, Standard deviation according to age- and sex-adjusted Finnish growth charts; Weight-to-height ratio, percentage of the mean weight for height for the normal population of the same chronological age and sex; Body mass index, weight in kg divided by height² in m; Body surface area, Mosteller formula; Midparental target height SD, (Mean parental height (cm) / 100)². *P < .05, SGA versus AGA. †P < .05, SGA versus control. ‡P < .05, AGA versus control.
Clinical Data Predict Neurodevelopmental Outcome Better than Head Ultrasound in Extremely Low Birth Weight Infants

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Objective  To determine the relative contribution of clinical data versus head ultrasound scanning (HUS) in predicting neurodevelopmental impairment (NDI) in extremely low birth weight infants.

Study design  A total of 2103 extremely low birth weight infants (<1000 g) admitted to a National Institute of Child Health and Human Development Neonatal Research Network center who underwent HUS within the first 28 days, a repeat one around 36 weeks’ postmenstrual age, and neurodevelopmental assessment at 18 to 22 months corrected age were selected. Multivariate logistic regression models were developed with clinical or HUS variables. The primary outcome was the predictive abilities of the HUS performed before 28 days after birth and closer to 36 weeks postmenstrual age, either alone or in combination with “Early” and “Late” clinical variables.

Results  Models with clinical variables alone predicted NDI better than models with only HUS variables at both 28 days and 36 weeks (both \( P < .001 \)), and the addition of the HUS data did not improve prediction. NDI was absent in 30% and 28% of the infants with grade IV intracranial hemorrhage or periventricular leukomalacia, respectively, but was present in 39% of the infants with a normal HUS result.

Conclusions  Clinical models were better than HUS models in predicting neurodevelopment. (J Pediatr 2007;151:500-5)

Advances in perinatal care have increased survival of extremely low birth weight (ELBW) infants (<1000 g). However, improvements in survival have not led to better neurodevelopmental outcomes. Many ELBW infants who survive have major physical or behavioral disabilities such as severe neurologic impairment, cerebral palsy, deafness, or blindness. In addition to these neurodevelopmental disabilities, survivors are at high risk for learning difficulties leading to school failure, stressed families, and increased health care costs.

Clinicians have attempted to predict neurodevelopmental impairment with many perinatal risk factors such as gestational age, race, maternal socioeconomic status, antenatal steroid use, mode of delivery, low Apgar scores, birth weight, severe intracranial hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, nosocomial sepsis, and necrotizing enterocolitis. Decisions to limit therapeutic interventions to avoid futile therapy and postponement of death are often based on a prediction of death and neurodevelopmental impairment. Identification of abnormal head ultrasonography (HUS) findings such as severe intracranial hemorrhage (grades III or IV) and periventricular leukomalacia are generally considered strong predictors of handicap and death. However, the variance in neurodevelopmental impairment explained by severe intracranial hemorrhage/periventricular leukomalacia has been generally low in these studies—8% for a low mental developmental index (<70 or below 2 SD of the mean) at 2 years of age and 5% to 7% for cognitive, language, and achievement performance at 8 years of age. The existing literature on the predictive ability of HUS for neurodevelopmental outcome consists mostly of studies from single centers with small numbers of patients. Identification of severe intracranial hemorrhage (grades III or IV) and periventricular leukomalacia may occur early in the first few hours after birth or later in the clinical course, with progression or resolution commonly observed.

From the University of Alabama at Birmingham (E.B., N.A., W.C.), Birmingham, Alabama; National Institute of Child Health and Human Development (R.H.), Bethesda, Maryland; Women and Infants’ Hospital (B.V.), Providence, Rhode Island; RTI International (A.D., B.B., K.M.), Research Triangle Park, NC; Stanford University (S.H.), Palo Alto, California.

Supported by cooperative agreements with the National Institute of Child Health and Human Development: U10 HD34216, U10HD27853, U10HD40461, U10HD21364, U10HD40461, U10HD27851, U10HD27856, U10HD21397, U10HD27881, U10HD40521, U10HD27880, U10HD27882, U10HD40521, U10HD40521, U10HD27882, U10HD27882, U10HD40521, U10HD40521, U10HD27882.

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Despite the uncertainty regarding the prediction of neurodevelopmental outcome, decisions to withdraw or withhold life-saving support are frequently based, at least in large part, on neurosonographic findings. Therefore this study was designed to compare clinical variables and HUS data in the prediction of neurodevelopmental impairment at 18 to 22 months corrected age.

**METHODS**

**Population**

This study analyzed data from a retrospective cohort of all ELBW infants (401-1000 g) who were admitted (both inborn and outborn) to any of the 19 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network from January 1, 1998, to June 30, 2001. Infants were included if they had at least 2 HUS scans, one within 28 days after birth and a later ultrasound scan close to 36 weeks postmenstrual age, as well as follow-up assessment at 18 to 22 months corrected age. Exclusion criteria were lethal congenital malformations and chromosomal abnormalities. Data were routinely collected by trained research personnel and entered into a database as previously described. Data collection was approved by the institutional review board at each of the participating institutions.

**Procedures**

A comprehensive assessment was performed at 18 to 22 months corrected age. This assessment consisted of medical history, physical and neurologic examinations, and developmental assessment. The neurologic assessment (including muscle tone, strength, reflexes, angle, and posture) was performed with the Amiel-Tison method. Cerebral palsy was defined as a nonprogressive central nervous system disorder characterized by abnormal muscle tone in at least one extremity and abnormal control of movement and posture. The developmental assessment consisted of the Bayley Scales of Infant Development II, which included the mental and psychomotor developmental indexes. Hearing impairment was defined as the use of hearing aids. Visual impairment was defined as blind with some functional vision or no useful vision. Neurodevelopmental impairment was defined as the infant having 1 or more of the following: psychomotor developmental index <70, mental developmental index <70, cerebral palsy, and hearing or visual impairment. Functional status was assessed by the presence or absence of independent walking and independent feeding.

**Assessment of HUS Scans**

According to the standardized Neonatal Research Network data collection procedures, early HUS (HUS-28) was the most abnormal HUS scan obtained within the first 28 days after birth, and HUS closer to 36 weeks (HUS-36) was the HUS scan obtained after day 28 and closest to 36 weeks postmenstrual age. HUS-28 data were classified as follow:

- normal, blood/echodensity in germinal matrix/subependymal area (grade I), blood/echodensity in the ventricles (grade II), ventricular size enlarged (grade III), blood/echodensity in the parenchyma (grade IV), cystic area in the parenchyma (if a previous grade IV hemorrhage was documented previously), or periventricular leukomalacia (cystic area in the parenchyma was also considered periventricular leukomalacia if no grade IV was documented previously)

**Variables Analyzed**

The variables analyzed were those that have been reported as associated with poor neurodevelopmental outcome by other investigators. Clinical variables were grouped as “Early” if they could be assessed by postnatal day 28. These included maternal education, antenatal steroids, antenatal antibiotics, mode of delivery, outborn, male sex, race, gestational age, 1-minute Apgar score <3, 5-minute Apgar score <3, 5 minute Apgar score 3-6, intubation at delivery, medications for resuscitation, birth weight (in 100-g increments), intrauterine infection, breech presentation, surfactant, indomethacin <24 hours, indomethacin for patent ductus arteriosus treatment, early sepsis (culture positive), late-onset sepsis (culture positive), proven necrotizing enterocolitis (≥Bell Stage II), seizures, pneumothorax, conventional ventilation, and high-frequency ventilation. Clinical variables were grouped as “All” if they could be assessed before discharge home, death, and at 120 days, and included the “Early” clinical variables, as well as supplemental O2 at 36 weeks postmenstrual age, steroids for bronchopulmonary dysplasia, and threshold retinopathy of prematurity. HUS variables were grouped as early (HUS-28) or late (HUS-36) depending on ultrasound timing.

**Statistical Analyses**

The data were randomly divided into a development set of 70% of the population (n = 1472) and a validation set of 30% (n = 631). Stepwise variable selection was performed on the development set to obtain clinical or sonographic variables significantly associated with neurodevelopmental impairment, at P = .1 for the entry and exit criteria. For the combined HUS/clinical models, the HUS variables were forced to remain in the model. Using the selected clinical and HUS variables, multiple logistic regression analysis was performed to develop a regression equation on the development set. This equation was applied to the validation set to predict neurodevelopmental impairment and its components. Neurodevelopmental impairment was defined as mental developmental...
index <70, psychomotor developmental index <70, cerebral palsy, deafness, or blindness. The process was repeated for HUS-28 and “Early” clinical variables, as well as for HUS-36 and “All” clinical variables alone and in combination. Predictive abilities of the different models were compared by use of the area under the curve of the receiver operating characteristic curves.

RESULTS

Demographic and Clinical Characteristics

Of 5867 ELBW infants admitted to any of the participating centers, 3096 infants had both HUS-28 and HUS-36 (Figure). HUS-28 was done before 7 days in 50%, between 7 and 14 days in 39%, and between 15 and 28 days of age in 12%. The median age at HUS-36 was day 57 (25th-75th percentile of 37 to 74 days).

Of the 3009 infants without major malformations/syndromes, death before and after discharge occurred in 6.6% of the patients with normal HUS scan or grade I intracranial hemorrhage, 11% of those with grade II intracranial hemorrhage, and 14% and 18% of those with grade III and IV intracranial hemorrhage, respectively. Cystic periventricular leukomalacia was noted in 5% of patients who died. A total of 2271 infants survived to follow-up at 18 to 22 month corrected age. Some or all neurodevelopmental impairment data were missing in 168 infants. Thus a total of 2103 infants were included in the analysis of neurodevelopmental impairment.

Prediction of Neurodevelopmental Impairment

Neurodevelopment impairment increased with worse head ultrasound findings (Table II). However, neurodevelopmental impairment was not present in 30% and 24% of the infants with grade IV intracranial hemorrhage and cystic periventricular leukomalacia, respectively, but was present in 39% of infants with normal HUS scans.

The “Early” and “All” clinical models were better predictors of neurodevelopmental impairment (areas under the curve = 0.68 for both), compared with the corresponding HUS-28 (areas under the curve = 0.58) and HUS-36 models (areas under the curve = 0.57) (P < .001 vs the clinical models) (Figure). The HUS-36 model did not improve prediction of neurodevelopmental impairment when compared
with the HUS-28 model ($P = .4$). The combined HUS and clinical models were comparable to isolated clinical models for neurodevelopmental impairment prediction for both “Early” ($0.68 \text{ vs } 0.68$, $P = .5$) and “All” models ($0.68 \text{ vs } 0.68$, $P = .9$).

Predictions of the major neurologic outcomes were comparable for the HUS-36 model and HUS-28 model except for non-independent walking for which the HUS-36 model was superior ($0.71 \text{ vs } 0.65$, $P < .01$). There was an improvement in the predictive ability for mental developmental index $<70 (0.72 \text{ vs } 0.69, P < .05)$, cerebral palsy ($0.78 \text{ vs } 0.72, P < .01$), and non-independent walking ($0.79 \text{ vs } 0.74, P < .01$) for the HUS-36/“All” clinical model as compared with the HUS-28/“Early” clinical model.

Multiple logistic regression analyses controlling for clinical variables and timing of HUS scanning revealed that only periventricular leukomalacia and shunt placement in HUS-36 were significantly associated with neurodevelopmental impairment, although some infants with abnormal HUS scans do not have significant impairment. Clinical models were stronger predictors for neurodevelopmental impairment and its components than HUS models. Isolated HUS findings had a poor predictive ability for neurodevelopmental outcome when compared with clinical data and generally demonstrated no improvement in predictive ability over time.

Only when combined with clinical data was the HUS scan closer to 36 weeks postmenstrual age better than an ultrasound scan in the first 28 days for the prediction of low mental developmental index, cerebral palsy, and non-independent walking. Overall, these models are not optimal for use in individual neonates because of lack of sufficient accuracy, but the models are suitable for evaluation of the relative importance of the predictors.

Periventricular leukomalacia was an important risk factor for neurodevelopmental impairment and its components, but only if considered after the first 28 days. Echodensities diagnosed early in life may partially or completely resolve and consequently may not predict neurodevelopmental impairment.Independent of the time of the examination, enlarged ventricles was the only HUS finding that predicted poor neurodevelopmental outcome. It is possible that enlarged ventricles may be a marker of abnormal white matter development.

Infants with normal HUS scans and grades I and II intracranial hemorrhage had an incidence of neurodevelopmental impairment ranging from 39% to 51%. When corrected for other variables by regression analysis, a normal HUS scan was not associated with normal outcome, which is consistent with the recent work by Laptook et al., who demonstrated that nearly 30% of ELBW infants with a normal HUS scan had either cerebral palsy or a low Mental Developmental Index. It is likely that neurodevelopmental impairment will not always be preceded by abnormal ultrasound findings. Detection of subtle white matter damage may be better with magnetic resonance imaging.

Severe intracranial hemorrhage and periventricular leukomalacia are believed to be strong predictors of poor neurodevelopmental outcome. Abnormal ultrasonographic findings are considered often in decisions to withdraw or

### DISCUSSION

This study addresses the ability of clinical models, HUS models, and their combination to predict neurodevelopmental impairment at 18 to 22 months corrected age. Many ELBW infants with a normal HUS scan later have neurodevelopmental impairment, although some infants with abnormal HUS scans do not have significant impairment. Clinical models were stronger predictors for neurodevelopmental impairment and its components than HUS models. Isolated HUS findings had a poor predictive ability for neurodevelopmental outcome when compared with clinical data and generally demonstrated no improvement in predictive ability over time.

<table>
<thead>
<tr>
<th>Head ultrasound variable</th>
<th>NDI</th>
<th>MDI $&lt;70$</th>
<th>PDI $&lt;70$</th>
<th>Cerebral palsy</th>
<th>Blindness</th>
<th>Deafness</th>
<th>Non-independent walking</th>
<th>Non-independent feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 1308)</td>
<td>39.4</td>
<td>31.9</td>
<td>18.8</td>
<td>10.1</td>
<td>1.6</td>
<td>1.5</td>
<td>7.7</td>
<td>12.8</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 (n = 244)</td>
<td>40.6</td>
<td>31.5</td>
<td>18.0</td>
<td>17.2</td>
<td>2.9</td>
<td>1.2</td>
<td>10.7</td>
<td>13.9</td>
</tr>
<tr>
<td>Grade 2 (n = 151)</td>
<td>51.0</td>
<td>36.9</td>
<td>22.3</td>
<td>17.2</td>
<td>4.0</td>
<td>3.3</td>
<td>9.3</td>
<td>13.9</td>
</tr>
<tr>
<td>Grade 3 (n = 215)</td>
<td>55.4</td>
<td>43.3</td>
<td>36.7</td>
<td>31.3</td>
<td>7.0</td>
<td>2.8</td>
<td>25.1</td>
<td>23.4</td>
</tr>
<tr>
<td>Grade 4 (n = 145)</td>
<td>69.7</td>
<td>52.6</td>
<td>55.5</td>
<td>51.4</td>
<td>11.2</td>
<td>4.9</td>
<td>42.4</td>
<td>28.5</td>
</tr>
<tr>
<td>Periventricular leukomalacia (n = 134)</td>
<td>72.4</td>
<td>60.3</td>
<td>52.8</td>
<td>50.0</td>
<td>10.5</td>
<td>3.7</td>
<td>44.0</td>
<td>29.1</td>
</tr>
<tr>
<td>Cystic periventricular leukomalacia (n = 50)</td>
<td>76.0</td>
<td>60.4</td>
<td>64.6</td>
<td>64.0</td>
<td>18.0</td>
<td>6.3</td>
<td>50.0</td>
<td>32.0</td>
</tr>
</tbody>
</table>

MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index.

All infants were counted only once and were assigned the highest grade of intracranial hemorrhage/leukomalacia from either head ultrasound scan. Missing values in either the row or column variable were excluded from the analysis.
 withhold therapy. Clinicians may consider cranial ultrasound scanning to provide additional prognostic data to the “pretest probability” estimated on the basis of multiple clinical variables (birth weight, antenatal variables, need for resuscitation, severity of illness). This study shows that HUS scans do not reliably predict neurodevelopmental impairment in survivors. When controlled for clinical variables and timing of the examination, only periventricular leukomalacia diagnosed closer to 36 weeks and shunt placement were significantly associated with subsequent neurodevelopmental impairment. The high prevalence of neurodevelopmental impairment in infants with normal HUS scans or minor grades of intracranial hemorrhage, and the frequent absence of severe neurodevelopmental impairment despite grade IV intracranial hemorrhage or periventricular leukomalacia indicate that the association between HUS findings and neurodevelopmental outcome is not as strong as previously believed.14,19

A limitation of this study is that the analysis was constrained to already existing data; however, the database was comprehensive and collected by trained personnel. Although HUS interpretations are subject to interobserver variability35,36 and central readers were not used, the effect of interreader variability was minimized by use of a predefined classification. Our study may also more closely approximate routine clinical practice because central readers are not used for clinical decision making. Another limitation is that the timing of the HUS scan (both early and late) were variable, and this variability in timing may influence the observations. Again, however, this may more closely approximate routine clinical practice in which timing is variable. Only infants who survived to follow-up were evaluated. Therefore differential bias is possible because infants in whom support was withdrawn as a result of severe intracranial hemorrhage would not have been included. Differential bias is also possible in this study because examiners during follow-up were not masked to the infants’ clinical course, HUS findings, or clinical findings on prior evaluations.

Important strengths of this study include the analysis of a large multicenter cohort of ELBW infants with a standardized and comprehensive evaluation of neurodevelopment at 18 to 22 months corrected age. Furthermore, the analyses performed on HUS findings were controlled not only for clinical variables but also for the time of the examination.

Clinical variables were stronger predictors than HUS findings because the addition of HUS data did not improve the predictive abilities of models with only clinical variables. The poor predictive ability for HUS may be partly explained by the use of a classification that considers increasing grades of IVH as a progression of a single disease with cumulative effect.37 Ventriclemongalagly is considered a consequence of intraventricular hemorrhage, although it may represent atrophy as a result of white matter damage from other causes.31 In addition to the anatomic site and extension of the hemorrhage,38,39 a classification that considers the degree of white matter damage,22 its location,40 and whether these findings are persistent or transient41 may improve the prediction of neurologic outcome. Additional limitations of the current methods of ultrasound analysis include the lack of standardization in determination of ventricular size and of reporting of cerebellar lesions. It is possible that a classification of HUS that takes into account the site, extension, and persistence of the hemorrhage, as well as the degree of white matter damage, may correlate better with longer-term outcome.

Clinicians often overestimate the incidence of major disability or death in these extremely sick babies, and this may lead to restriction of life support therapies.2,43 This study documents that HUS findings are poor predictors of outcome and indicates that decisions on withdrawal or withholding support in preterm infants should not be made solely on the basis of HUS findings. A large study with more accurate imaging techniques or classifications is required to identify specific characteristics that may improve the predictive ability of imaging studies for neurodevelopmental outcomes.

REFERENCES


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Table III. Odds ratios and 95% confidence intervals of clinical and head ultrasound predictors (at \( P < .05 \)) on neurodevelopmental outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>“Early” predictors OR (CI 95%)</th>
<th>“All” predictors OR (CI 95%)</th>
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</thead>
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<tr>
<td>Neurodevelopmental impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.0 (1.6-2.5)</td>
<td>Male</td>
</tr>
<tr>
<td>Race*</td>
<td>1.3 (1.0-1.6)</td>
<td>Race</td>
</tr>
<tr>
<td>Surfactant</td>
<td>1.7 (1.2-2.3)</td>
<td>Surfactant</td>
</tr>
<tr>
<td>High frequency ventilation</td>
<td>1.5 (1.2-2.0)</td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Seizure</td>
<td>2.2 (1.3-3.7)</td>
<td>Late onset sepsis</td>
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<tr>
<td>Late onset sepsis</td>
<td>1.7 (1.4-2.2)</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>Birth weight†</td>
<td>0.8 (0.7-0.9)</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Head ultrasound</td>
<td>None statistically significant at ( P &lt; .05 )</td>
<td>Periventricular leukomalacia</td>
</tr>
<tr>
<td>Mental Developmental Index &lt;70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.4 (1.9-3.0)</td>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
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<td>Surfactant</td>
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<td>Seizure</td>
<td>2.2 (1.4-3.6)</td>
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<td>Birth weight</td>
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<td>Psychomotor Developmental Index &lt;70</td>
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<td>Clinical</td>
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<td>Male</td>
<td>1.5 (1.1-1.9)</td>
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<tr>
<td>High-frequency ventilation</td>
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<td>Steroids for bronchopulmonary dysplasia</td>
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<td>Seizure</td>
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### Appendix. List of Participating NICHD Neonatal Research Network Centers during the period of the study

<table>
<thead>
<tr>
<th>Center</th>
<th>Principal Investigator (PI)</th>
<th>Follow-up Principal Investigator (FPI)</th>
<th>Network Coordinator (NC)</th>
<th>Follow-up Coordinator (FC)</th>
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<tbody>
<tr>
<td>1 Brown University</td>
<td>William Oh, MD</td>
<td>Betty Vohr, MD</td>
<td>Angelita Hensman, RNC</td>
<td>Lucy Noel, RNC</td>
</tr>
<tr>
<td>2 Case Western Reserve University</td>
<td>Avroy A. Fanaroff, MB BCh</td>
<td>Dee Wilson, MD</td>
<td>Nancy Newman, RN</td>
<td>Bonnie Siner, RN</td>
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<tr>
<td>3 Duke University</td>
<td>Ronald N. Goldberg, MD</td>
<td>Ricki Goldstein, MD</td>
<td>Kathy Auten, RN, BS</td>
<td>Melody Lohmeyer, RN</td>
</tr>
<tr>
<td>4 Emory University</td>
<td>Barbara J. Stoll, MD</td>
<td>Barbara J. Stoll, MD</td>
<td>Ellen Hale, RNC, BS</td>
<td>Ellen Hale, RNC, BS</td>
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<tr>
<td>5 Harvard University</td>
<td>Ann R. Stark, MD</td>
<td>Ann R. Stark, MD</td>
<td>Kerri Fournier, RN</td>
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<tr>
<td>6 Indiana University</td>
<td>James A. Lemons, MD</td>
<td>Anna Dusick, MD</td>
<td>DeeDee Appel, RN</td>
<td>Leslie Richards, RN</td>
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<tr>
<td>7 Stanford University</td>
<td>David K. Stevenson, MD</td>
<td>Susan Hintz, MD</td>
<td>Bethany Ball, RN, BS</td>
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<td>8 University of Alabama</td>
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<td>Kathy Nelson, MD</td>
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<td>Viviah Phillips, RN</td>
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<td>9 University of California, San Diego</td>
<td>Neil N. Finer, MD</td>
<td>Yvonne Vaucher, MD</td>
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<td>Martha Fuller, RN</td>
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<td>10 University of Cincinnati</td>
<td>Edward F. Donovan, MD</td>
<td>Jean Steichen, MD</td>
<td>Cathy Grisby, RN</td>
<td>Tari Gratton, RN</td>
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<td>11 University of Miami</td>
<td>Shahnaz Duara, MD</td>
<td>Charles Bauer, MD</td>
<td>Ruth Everett, RN</td>
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<td>Lu-Ann Papile, MD</td>
<td>Lu-Ann Papile, MD</td>
<td>Conra Backstrom, RN</td>
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<tr>
<td>13 University of Rochester</td>
<td>Dale L. Phelps, MD</td>
<td>Gary Myers, MD</td>
<td>Linda Reubens, RN</td>
<td>Diane Hust, RN</td>
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<td>14 University of Texas, Houston</td>
<td>Jon E. Tyson, MD, MPH</td>
<td>Brenda Morris, MD</td>
<td>Georgia McDavid, RN</td>
<td>Shannon Rossi</td>
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<td>15 Wake Forest University</td>
<td>T. Michael O'Shea, MD</td>
<td>Robert Dillard, MD</td>
<td>Nancy Peters, RN</td>
<td>Barbara Jackson, RN</td>
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<td>16 Wayne State University</td>
<td>Seetha Shankaran, MD</td>
<td>Yvette Johnson, MD</td>
<td>Gerry Muran, BSN</td>
<td>Debbie Kennedy, RN</td>
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<tr>
<td>17 Yale University</td>
<td>Richard A. Ehrenkranz, MD</td>
<td>Linda Mayes, MD</td>
<td>Pat Gettner, RN</td>
<td>Elaine Romano, MSN</td>
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<tr>
<td>18 NICHD</td>
<td>Linda L. Wright, MD, Rosemary D. Higgins, MD</td>
<td></td>
<td>Beth B. McClure, MS</td>
<td></td>
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<tr>
<td>19 Research Triangle Institute</td>
<td>W. Kenneth Poole, PhD</td>
<td>W. Kenneth Poole, PhD</td>
<td>Betty Hastings, Carolyn Petrie, MS</td>
<td>Beth B. McClure, MS</td>
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</table>

*Appendix. Table III. Continued*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>“Early” predictors OR (CI 95%)</th>
<th>“All” predictors OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-independent walking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>0.6 (0.4-0.9)</td>
<td>Steroids</td>
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<tr>
<td>Male</td>
<td>1.4 (1.0-2.1)</td>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Seizure</td>
<td>4.5 (2.7-7.3)</td>
<td>Seizure</td>
</tr>
<tr>
<td>High-frequency ventilation</td>
<td>1.6 (1.1-2.4)</td>
<td>High frequency ventilation</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>1.8 (1.3-2.6)</td>
<td>Late onset sepsis</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.9 (0.7-1.0)</td>
<td>Birth weight</td>
</tr>
<tr>
<td>Head ultrasound</td>
<td></td>
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<tr>
<td>Periventricular leukomalacia</td>
<td>2.4 (1.0-5.5)</td>
<td>Periventricular leukomalacia</td>
</tr>
<tr>
<td>Parenchymal blood</td>
<td>2.2 (1.2-4.0)</td>
<td>Ventricular enlargement</td>
</tr>
<tr>
<td>Ventricular enlargement</td>
<td>3.0 (1.7-5.3)</td>
<td>Shunt</td>
</tr>
</tbody>
</table>

*Race compares black and non-Hispanic versus others.*
†Odds ratios for birth weight are given for every 100-g increment in birth weight.
‡Comparison of maternal education up to 12th grade versus college/graduate degree.

Clinical Data Predict Neurodevelopmental Outcome Better than Head Ultrasound in Extremely Low Birth Weight Infants
505.e2
Early Umbilical Cord Clamping Contributes to Elevated Blood Lead Levels among Infants with Higher Lead Exposure

CAMILA M. CHAPARRO, PhD, RAYMOND FORNES, MS, LYNNETTE M. NEUFELD, PhD, GILBERTO TENA ALAVEZ, MD, RAÚL EGÚÍA-LÍZ CEDILLO, MD, AND KATHRYN G. DEWEY, PhD

Objective To investigate whether infant iron status, modified by umbilical cord clamping time and infant feeding mode, affected infant blood lead concentration at 6 months of age.

Study design Participants were a subset of women and their infants randomized to receive early (10 seconds) or delayed (2 minutes) umbilical cord clamping and were monitored to 6 months postpartum in Mexico City. Iron and lead status was analyzed in maternal, placental, and 6-month infant blood samples. Baseline maternal lead exposure data and infant feeding data at 2, 4, and 6 months were collected.

Results In the total sample, maternal blood lead concentration, infant ferritin, and breast-feeding practices predicted infant blood lead concentration. Among infants with higher placental blood lead concentration and breast-fed infants not receiving any iron-fortified formula or milk at 6 months, early clamping increased infant blood lead concentration, an effect mediated in part via decreased infant iron status.

Conclusions Early cord clamping, by decreasing infant iron status, contributes to higher blood lead concentrations at 6 months of age among infants at high risk. (J Pediatr 2007;151:506-12)
which could be important in preventing lead absorption.  

The objective of these analyses was to investigate how maternal lead burden is related to infant lead burden in this population and whether infant iron status, as affected by infant feeding practices and umbilical cord clamping time, modifies infant lead status at 6 months of age.

METHODS

Subjects were a subset of participants in a randomized controlled trial investigating the effect of the timing of umbilical cord clamping on infant iron status. We included all subjects for whom sufficient blood sample was available to analyze whole blood lead and iron outcome measures. Methods for the randomized trial have been presented elsewhere. Briefly, 476 healthy mothers with uncomplicated pregnancies, vaginally delivering single, healthy, term, normal birth weight (>2500 g) infants, were randomized with their written, informed consent, to “early” umbilical cord clamping (intended time 10 seconds from the appearance of the infant’s shoulders; actual mean time: 6.5 ± 6.4 seconds) or “delayed” umbilical cord clamping (intended time: 2 minutes from the appearance of the infant’s shoulders; actual mean time: 93.8 ± 44.2 seconds). Venous blood samples were taken from the mother before delivery and from the umbilical vein of the placenta immediately after delivery. Infant weight and recumbent length were measured at birth. A baseline interview (including socioeconomic, demographic, medical history, and lead exposure data) with the mother was done before discharge from the hospital. Lead exposure data included previous and current occupational exposure, environmental exposure (source of drinking water, exposure to dust from construction or remodeling, and location of house near lead producing industries), and dietary exposure through lead-glazed ceramics (frequency of use for storing and preparing food). Visual aids were provided to correctly identify the type of ceramics that contain lead glaze. Mothers reporting use of ceramics were informed of the associated lead exposure risk. At 2, 4, and 6 months of age, morbidity and dietary intake data for the infant were collected through a hospital visit or by phone. When the interview occurred in the hospital, infant weight and recumbent length were measured. Maternal height and weight were measured at 2 months postpartum. At the 6-month visit, a venous blood sample was taken from the infant. This study was reviewed and approved by the Human Subjects committees of the University of California, Davis, the National Institute of Public Health of Mexico, and the Mexican Institute of Social Security.

Blood Collection and Analysis of Iron and Lead Status

The placental, maternal, and infant venous blood samples were taken with precautions to minimize the potential for environmental lead contamination of the sample (ie, cleaning and rinsing the venipuncture site with deionized water). All venous blood samples were collected into Vacutainer Trace Element Free tubes with Na₂EDTA (Becton-Dickinson, Franklin Lakes, NJ).

As soon as possible after collection, the whole blood was analyzed by use of the HemoCue hemoglobinometer (HemoCue, Lake Forest, CA) and Coulter Ac-T 8 automated analyzer (Beckman Coulter, Fullerton, CA) for hemoglobin concentration and hematologic profile, respectively. The calibration of both analyzers was checked daily with appropriate controls. Samples were spun in a centrifuge (15 minutes, × 1090 g, room temperature) and plasma was stored at −20°C until transferred on dry ice to the University of California, Davis, for analysis of plasma ferritin (by radioimmunoassay; DPC, Los Angeles, CA), transferrin receptor (TfR, by enzyme-linked immunoassay; Ramco, Stafford, TX), and C-reactive protein (by radial immunodiffusion; The Binding Site, Birmingham, United Kingdom).

When sufficient sample was obtained for the principal iron and hematologic analyses of the main study, a 1-mL aliquot of whole blood was stored in Nunc cryovials (NNI, Rochester, NY), previously tested to be lead free, for later analysis of blood lead. Samples were frozen at −20°C until transferred to the California Department of Health Services for further analyses. Whole blood lead was analyzed at the Environmental Health Laboratory of the California Department of Health Services by Electro Thermally Heated Atomic Absorption Spectroscopy. All analyses were done in duplicate.

Indicators and Definitions of Infant Iron and Lead Status and Feeding Mode

Infant body iron at 6 months of age was estimated as the sum of the iron contained in Hgb, in storage (BSI), and in myoglobin and enzymes per kilogram of body weight. Iron in Hgb was calculated from the following equation: Iron in Hgb = body weight (kg) × blood volume (L/kg) × Hgb concentration (g/L) × 3.47 mg Fe/g Hgb, where blood volume was estimated to be 0.075 L/kg body weight. Myoglobin/enzyme iron was estimated to be approximately 20% of the amount of iron in Hgb. BSI was calculated from the following equation derived for infants: BSI = (log₁₀ plasma ferritin − 1.345)/0.0439 × body weight.

Infant ferritin values were excluded if the C-reactive protein value was >10 mg/L (indicative of an acute phase response, which can elevate ferritin levels despite iron deficiency). We defined anemia at 6 months as Hgb <117 g/L, on the basis of the recommended cutoff of 105 g/L at 6 months of age adjusted for the altitude of Mexico City (2240 m). ID was defined as a ferritin concentration <9 µg/L. Iron deficiency anemia was defined as both ferritin and Hgb below their respective cutoff points.

The current clinical cutoff for elevated blood lead level according to CDC guidelines is greater than 10 µg/dL. Because no non-zero blood lead concentration can be considered “safe,” in addition to the CDC proposed cutoff, we used a slightly lower cutoff for categorization of elevated infant blood lead concentration at 6 months of age: above 8
Table. Characteristics of subjects with infant blood lead assessment (by cord clamping treatment group)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All subjects (N = 266)</th>
<th>Early clamping (N = 127)</th>
<th>Delayed clamping (N = 139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal weight (kg)</td>
<td>61.5 ± 9.9 [260]</td>
<td>63.3 ± 10.3 [124]†</td>
<td>60.0 ± 9.3 [136]</td>
</tr>
<tr>
<td>Maternal education (y completed)</td>
<td>11.7 ± 3.2</td>
<td>11.7 ± 3.1</td>
<td>11.7 ± 3.3</td>
</tr>
<tr>
<td>Mother employed (%)</td>
<td>45</td>
<td>52‡</td>
<td>39</td>
</tr>
<tr>
<td>Took prenatal supplement containing iron (%)</td>
<td>90</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>Current use of lead-glazed ceramics (%)</td>
<td>18</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>Past use of lead-glazed ceramics (%)</td>
<td>54 [260]</td>
<td>61 [121]‡</td>
<td>47</td>
</tr>
<tr>
<td>Blood lead concentration (μg/dL)§</td>
<td>5.1 (3.1, 7.8) [251]</td>
<td>5.2 (3.2, 7.7) [121]</td>
<td>5.1 (3.1, 7.8) [130]</td>
</tr>
<tr>
<td>Placental blood lead concentration (μg/dL)§</td>
<td>3.9 (2.5, 5.9) [228]</td>
<td>4.1 (2.7, 6.0) [111]</td>
<td>3.6 (2.4, 5.8) [117]</td>
</tr>
<tr>
<td>Infant characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>50</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39.1 ± 1.1</td>
<td>39.3 ± 1.1</td>
<td>39.0 ± 1.0</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3183 ± 364</td>
<td>3192 ± 374</td>
<td>3174 ± 356</td>
</tr>
<tr>
<td>Weight gain, 0-6 months (g)</td>
<td>4092 ± 741</td>
<td>4072 ± 734</td>
<td>4111 ± 749</td>
</tr>
<tr>
<td>Blood lead concentration (μg/dL)§</td>
<td>2.7 (2.0, 4.1)</td>
<td>3.0 (2.0, 4.4)</td>
<td>2.7 (1.9, 3.9)</td>
</tr>
<tr>
<td>Anemic (%)</td>
<td>15</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Ferritin (μg/L)¶</td>
<td>38.6 (24.5, 77.1) [253]</td>
<td>36.0 (22.1, 66.8) [124]†</td>
<td>46.5 (25.9, 80.0) [129]</td>
</tr>
<tr>
<td>Iron deficient (%)#</td>
<td>6</td>
<td>9**</td>
<td>2</td>
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<tr>
<td>Iron deficiency anemia (%)‡‡</td>
<td>2</td>
<td>5‡‡</td>
<td>0</td>
</tr>
<tr>
<td>TFR (μg/mL)</td>
<td>5.0 ± 1.3 [265]</td>
<td>5.1 ± 1.3 [126]</td>
<td>4.8 ± 1.2</td>
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<tr>
<td>Body iron (mg/kg)</td>
<td>41.7 ± 8.4 [253]</td>
<td>40.3 ± 9.0† [124]</td>
<td>43.1 ± 7.5 [129]</td>
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<tr>
<td>Body storage iron (mg)</td>
<td>43.2 ± 58.1 [253]</td>
<td>34.0 ± 61.9† [124]</td>
<td>52.0 ± 53.0 [129]</td>
</tr>
</tbody>
</table>

*Sample size in brackets for variables with missing data. Means and SD presented unless otherwise indicated.
†Significantly different from delayed-clamping group (Student’s t test, P = .01).
‡Significantly different from delayed-clamping group (χ², P = .03).
¶Median, first quartile (Q1), third quartile (Q3) of untransformed data presented, data were log₁₀ transformed for analyses.
††Excluding all infant blood samples positive for C-reactive protein (>10 mg/L). Median, first quartile (Q1), third quartile (Q3) of untransformed data presented, data were log₁₀ transformed for analyses.
#Defined as ferritin <9 μg/L.16
**Significantly different from delayed-clamping group (χ², P = .02).
‡‡Defined as ferritin <9 μg/L and Hgb <117 g/L.

μg/dL, equivalent to the 95th percentile of our distribution. Feeding status at 6 months of age was defined as breastfeeding and not receiving any iron-fortified formulas or milk (NFM) versus receiving iron-fortified formulas or milk with or without breast milk (FM).

Statistical Analyses

All statistical analyses were done with SAS Version 8.02 (SAS Institute, Cary, NC). Descriptive statistics and distributional plots were done for all outcome and explanatory variables. Variables not normally distributed (infant ferritin; maternal ferritin and Tfr; and maternal, placental and infant blood lead concentrations) were log (base e or base 10) transformed for analysis. To determine predictors of maternal and infant lead, bivariate correlations and multiple linear regression were done between the lead variable and potential explanatory variables. Two-way interaction effects (eg, treatment by breastfeeding status, or treatment by placental lead level) were analyzed with analysis of covariance or logistic regression, controlling for covariates related to both treatment and infant lead level (eg, maternal employment, maternal weight, previous use of lead-glazed ceramics). Finally, to examine whether cord clamping time was acting on infant lead concentration by affecting infant iron status, path analysis was done.19 Statistical significance was considered at P <.05 for independent variables and P <.10 for 2-way interaction effects.

RESULTS

Of the 476 women recruited into the trial, 358 (75%) mother-infant pairs completed the main trial. Of those that completed the study, there were 266 infant, 251 maternal, and 228 placental blood samples available for lead analysis. Descriptive statistics for the 266 mothers and infants included in these analyses are shown in the Table. Because inclusion in these analyses was based solely on the amount of blood sample collected, the group of mothers and infants included (n = 266, 74%) was similar to mothers and infants who were not included (n = 92) (data not shown).
Determinants of Maternal Blood Lead Concentration

Of the 266 mothers, 15% had elevated blood lead levels (>10 μg/dL). Median maternal blood lead concentration was higher than the median lead concentration in both the placental and infant blood. Maternal, placental, and infant blood lead concentrations were highly correlated (Pearson correlation coefficients: maternal/placental 0.83; infant/maternal: 0.49; infant/placental .56; \( P < .001 \) for all correlations). In multiple regression analysis, a 1-year greater maternal age was associated with a 2% higher maternal blood lead concentration (β-coefficient = .02, \( P < .001 \), partial \( R^2 = .05 \)). Current use of lead-glazed ceramics was associated with a 51% higher maternal blood lead concentration (β-coefficient = .41, \( P < .001 \), partial \( R^2 = .06 \)). Among the mothers using lead-glazed ceramics at baseline (n = 49), an increase in lead-glazed ceramic use of 1 time per week was associated with a 10% higher maternal blood lead concentration (\( P < .001 \)). No other lead exposure variable was significantly associated with maternal blood lead concentration.

Determinants of Infant Blood Lead Concentration at 6 Months of Age

At 6 months of age, 65% of infants were still breastfed; however, only 30% were breastfed without receiving any iron-fortified infant formulas or milks (9 of whom were receiving non-iron–fortified milk). Approximately 1% of infants had elevated blood lead (>10 μg/dL). In multiple regression analysis, infant blood lead concentrations were predicted by breastfeeding status, infant iron status and maternal blood lead concentration. Being breastfed and not receiving iron-fortified formula or milk was associated with a 25% higher infant blood lead concentration (β = .22, \( P = .002 \), partial \( R^2 = .05 \)). Each additional milligram of iron in stores at 6 months of age was associated with a 1% lower infant blood lead concentration (β = -.002, \( P < .001 \), partial \( R^2 = .03 \)), and a 10% higher maternal blood lead concentration was associated with a 4% lower infant blood lead concentration at 6 months of age (β = .44, \( P < .001 \), partial \( R^2 = .22 \)).

Does Cord Clamping Time Modify the Effect of Postnatal Lead Exposure on Infant Blood Lead?

We examined whether the timing of cord clamping modified the relationship between placental blood lead concentration (as a continuous variable) and infant blood lead concentration at 6 months of age, controlling for placental blood lead concentration, maternal employment and weight, and previous use of lead-glazed ceramics. Because we were unable to analyze breast milk lead concentrations, we used placental blood lead concentration as a proxy measure of the level of lead an infant might be receiving through breast milk,
given that breast milk lead concentration is correlated with maternal and umbilical cord blood lead. At greater placental blood lead concentrations, infants in the early clamping group had higher infant blood lead concentrations at 6 months of age (with delayed clamping versus early clamping, n = 42).

**Does Cord Clamping Time Modify the Effect of Infant Feeding Mode on Infant Blood Lead?**

Because maternal blood lead concentration is correlated with breast milk lead concentration, infants who are predominantly breast-fed by mothers with higher lead burden may be exposed to more lead through breast milk. We examined whether cord clamping time modified the relationship between infant feeding mode and infant lead status, controlling for maternal weight and previous use of lead-glazed ceramics. There was a significant 2-way interaction between feeding status and cord-clamping treatment group: NFM infants whose cords were clamped early had significantly higher blood lead concentrations at 6 months of age (P = .017 for the interaction term) as compared with infants in the delayed clamping group (Figure 1).

**Path Analysis**

Path analysis showed that the magnitude of the “total” effect of clamping time on infant blood lead concentration was −.119 (standardized β-coefficient for the linear regression of treatment on infant blood lead), and the “direct” effect of clamping on infant blood lead concentration (standardized β-coefficient of treatment on infant blood lead, controlling for infant iron status) was −.091. The “indirect” effect of clamping time on infant lead status (ie, the portion acting through iron status) is the difference between these 2 coefficients, or −.0085. Thus 23% of the “total” effect of delayed clamping on infant lead status could be explained by the increase in iron status.

**DISCUSSION**

These results demonstrate that early cord clamping, acting partially by reducing infant iron status, leads to higher infant blood lead concentrations at 6 months of age among infants with higher postnatal lead exposure. These “high-risk” infants include those born with higher placental blood lead levels (which may reflect a higher level of lead received through breast milk), and those who are breast-fed without receiving any iron-fortified formula or milk. The most plausible mechanism for these results is the up-regulation of DMT-1 expression in response to lowered iron status, resulting in greater uptake of lead. Some studies have indicated that DMT-1 regulation by iron status may not be completely mature in infants before 6 months of age, as compared with adults. However, a recent study of 5- to 6-month-old infants showed that iron absorption was up-regulated in infants with lower iron status, indicating sufficient maturation by 6 months of age to potentially affect lead uptake.

There are several possible reasons why only about a quarter (23%) of the total effect of clamping time on infant lead status could be attributed to changes in infant iron status. First, we may not fully capture the effect of clamping time on iron status or the total effect of iron status on lead status through the variables used as indicators of iron status (ie, ferritin). In this age group, ferritin and TfR may not be as reflective of “true” iron status as they are in adults. Second, the total effect of cord clamping on iron status during infancy may not be adequately represented by measurements at 6 months of age, when the difference between groups would be expected to be smaller than at younger ages because of other factors that affect iron status by 6 months. It is possible that the differences in iron status earlier in infancy, when breast milk lead levels are generally higher and infants are receiving relatively more of their nutrition from breast milk, are most influential with regard to the accumulation of lead in the infant postnatally. Third, we cannot rule out the possibility that cord clamping time acts on infant lead concentration in a manner unrelated to iron status, for example, by affecting the status of other nutrients, such as zinc, or gastrointestinal function. Zinc supplementation of lead-exposed rats decreased body lead concentrations, and zinc-deficient rats...
pups had greater body lead accumulation. However, we expect this to have little impact compared with iron, because the effect of delayed clamping on newborn zinc status is small (a 1% to 2% increase in total body zinc). Finally, there are gastrointestinal transporters other than DMT-1 that can transport lead and whose contribution to infant lead status we cannot account for in these analyses.

In 2 previous studies, breast milk lead concentration explained 12% and 10% of the variation in infant blood lead concentrations at 1 and 6 months of age, respectively. In our study, the combined contribution of breast-feeding status and infant iron status to infant blood lead concentration was similar in magnitude (approximately 8%). Breast-feeding may affect infant blood lead concentration in 2 ways: (1) via lower infant iron intake and status compared with formula-fed infants (in our study breast-fed infants had relatively lower iron status as compared with infants receiving formula, data not shown); and (2) via lead intake from breast milk. Our study is unique in that we were able to assess the relationship of infant blood lead concentration to iron status separately from the relationship to breast-feeding status. Although infants may be exposed to lead via breast milk, our data suggest that they can be protected from this by delayed cord clamping. In any event, infants exposed to lead via breast milk have already been exposed prenatally, and the benefits of breast-feeding likely outweigh any potential adverse consequences of the additional lead transferred by breast milk.

There are several limitations to our study, particularly with regard to assessment of lead exposure and generalizability of our results to other populations. The multiple regression models predicted only 30% and 11% of the variability in infant and maternal blood lead concentration, respectively. Because use of lead-glazed ceramics was only assessed at baseline, we did not know whether preparation and storage practices had changed by the 6-month visit or whether lead-glazed ceramics were used for preparation of infant foods. Because we informed mothers who were using traditional ceramics at baseline that such products were a source of lead, their use may have decreased between baseline and 6 months postpartum. Previous and current occupational lead exposure of the mother was recorded; however, we did not assess her partner’s occupational exposure history. Lead contamination can be brought into the home from occupational exposure, so this variable may have been important. Also, not all potential sources of lead exposure were assessed. Second, breast milk lead concentrations were not available for these analyses, and we were not able to measure lead levels in infant formula or other foods in the infants’ diet. Most infants were consuming other foods and liquids before 6 months of age, so these could be another source of variability. It is difficult to determine quantitatively the contribution of lead from breast milk or other dietary sources to infant blood lead concentrations. Results from 1 study showed lead levels in formula that were comparable to those of breast milk; in another study, however, breast milk lead was strongly correlated with infant blood lead, although formula lead was poorly asso-

ciated with infant blood lead concentration. Finally, in comparison to a similar cohort from 1994 to 1995, our study mothers had relatively low median blood lead concentration at delivery (4.9 vs 8.4 µg/dL from 1994-1995), likely because of recent reductions in air lead contamination and other sources of exposure (eg, elimination of lead-soldered cans for food storage) occurring during the past decade in Mexico City, as well as a lower use of lead-glazed ceramics in our study population (18% vs 49%). Although this is a very positive finding, it limits the generalizability of our findings to populations with higher lead exposure, and it indicates the need for replication of these studies in populations with higher risks of elevated blood lead and iron deficiency.

We conclude that in particular subgroups with a higher risk of postnatal lead exposure, early cord clamping increases the effect of exposure to lead through breast milk, in part by lowering infant iron status and thereby increasing lead absorption. This is an important finding for populations with current and previous high lead exposure and in settings where early cord clamping is routinely practiced. Further research is needed to better elucidate the relationship between iron status and lead status, especially in this vulnerable age group.

We would like to thank Martha Maria Téllez Rojo, Adriana Mercado García, and Beatriz Escobedo Maya for their advice and assistance with data and sample collection for assessing lead exposure in Mexico City and follow-up of our participants. We would also like to thank the California Department of Health Services, Environmental Health Laboratory Branch for performing the analysis of whole blood lead.

REFERENCES


50 Years Ago in The Journal of Pediatrics

MEDICAL PROGRESS: HYALINE MEMBRANE DISEASE

Curtis P. J Pediatr 1957;51:726-41

Timing is everything. Paul Curtis wrote an extensive medical progress report on hyaline membrane disease that was published in 1957, just 2 years before the real progress that resulted from the 1959 Avery and Mead report linking hyaline membrane disease to surfactant deficiency. The Curtis article contains good descriptions of the epidemiologic associations of prematurity, maternal diabetes, and cesarean section with hyaline membrane disease; however, the extensive discussion of the etiology of hyaline membranes as somehow causing the disease missed the mark. At the time, there were three theories about this anatomic finding. The general theories were that hyaline membranes resulted from aspiration of anatomic fluid or gastric contents, from transudation resulting from some sort of unique heart failure occurring only in infants, or from exudation due to toxicity from oxygen or other agents. The references to the possible causes of hyaline membrane disease reads like a “who’s who” of pediatrics at the time: Landing, Apgar, Caffey, Smith, Cook, Sutherland, Gitlin, Gellis, Ylppo, and others. The report does provide a rather detailed physiological description of the pulmonary abnormalities in infants with hyaline membrane disease, including increased pCO₂ values, increased dead space, decreased compliance, and increased work of breathing. The section on therapy highlights the lack of effective treatments other than supplemental oxygen.

This article makes for very interesting reading about the state of confusion about a disease just before the identification of the essential pathophysiological factor—surfactant deficiency. Each hypothesis contained a grain of truth for some infants or was a process that contributed to the respiratory failure, but there was no unifying principle for or consensus about the pathophysiology of hyaline membrane disease. The disease process is no longer referred to as hyaline membrane disease because so few infants die of surfactant deficiency; rather, they have respiratory distress syndrome, a treatable disease in most cases. The anatomic findings of hyaline membranes are almost historic curiosities.

Alan H. Jobe, MD, PhD
Children’s Hospital Medical Center
Cincinnati, Ohio
10.1016/j.jpeds.2007.06.009
Objective To assess an intervention strategy—a 6-week obesity intervention program, Project KidFIT, at 3 Houston, Texas park centers—to address the obesity epidemic in minority children.

Study design Project KidFIT is a physical fitness and nutrition education program aimed at promoting the benefits of physical activity and improving nutrition knowledge in overweight (body mass index [BMI] ≥ 95th percentile) minority children.

Results A total of 120 minority children (77 boys and 43 girls; mean age, 10.1 years) were enrolled in the program. Approximately 71% of these children were at risk of overweight (BMI > 85th percentile), and 54% were overweight. Decreases in body weight (0.3 ± 0.2 kg [mean ± standard error]) and BMI (0.1 ± 0.1 kg/m²) were detected in the overweight children, whereas increases in body weight (0.4 ± 0.1 kg) and BMI (0.2 ± 0.1 kg/m²) were observed in the children with normal body weight (BMI < 85th percentile but > 5th percentile). Significant improvements (P < .05) in flexibility, muscular endurance, and muscular strength were detected in all children, regardless of weight status.

Conclusions The findings suggest that the city park-based KidFIT program might be effective at promoting stabilization for body weight and BMI and improving physical activity performance and nutrition knowledge in overweight minority children. (J Pediatr 2007;151:513-7)

Obesity is a major health problem in the United States because of its association with increased risk of hypertension, coronary heart disease, diabetes, cancer, sudden death, stroke, digestive diseases, orthopedic problems, respiratory disease, hepatic steatosis, gallbladder disease, endocrine abnormalities, and total mortality.1-13 Obesity affects minority and low-income populations disproportionately, especially African Americans and Hispanics.14-22

The Institute of Medicine has recommended that community organizations should collaboratively develop and promote programs that encourage healthful eating behaviors and regular physical activity, particularly among the high-risk populations.23

The American Academy of Pediatrics has issued a policy statement encouraging all pediatricians to partner with their communities to create and disseminate innovative programs to improve child health.24

A recent survey found that 46% of US adults believed their neighborhoods to be unsafe.25 Parents in minority populations were twice as likely as non-Hispanic whites to report an unsafe neighborhood. Consequently, promoting physical activity in minority populations requires accessible and safe opportunities for physical activity in their environment.26

METHODS

Subjects

After a citywide recruitment effort including media exposure, a total of 128 children registered for the Project KidFIT program. Project KidFIT was designed to target youth age 6 to 12 years. Before a child was enrolled into the program, written authorization was
obtained from the parents or legal guardians according to the policy and guidelines of the HPARD. Eight children registered but did not participate in the program. A total of 120 children were enrolled at the 3 designated HPARD community centers (Table I).

Participants with missing data, such as age and pretest or posttest measurements, were counted as dropouts. Each participant’s involvement was completely voluntary. Every participant received a certificate and a T-shirt on completing the program; no additional incentives or awards were provided.

**HPARD Community Centers**

Three community centers were selected for the study, based on the availability of indoor and outdoor facilities to accommodate the physical activity and nutrition education curriculum of the KidFIT program, and because of their location in low socioeconomic status neighborhoods populated by minorities.

**Community Partners**

Project KidFIT was a unique collaboration among BCM, TCH, HPARD, and METRO. The nutrition staff at TCH was responsible for the development of the program’s nutrition education curriculum.

HPARD oversees 337 developed parks and more than 200 open spaces totaling over 18,000 acres in the greater Houston metropolitan area. The department owns and operates 56 community centers across the city. HPARD’s Fitness Director developed the physical activity curriculum for the project and provided the staff training.

METRO is an innovative organization partnering with public and private organizations to deliver an effective, efficient, safe, and high-quality transportation system throughout the greater Houston metropolitan area. Along with the color brochures and posters, METRO also provided reduced bus fares (60% off) in the form of Go-Cards issued to the children participating in the pilot project at the kick-off event.

**Program Design**

The primary goals of Project KidFIT were to instill the benefits of daily physical activity and good nutrition in its participants and to give the participants the tools to support a long-term healthy lifestyle.

**Physical Activity Curriculum.** The physical activity component of the KidFIT program was based on the recommendation of the National Association for Sport and Physical Education (NASPE) that school-aged children should engage in at least 30 to 60 minutes of age-appropriate and developmentally appropriate physical activity on all or most days of the week. Project KidFIT fulfilled the NASPE recommendation by providing more than 1 hour of physical exercise to youth twice a week with structured physical education curricula. The program offered 30 minutes of classroom nutrition education and 90 minutes of structured physical activity twice a week. The duration and frequency of the sessions were based on the preferences of the children and the parents who participated in the 2 pilot studies, to maximize the interest of the children and minimize the time burden on the children and parents. The physical activity and nutrition education components were designed to communicate the formula exercise + good eating habits = KidFIT. Furthermore, the physical activity curriculum included numerous age-appropriate and culturally sensitive activities that kept the children moving and engaged at all times. Children registered in Project KidFIT were free to return to the community centers and use the facilities during their normal operating hours.

During the KidFIT program, the children participated in various physical activities, including outdoor fitness drills, Pilates training, agility ladder training, obstacle courses, resistance training, BOSU balls, physio balls, and group games. HPARD staff provided creative, fun-filled activities in a participatory environment. The physical activities included plyometric drills using BOSU balls and plyometric boxes to apply an overload to the muscles, with the goal of improving speed and strength. The plyometric drills included lateral hopping, bounding, sprinting, and rapid eccentric movements to evoke the stretch reflex. The curriculum also used Pilates training to teach the basic Pilates movements on the mat apparatus, with a focus on breathing techniques and improving flexibility and strength. Agility drills were used to improve the ability to change the direction of the body or body parts rapidly under control. The children also participated in group games that were all-inclusive and goal-oriented. All activities promoted continuous movement while building camaraderie, sports-

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**Table I. Age, sex, ethnicity, and physical characteristics of study participants**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Age*</th>
<th>Sex†</th>
<th>Weight (kg)*</th>
<th>Height (cm)*</th>
<th>BMI (kg/m²)*</th>
<th>BMI ≥ 85th percentile‡</th>
<th>BMI ≥ 95th percentile§</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>9.9 ± 1.2</td>
<td>42/31</td>
<td>52.4 ± 18.1</td>
<td>149.8 ± 11.0</td>
<td>23.2 ± 6.6</td>
<td>73.6%</td>
<td>50.9%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>10.3 ± 1.5</td>
<td>35/12</td>
<td>54.4 ± 19.6</td>
<td>146.1 ± 10.7</td>
<td>24.6 ± 6.4</td>
<td>66.7%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Total</td>
<td>10.1 ± 1.3</td>
<td>77/43</td>
<td>53.1 ± 18.5</td>
<td>148.5 ± 11.0</td>
<td>23.7 ± 6.6</td>
<td>71.1%</td>
<td>54.2%</td>
</tr>
</tbody>
</table>

*Values expressed as mean ± standard deviation.
†Number of males/number of females.
‡Percentage of children with BMI ≥ 85th percentile.
§Percentage of children with BMI ≥ 95th percentile.
manship, and team spirit. KidFIT games included broom ball, sack racing, lolo ball, jump rope, and relay races. Before beginning any activity, the children went through a warm-up routine; after the activity, they performed a cool-down routine. Appropriate music was played during warm-up, Pilates training, aerobic activities, and cool-down through the use of portable full-featured multimedia amplifiers and CD players.

Nutrition Education Curriculum. The cognitive nutrition education curriculum and evaluation tool was developed to be appropriate for children of all races. The lessons were designed to include appropriate fun, interactive activities. The children participated in a different activity or game each lesson to improve their knowledge of the food guide pyramid, food groups, main functions of each food group, portion sizes, food labels, fast food facts, fat content of foods, and food safety. The curriculum was delivered in a classroom setting at the selected HPARD community centers. BCM provided nutritional support and assisted the HPARD staff in delivering the nutrition curriculum to the children.

Staff and Training

The Project KidFIT program was staffed with HPARD employees who have a cultural familiarity with the respective facilities, communities, and, most importantly, the children. The relationship between the staff and families was established well before the KidFIT program began. The HPARD provided continuous positive reinforcement. To participate in the KidFIT program, staff members must have participated in 24 hours of fitness and nutritional training before the program’s start.

Testing and Data Collection

Each participant’s body weight and height were measured at the beginning and at the end of the 6-week session. Weight was measured after the child had removed shoes, heavy outer clothing, belts and had emptied all pockets. Height, also without shoes, was measured using a stadiometer. The child’s average weight and height values were used to calculate his or her body mass index (BMI) as weight in (kg) divided by height (m²). A child was considered at risk of overweight or overweight if his or her BMI was equal to or greater than the age- and sex-specific 85th or 95th percentile. During the 6-week KidFIT program, body weight was reduced by 0.33 ± 0.24 kg (average change ± SE) and BMI was reduced by 0.11 ± 0.11 kg/m² in the overweight children, and body weight was increased by 0.33 ± 0.17 kg and BMI increased by and 0.18 ± 0.08 kg/m² in the non-overweight children. The changes within each group were not significant, probably due to the small sample size. The differences between the 2 groups were statistically significant. A post hoc power analysis found that a sample size of 157 overweight children was needed to detect a 0.33-kg improvement in body weight, whereas a sample size of 272 overweight children is needed to detect a 0.11 kg/m² improvement in BMI at a significance level of .05 and a power of 0.8. The children who were at risk of overweight also

![Figure 1. Comparison of changes (from pretest to posttest) in body weight (Wt) and BMI between overweight and non-overweight children who participated in the KidFIT program. An asterisk indicates a significantly (P < .05) different change between the groups. The error bars represent the standard error of the changes.](image)
when the children were segregated by BMI not statistically significant. Similar results were obtained were also observed in the overweight children, the change was significant improvements in speed and agility were found in the non-overweight children after the 6-week KidFIT program. Significant improvements in body weight, BMI, physical performance, and nutrition knowledge demonstrates the program’s potential effectiveness in preventing or treating childhood obesity, particularly among minority children. Although parents were invited to attend the KidFIT program, levels of parental attendance and involvement were extremely low, possibly due to the after-school hours.

The results of the pilot KidFIT program support the recommendations of the Institute of Medicine and the National Academies that community organizations should collaboratively develop and promote programs to encourage healthful eating behaviors and regular physical activity, particularly in high-risk populations.

Project KidFIT is a practical model that can be developed in other communities using parks and recreation facilities as program sites. The key to its success is close collaboration among medical and research professionals with expertise in nutrition training and curriculum development, trained fitness professionals knowledgeable and experienced in working with children in a physical fitness setting and involved in the program design, and a city organization, such as METRO, to provide marketing support and transportation services.

The limitations of the KidFIT program include the availability of qualified instructors to implement the program, the availability of facilities that can accommodate the physical activity and nutrition components of the program, and, most importantly, the availability of funding to support it. The children who participated in the pilot program were encouraged to return to the community centers and use the facilities during the normal operating hours. Their use of the HPARD facilities outside of the KidFIT program or nonstudy time was not documented, due to a lack of personnel and funding.

A year-long KidFIT program with accurate body composition measurements is needed to determine whether the beneficial effects can be sustained and whether the improvement in body weight will result in a reduction in body fat.

**REFERENCES**

Fifty years ago in *The Journal of Pediatrics*, Crump et al. established that African-American infants were smaller at birth than Caucasian infants. This disparity did not stem exclusively from genetic origins, but from prevailing social conditions, particularly those more common to African-American mothers. These authors’ findings supported the notion that African-American mothers were indeed an economically underprivileged group who were more likely to conceive at young age, to have little to no prenatal care, and to have a lower socioeconomic status.

Over the last 50 years, despite efforts to narrow the gap, there has been little change in the birth weight and socioeconomic differences between African-Americans and Caucasians. Today, the average weight of African-American newborns is 3,089 g, compared with 3,446 g for Caucasian newborns. Statistic show that African-American women continue to have higher rates of teen pregnancy, even given a 59% decrease since 1991; continue to lag behind in prenatal care, even though first-trimester care has increased by 24% from 1990; and continue to have lower socioeconomic status. The general trends remain sadly the same, and as a result, this underprivileged group continues to produce smaller infants.

Clearly, there is no simple solution to eliminate inequalities in birth weight. Enacting social reform programs that aim to decrease teen pregnancy and improve socioeconomic status for African-Americans seems logical, essentially a legacy of President Lyndon Johnson’s 1964 War on Poverty. But even after such an epic battle, a significant birth weight discrepancy remains. Perhaps closure of this divide can be achieved more rapidly by other means, instead of an ambitious attempt to eradicate all poverty.

Social welfare programs, such as Medicaid, are beneficial, but will never address the fundamental issue: ensuring that every developing fetus and pregnant mother receive proper health care. Current programs that meet the needs of only the extremely underprivileged, although well intended, fail to serve lower- and middle-class African-American women, who toil daily to provide for families and are increasingly uninsured. An alternative approach could be to broaden the availability of and accessibility of prenatal health care. Implementing a system of universal health care for children and pregnant women would guarantee that expectant mothers of all races, all socioeconomic strata, and all ages, even teens, could receive and become accustomed to first-rate medical care. A half-century after Crump’s report, we must not only “mind the gap,” as our British friends would say, but also now seek new, more efficient ways to close the gap.

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10.1016/j.jpeds.2007.06.010

REFERENCES

<table>
<thead>
<tr>
<th>Question</th>
<th>Answers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Which food group does yogurt belong to?</td>
<td>a. meat; b. dairy; c. grain; d. sweets</td>
</tr>
<tr>
<td>2. What kinds of food should we eat the most of?</td>
<td>a. red meat (eg, steak, hamburger); b. vegetables (eg, corn, lettuce); c. fruit (eg, bananas, strawberries, apples); d. grains (eg, bread, pasta, rice)</td>
</tr>
<tr>
<td>3. Which activity will use the most calories?</td>
<td>a. playing a video game; b. doing homework; c. watching TV; d. cleaning your room</td>
</tr>
<tr>
<td>4. Which food will give you more energy when you go out to play?</td>
<td>a. bread; b. butter; c. cheese; d. ham</td>
</tr>
<tr>
<td>5. Eating breakfast will help you think better while in school?</td>
<td>a. true; b. false</td>
</tr>
<tr>
<td>6. What mineral is most important for strong bones and is found in milk?</td>
<td>a. sugar; b. fiber; c. calcium; d. sodium</td>
</tr>
<tr>
<td>7. When should leftover food be placed in the refrigerator?</td>
<td>a. only if you feel like it; b. just before you go to bed; c. immediately after you eat; d. the next morning when you wake up</td>
</tr>
<tr>
<td>8. What should you do if you want to lose weight?</td>
<td>a. become more physically active; b. stop eating breakfast; c. eat smaller portions; d. both a and c</td>
</tr>
<tr>
<td>9. Stretching does NOT count as physical activity?</td>
<td>a. true; b. false</td>
</tr>
<tr>
<td>10. Which food is highest in fat?</td>
<td>a. bananas; b. green beans; c. fried chicken; d. skim milk</td>
</tr>
<tr>
<td>11. How many servings of vegetables do you need every day to stay healthy?</td>
<td>a. 1-2; b. 3-5; c. 4-5; d. 6-11</td>
</tr>
<tr>
<td>12. What is the “danger zone” temperature for food?</td>
<td>a. –60 to 0 degrees; b. 0 to 35 degrees; c. 40-140 degrees; d. 150 to 290 degrees</td>
</tr>
<tr>
<td>13. Beans belong to the meat group (protein)?</td>
<td>a. true; b. false</td>
</tr>
<tr>
<td>14. How many sodas or pop do you need to drink every day to stay healthy?</td>
<td>a. 0; b. 1-3; c. 4-5; d. 6-11</td>
</tr>
<tr>
<td>15. After touching raw chicken, you should:</td>
<td>a. do nothing; b. wash your hands with soap and water; c. wipe your hands off with a towel; d. just rinse your hands with hot water</td>
</tr>
<tr>
<td>16. How many days per week should you be physically active to stay healthy?</td>
<td>a. 0-1; b. 1-3; c. 3-5; d. 5-7</td>
</tr>
<tr>
<td>17. When eating at McDonald’s, which would be the most healthy choice?</td>
<td>a. Big Mac; b. grilled chicken sandwich; c. double bacon cheeseburger; d. quarter-pounder with cheese</td>
</tr>
<tr>
<td>18. How many servings of fruit do you need every day to stay healthy?</td>
<td>a. 2-3; b. 2-4; c. 3-5; d. 6-11</td>
</tr>
<tr>
<td>19. The maximum number of calories you should have in a day is 3500:</td>
<td>a. true; b. false</td>
</tr>
<tr>
<td>20. Which food should you always wash before eating?</td>
<td>a. bananas; b. ice cream; c. strawberries; d. both a and c</td>
</tr>
</tbody>
</table>
Daytime Sleepiness and Associated Factors in Japanese School Children

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Objective To examine daytime sleepiness and sleepiness interrelationship with sleep-wake patterns, eating habits, physical activity, and TV/video game time.

Study design A cross-sectional survey with 9,261 school children (mean age of 12.8 years) from 93 junior high schools in Toyama prefecture, Japan.

Results The main outcome measures were daytime sleepiness during schooldays and sleepiness interrelationship with sleep-wake patterns, eating habits, physical activity, and visual media use. A total of 2,328 children (25.2%) reported sleepiness almost always and 4,401 (47.6%) sleepiness often. Regarding sex difference, a higher proportion of girls reported sleepiness in comparison to boys (79% vs 66%, \(P < .001\)). Higher body mass index values were associated with the presence of sleepiness. In girls with preferences for daily snack (versus those who reported no snack) sleepiness presented significantly \((P < .001)\) higher values. Reduced sleep time was significantly associated with sleepiness. The prevalence of sleepiness did not significantly differ among groups who had 7.5 hours sleep or more. A dose-response relation was found between sleepiness and sleep disturbances, physical activity, and media use time.

Conclusions Sleep insufficiency represents a main cause for daytime sleepiness in Japanese junior high school children. Proper sleep habits, high physical activity level, and limited TV viewing time should be promoted among school children. (J Pediatr 2007;151:518-22)

Issues surrounding the sleepiness of schoolchildren have become one of the major concerns of health professionals, teachers, parents, and children. It has been demonstrated that sleepiness drastically interferes with many daily routines and activities and generally reduces normal functioning, with an evident negative impact especially on academic performance, behavioral changes, and psychological problems.\(^1\)\(^,\)\(^2\) Sleepiness especially affects school children because they are partially sleep-deprived.\(^3\)-\(^7\)

In Japan, junior high school children are noted for obtaining insufficient sleep during schooldays and to extend their sleep during weekends.\(^8\) Sleepiness is a very common complaint among school children, and data on its actual prevalence differs from study to study. The varying prevalence of daytime sleepiness has depended on the questions used, sample sizes, study area (countries), the year the survey was conducted, age, ethnicity, and so forth. In adolescents, estimates of the prevalence have been between 10% to 53%.\(^7\)-\(^9\),\(^12\) Few methods have been developed to estimate sleepiness. The best measure for sleepiness is the Multiple Sleep Latency Test.\(^13\)

To reduce the negative impact of sleepiness in the United States, some school districts have adjusted their school schedule to accommodate the children’s sleep-wake schedule.\(^14\) However, at most Japanese junior high schools, the school start time is around 8:30 AM. Many teachers and parents have noted that an increasing number of children are taking naps or dozing during lessons or breaks, in public transport, and so forth.

The purpose of the present study was to describe, in a population of Japanese junior high school children, the relation between self-reported sleepiness and the sleep-period, physical activity, eating habits, and television and video game time. The present study also aimed to examine the association between sleepiness and other sleep-wake variables.

METHODS

Study Site

The study was conducted in 93 public junior high schools, located in Toyama prefecture, on the Japan Sea side of the central part of Honshu main island, northwestern

BMI Body mass index

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Japan. Toyama prefecture is a typical postindustrial province, with no significant economic, social, or cultural differences between the cities (n = 9), towns (n = 18) and villages (n = 8) that participated in the present study. The area is highly developed and the economy is predominately industrial and high technology. The prefecture has a high ratio of households in which both parents work. The rate of private home ownership is around 80.4%.

Participants

The Toyama birth cohort study is a population-based cohort study, focused on children’s development and lifestyle. Data collection was carried out from June to July 2002. A questionnaire was mailed to all public junior high schools (n = 93) and then distributed to pupils (n = 10,453) There was a response rate of 93% (9718). Overall, there were no more than 4% missing answers for sleep-wake habit variables, and 9261 children responded to all answers regarding sleepiness. All participants were schoolchildren in the first junior high school grade (4606 female, 4655 male). The pupils ranged in age from 12 to 13 years, with an average age of 12.8 years. The mean body mass index (BMI) was 19.3 (3.2) for boys and 19.1 (2.9) for girls.

Procedure

The principal and schoolteachers received information about the survey and agreed to cooperate. Each information set consisted of a covering letter, a questionnaire, and an envelope for returning the questionnaire. The questionnaire was distributed to the participants through their schools and returned to their schools in a sealed envelope. The students were told to respond to the questionnaire primarily during class time. All subjects participated voluntarily. Results of the study were later provided to each school.

Questionnaire

The questionnaire (Appendix; available at www.jpeds.com) included basic demographic, self-reported health, lifestyle habits, and sleep-wake patterns information. The full questionnaire8,14,15 consisted of seven sections, but in the present study we used only demographic data, eating habits, media use, and sleep-wake habit variables.

Statistical Analysis

To assess the relation between sleepiness and other factors (sleep patterns, mass media use, BMI), the t test and χ² test (or Fisher exact test when appropriate) were performed. Logistic regression analysis was used to evaluate whether sleepiness and other variables were associated. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. Goodness of fit was assessed by the Hosmer-Lemeshow test. The first two responses regarding sleepiness (often and sometimes) were combined to derive the measure “evidence for sleepiness.” Similarly, the two response options for absence of sleepiness (seldom and rare) were combined to derive the measure “no evidence for sleepiness.” Absence of sleepiness was used as the reference category. The statistical level for significance was set at .05. Statistical analyses were performed by SPSS (SPSS, Inc, SPSS 10.0(J) for Windows. Tokyo: SPSS Inc; 1999).

RESULTS

The Figure shows the characteristics of the subjects by sex. Sleepiness episodes were reported as almost always or often by 25.2% and 47.6%, respectively. No episode of sleepiness was reported only by only 10.4%. After combining the categories of “almost always” and “often” into one group to derive the measure of sleepiness, in parallel with the categories “seldom” and “never” to derive the measure of “no sleepiness,” we examined the difference by sex; 34% of boys versus only 20.8% of girls reported no episodes of sleepiness (P < .001).

We found no significant relation between sleepiness and the demographic variables, such as family structure, presence or absence of parents, grandparents, brothers, and sisters. A trend was found for sleepiness and mother’s employment status; children of mothers with full-time employment status were more likely to report sleepiness.

A significant relation was found for BMI and self-reported sleepiness both in boys and girls. Increased BMI was associated with the presence of sleepiness in boys [19.4 (3.2) vs 19.0 (3.1) respectively; P = .003], girls [19.2 (2.8) vs 18.7 (2.9) respectively; P < .001], and in the overall sample [19.3 (3.0) vs 18.9 (3.0) respectively; P < .001]. We also tested the relation between BMI for respondents in the “almost always” and “often” categories. In boys, this relation was not significant (P = .167). In girls, those in the category “almost always” sleepiness had a BMI of 19.41 (2.87) vs 19.10 (2.80) for subjects with “often” sleepiness (P = .003). The overall sample also presented a significant difference: BMI 19.44 (3.06) in children with “almost always” sleepiness category versus BMI 19.19 (2.98) in children in the “often” sleepiness category (P = .002).

In boys, the relation between sleepiness and eating habits only trended toward significance for the breakfast and...
evening snack variables (\( P = .096 \) and \( P = .062 \), respectively). Those who skipped breakfast and the evening snack were more likely to report sleepiness. However, we found a significant difference for snack-eating between meals in girls. Daily snack (regular versus irregular) in girls was significantly associated with the presence of sleepiness (64.6% vs 57.4%, \( P < .001 \)).

Sleepiness was significantly associated with physical activity. In comparison with the “almost always” group, those who reported “often,” “seldom,” and “almost never” physical activity levels demonstrated ORs of 1.25, 1.55, and 1.80, respectively (\( P < .001 \) all) in developing sleepiness.

As expected, a significant increase in the risk of sleepiness was associated with insufficient sleep time (Table I; available at www.jpeds.com). For example, a sleep time between 6 and 6.5 hours (severe sleep insufficiency) had an OR 1.74 for sleepiness. For the sleep time interval more than 8 hours, there was no increase in the risk of sleepiness.

Regarding sleepiness and nap time, we observed a significant relation between these two variables. We found that an increase in sleepiness was associated with an increase in nap time (eg, a nap duration of 1/2 hour presented an OR of 1.45 and one between 1 hour and 1.5 hours increased the OR to 2.74). After adjusting for age, sex, and BMI, the same tendency for both sleep time and nap time persisted.

A dose-response relation was found between the sleepiness and media use time (Table II; available at www.jpeds.com). Because girls and boys presented different patterns in media use time, the analyses were performed separately for both sexes. With respect to TV viewing time, a gradual increase in TV time was also associated with an increase in risk of sleepiness in boys. A TV viewing time of 3 hours or more significantly affected the child's sleepiness. The maximum risk (OR, 1.73) was found for a TV viewing time of more than 4 hours. In girls, a TV viewing time starting from 1 hour significantly affected the child's sleepiness; interestingly, 4 hours or more spent on such activities presented a higher risk (OR, 2.30) in comparison to boys.

In girls, computer and TV video games had no impact on sleepiness. However, in boys, more than 1 hour of computer and TV video games significantly affected the child's sleepiness. Thus, more than 1 hour spent on such activities significantly increases the risk for sleepiness (OR, 1.41).

In the logistic regression model, the dependent variable was defined as the reference if the item rated as no sleepiness. The results obtained demonstrated that all sleep problems were associated with increased ORs for sleepiness. The strongest associations of sleepiness were related to how children felt in the morning (for the very bad category of response OR 7.57) and sleep in general (for the very bad response category, OR 7.12) (Table III; available at www.jpeds.com). Gradual increases in sleep problems were associated with gradual increases in sleepiness. For example, children who reported one awakening per night presented an OR of 1.19 for sleepiness, whereas children who woke up three times per night presented an OR of 1.89. After adjustment, being female and having higher BMI were risk factors for sleepiness.

**DISCUSSION**

Junior high school appears to be a high risk period for the development of sleepiness and other sleep disturbances as a result of chronic sleep deficiency.\(^{16,17}\) In our sample of children, 25.1% and 47.5%, respectively, reported their sleepiness episodes as almost always or often. In adolescent studies, the prevalence of sleepiness starts at 10%, with upper reported values between 20% and 60%.\(^{12,18-21}\) Saarenpaa-Heikkila et al\(^{22}\) mentioned that sleepiness was more common in adolescents versus preadolescents along with daily sleep urges. In a sample of Japanese adolescents, Ohida et al\(^{20}\) reported excessive daytime sleepiness of 33.3% in boys and 39.2% in girls. However, different values are often dependent on the definitions used by researchers, sample size, and sociocultural determinants.\(^{22}\) A marked sex difference is also noteworthy in this study. One possible explanation for the sex differences could be the higher prevalence of sleep problems in general in Japanese girls.\(^{23}\) Moreover, a higher prevalence of excessive daytime sleepiness among women has been reported\(^{24,25}\); however, studies have also reported no difference\(^{26}\) or a higher prevalence among male subjects.\(^{27}\)

The issue of sleepiness depends on self-perception or the definition of sleepiness. Unfortunately, sleepiness is a multidimensional entity, and no clear consensus exists in terms of what constitutes sleepiness. Every study will capture only limited aspects of sleepiness, and this must be considered when interpreting the results.

Interestingly, there was a significant relation between sleepiness and BMI among both boys and girls. This could be related to preference for a sedentary lifestyle, obesity, and higher incidence of sleep apnea among such children.\(^{28,29}\) According to Gozal et al,\(^{29}\) excessive daytime sleepiness tends to develop among obese children. Similarly, Landis et al\(^{30}\) reported that sleep disruptions (particularly lighter and less deep sleep) were associated with increased BMI. The strong relation between sleepiness and BMI is also confirmed by our results relating to eating habits. A significant relation was found for sleepiness and daily snacks, especially in girls. This finding is confirmed by the higher proportion of sleepiness among girls in our sample. Because girls have a later bedtime (in our study, 75% of boys versus 62.5% of girls reported a bedtime before 11:00 PM) (\( P < .001 \)), the preference for snacks becomes obvious. Some studies of adults have assessed the effect of eating on sleepiness.\(^{31,32}\) However, in our study, the typical Japanese snack (oyatsu) is composed of high-calorie, high-carbohydrate substances; therefore, meal patterns may contribute toward the onset of obesity and subsequently to an increase in sleepiness. The relation between sleep and eating habits in boys presented only a trend toward significance. Previous reports from this study group (see Sekine et al\(^{33}\)) showed that for children 6 to 7 years old, there was a significant dose-response relation between late bedtime or short sleeping hours and childhood obesity. We also found
that children of mothers with full-time employment reported higher prevalences of sleepiness, and this could be related to later dinner time in comparison with children of mothers who worked part-time or were unemployed.

Sleep quality, sleep quantity, and circadian rhythms are the main determinants of sleepiness. Among them, the most interesting findings relate to the complex interrelation between sleepiness and sleep time. Among the sleep-wake patterns included in the analyses, less sleep was a significant predictor of sleepiness. Sleepiness etiology is associated with insufficient nocturnal sleep.3,4,16,34 In agreement with other studies,35 the present results strongly suggest that children with a short sleep period are at greater risk of daytime sleepiness. We found a U-shaped relation between sleep time and sleepiness. As expected, sleep insufficiency was related to a significantly elevated risk of sleepiness and vice versa; with gradual increases in sleep time, the relation becomes insignificant. For example, severe sleep insufficiency (≤6.5 hours) presented a serious increase in the risk of sleepiness (OR, 1.7), and a sleep time of more than 7.5 hours did not affect sleepiness. Furthermore, we found that the optimal sleep time started from at least a 7.5- to 8-hour period. After adjustment, girls and those with higher BMI values presented a significant risk for sleepiness.

We also found a strong relation between sleepiness and nap time. A higher sleepiness risk was associated with a longer nap time. It has been demonstrated in young adults that a nap of less than 30 minutes provides a recuperative effect.36 Especially for junior high school children, a daytime nap could serve as a significant restorative factor.

An increase in TV watching time was followed by an increase in sleepiness risk. We observed that girls were more sensitive to the negative effect of TV watching. Thus, in boys, a significant increase in sleepiness risk started from 3 hours of TV watching, although, in girls, even 1 hour significantly increased the risk of sleepiness. Moreover, long-term (>4 hours) TV watching presented a higher risk of sleepiness in girls versus boys (OR, 2.3 vs 1.7, respectively). The findings could be attributable to different TV viewing times for junior high schoolchildren in Japan. It has been reported that the time spent watching TV was 2.0 hours and 1.6 hours in boys and girls, respectively.37 The above data are partially in agreement with the AAP recommendations of no more than 2 hours of daily viewing.38 However, extensive television viewing has been associated with diverse sleep disturbances during adolescence.39 Furthermore, the presence of a computer or TV in a child’s room significantly modifies sleep–wake time48 and can serve as the most significant predictor of overall sleep disturbance and bedtime resistance.39,40 In the same way, computer and TV video game times provided a significant impact on sleepiness, but only in boys. However, 1 hour or less engaged in such activities has no effect on sleepiness. Our findings are similar to those of Van den Bulck,39 who reported negative influence of computer games on sleep behavior.

In the Japanese adult population, Liu et al41 reported that excessive daytime sleepiness was associated with short sleep duration, symptoms of insomnia, and subjective sleep insufficiency. In the same way, in a representative general sample of the Japanese population Kaneita et al27 reported that excessive daytime sleepiness was associated with male sex, young age, short sleep duration, subjective insuffient sleep, and loss of deep sleep. In agreement with our findings, Yang et al142 reported significantly higher sleepiness among Korean girls versus boys. Some of the sleep patterns seem to be similar in North America and Asia. For example, Liu et al41 reported the association between sleepiness, sleep duration, and sleep problems in both US and Chinese school children. Per contra, LeBourgeois et al44 reported significant divergence between American and Italian children in sleep hygiene. In accordance with other reports,45 some differences or similarities in sleep hygiene could be explained by cross-cultural, educational, or social aspects.

Although many researchers consider the Multiple Sleep Latency Test to be the “gold standard” of the sleepiness measures,46 the issue of sleepiness measurement remains open.47 It has been stated that subjective and objective sleepiness are not the same, and physiological sleepiness may not be detected until extreme subjective sleepiness is reported.34,48 Moreover, the different survey instruments used (Stanford Sleepiness Scale, SSS; Profile of Mood States, POMS; Kwansei Gakuin Sleepiness scale, KSS; and so forth) measure different aspects of sleepiness. Furthermore, the use of different expressions in relation to the meaning of sleepiness may lead to divergence with respect to sleepiness interpretation. In our study, single-item assessment and self-perception of sleepiness could affect the results. However, the questions used in our survey have been validated and used in sleep surveys in Japan.8,14,15 Some other limitations should also be mentioned. Self-report studies are subject to error, especially among poor sleepers. However, in our study, only a small proportion reported poor sleep quality. In addition, the present study could not establish the symptom pathway and demonstrate causality. Sleepiness has also been linked also to some psychosocial problems,49,50 such as decreased mood or depressive state and fatigue, and we did not investigate these aspects. Some cultural influences should also be considered in the interpretation of our results.45

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REFERENCES

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APPENDIX (TRANSLATION FROM JAPANESE)

1. During schooldays, how often do you have sleepiness? (almost always, often, seldom, never)
2. How long does it take to fall asleep from the time you entered the bed? (≤5, 10, 20, 30, 40, 50, 60, >60 minutes)
3. Do you feel it is easy to fall asleep? (very easy, easy, fair, difficult, very difficult)
4. How many times do you wake up during your sleep? (0, 1, 2, 3, 4 times or more)
5. How is your sleep depth in general? (very well, well, normal, bad, very bad)
6. How do you feel when you wake up in the morning? (very good, good, fair, poor, very poor)
7. Do you feel your sleep duration is sufficient? (very short, short, fair, long, very long)
8. Generally speaking, how is your sleep? (very well, well, fair, bad, very bad)
9. During schooldays, on average how long do you watch TV? (never, <1 h, 1 to 2 h, 2 to 3 h, 3 to 4 h, 4 to 5 h, 5 h or more)
10. During schooldays, on average how long do you play games (TV games; Play Station; Game Boy types; PC games)? (never, <1 h, 1 to 2 h, 2 to 3 h, 3 to 4 h, 4 to 5 h, 5 h or more)
11. During schooldays, how often do you eat breakfast (snack, evening snack)? (every day; almost everyday; seldom, almost never)
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<tr>
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<th>CI Lower</th>
<th>CI Upper</th>
<th>Adjusted OR</th>
<th>CI Lower</th>
<th>CI Upper</th>
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<th>Crude OR</th>
<th>CI Lower</th>
<th>CI Upper</th>
<th>Adjusted OR</th>
<th>CI Lower</th>
<th>CI Upper</th>
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<th>Nap time</th>
<th>n (%)</th>
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<th>CI Lower</th>
<th>CI Upper</th>
<th>Adjusted OR</th>
<th>CI Lower</th>
<th>CI Upper</th>
<th>P value</th>
<th>Crude OR</th>
<th>CI Lower</th>
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<th>CI Lower</th>
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<td>Reference</td>
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<td>&lt;.001</td>
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<td>1.29</td>
<td>2.37</td>
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<td>1 h−1.5 h</td>
<td>148 (1.6)</td>
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<td>2.74</td>
<td>1.69</td>
<td>4.44</td>
<td>&lt;.001</td>
<td>2.93</td>
<td>1.73</td>
<td>4.96</td>
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<td>1.5 h−2 h</td>
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<td>2.26</td>
<td>.484</td>
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<td>0.71</td>
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<tr>
<td>&gt;2 h</td>
<td>81 (0.9)</td>
<td>.007</td>
<td>2.32</td>
<td>1.25</td>
<td>4.29</td>
<td>.013</td>
<td>2.58</td>
<td>1.22</td>
<td>5.45</td>
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</table>

OR, Odds ratio; CI, 95% confidence interval, adjusted for sex, age, and body mass index.
|                      | Boys n (%) | P value | OR   | Lower | Upper | CI   | Girls n (%) | P value | OR   | Lower | Upper | CI   |
|----------------------|------------|---------|------|-------|-------|------|--------------|---------|------|-------|-------|------|------|
| **TV time**          |            |         |      |       |       |      |              |         |      |       |       |      |      |
| <1 h                 | 637 (14.1) | 1       | Reference | 634 (13.9) | 1     | Reference |            |         |      |       |       |      |      |
| 1 h~2 h              | 1792 (39.8)| .479    | 0.94 | 0.78 | 1.13 | 1599 (35.2)| .029    | 1.27 | 1.02 | 1.57 |      |      |
| 2 h~3 h              | 1253 (27.8)| .101    | 1.18 | 0.97 | 1.44 | 1206 (26.5)| .012    | 1.33 | 1.07 | 1.67 |      |      |
| 3 h~4 h              | 483 (10.7) | .002    | 1.49 | 1.16 | 1.93 | 604 (13.3) | .012    | 1.41 | 1.08 | 1.84 |      |      |
| >4 h                 | 342 (7.6)  | <.001   | 1.73 | 1.29 | 2.32 | 502 (11.0) | <.001   | 2.3  | 1.68 | 3.15 |      |      |
| **Computer and TV-video games** |          |         |      |       |       |      |              |         |      |       |       |      |      |
| 0 h                  | 914 (20.0) | 1       | Reference | 2595 (56.1) | 1     | Reference |            |         |      |       |       |      |      |
| <1 h                 | 1884 (41.1)| .294    | 1.09 | 0.93 | 1.29 | 1309 (28.3)| .053    | 1.18 | 1     | 1.39 |      |      |
| 1 h~2 h              | 1272 (27.8)| <.001   | 1.41 | 1.18 | 1.69 | 484 (10.5) | .125    | 1.21 | 0.95 | 1.55 |      |      |
| 2 h~3 h              | 330 (7.2)  | .001    | 1.58 | 1.2  | 2.08 | 144 (3.1)  | .934    | 0.98 | 0.66 | 1.42 |      |      |
| >3 h                 | 179 (3.9)  | <.001   | 1.42 | 1.18 | 1.72 | 97 (2.1)   | .431    | 1.23 | 0.73 | 2.07 |      |      |

OR, Odds ratio; CI, 95% confidence interval, adjusted for age and body mass index.
Table III. Binominal logistic regression for sleepiness and sleep-wake patterns among junior high school children

<table>
<thead>
<tr>
<th></th>
<th>Crude OR</th>
<th>Crude CI</th>
<th>Adjusted OR</th>
<th>Adjusted CI</th>
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<td></td>
<td>P value</td>
<td>Lower</td>
<td>Upper</td>
<td>P value</td>
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<td><strong>Sleep latency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>≤5 min</td>
<td>.181</td>
<td>0.917</td>
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<td>.224</td>
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<tr>
<td>10 min</td>
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<td>1.10</td>
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<td>30 min</td>
<td>.019</td>
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<td>1.72</td>
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<td>40 min</td>
<td>.076</td>
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<td>0.96</td>
<td>1.12</td>
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<td>50 min</td>
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<td><strong>Falling asleep</strong></td>
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<td>1.33</td>
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<td>8.44</td>
</tr>
<tr>
<td>Very bad</td>
<td>&lt;.001</td>
<td>7.12</td>
<td>4.70</td>
<td>10.77</td>
</tr>
</tbody>
</table>

OR, Odds ratio; CI, 95% confidence interval, adjusted for sex, age, and body mass index.
Body Mass Index in Children with Newly Diagnosed Inflammatory Bowel Disease: Observations from Two Multicenter North American Inception Cohorts

SUBRA KUGATHASAN, MD, JUSTIN NEBEL, BA, JOSEPH A. SKELETON, MD, JAMES MARKOWITZ, MD, DAVID KELJO, MD, PhD, JOEL ROSH, MD, NEAL LELEIKO, MD, DAVID MACK, MD, ANNE GRIFFITHS, MD, FRCP(C), ATHOS BOUVAROS, MD, MPH, JONATHAN EVANS, MD, ADAM MEZOFF, MD, SUSAN MOYER, MD, MARIA OLIVA-HEMKER, MD, ANTHONY OTLEY, MD, MARIANN PFEFFERKORN, MD, WALLACE CRANDALL, MD, ROBERT WYLIE, MD, AND JEFFREY HYAMS, MD, WISCONSIN PEDIATRIC INFLAMMATORY BOWEL DISEASE ALLIANCE AND PEDIATRIC INFLAMMATORY BOWEL DISEASE COLLABORATIVE RESEARCH GROUP

Objective  To conduct a systematic review of children with newly diagnosed inflammatory bowel disease (IBD) from 2 prospective inception cohorts to examine body mass index (BMI) status at presentation.

Study design  Clinical, demographic, and BMI data were obtained from 783 patients with newly diagnosed IBD. National Health and Nutrition Examination Survey data for 2748 healthy children were used as a control.

Results  Most children with Crohn’s disease and ulcerative colitis had a BMI in the normative range (5%-84%). Low BMI (<5%) was seen in 22% to 24% of children with Crohn’s disease and 7% to 9% of children with ulcerative colitis. Ten percent of children with Crohn’s disease and 20% to 30% of children with ulcerative colitis had a BMI at diagnosis consistent with overweight or risk for overweight.

Conclusion  Children with IBD are affected by current population trends toward overweight. A significant subgroup of children with newly diagnosed IBD has a BMI categorized as overweight or at risk for overweight. Clinicians should be aware of possible IBD diagnosis in the presence increased BMI. (J Pediatr 2007;151:523-7)

Becase inflammatory bowel disease (IBD) primarily affects the gastrointestinal tract, weight loss and low body mass index (BMI) are common presenting features for both Crohn’s disease (CD) and ulcerative colitis (UC).1,2 Typically, weight loss and low BMI are more common and severe in CD than in UC.3-5 Reports indicate that as many as 55% to 63% of patients with newly diagnosed CD and as many as 23% of patients with UC had significant weight loss or poor weight gain at presentation.3-5 In addition, obesity was uncommon in IBD either at presentation or throughout the disease process.6

At the turn of the 21st century, numerous reports have concluded that the BMI in North American children is increasing.7,8 More specifically, recent data by National Health and Nutrition Examination Surveys (NHANES) involving thousands of U.S. children have demonstrated that the percentage of children at risk of overweight (BMI 85th to 94th percentile of the sex-specific BMI-for-age growth chart), overweight (BMI ≥95th percentile of the sex-specific BMI-for-age growth chart), or both continues to increase in the U.S. pediatric and adolescent population. According to the recently published NHANES report, 31.5% of children in the United States are at or above the 85th percentile for BMI (at risk for overweight or overweight), and 16.5% of U.S. children are at or above the 95th percentile (overweight).9 The effects of the “obesity epidemic” in

<table>
<thead>
<tr>
<th>BMI</th>
<th>Body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
</tbody>
</table>

From the Medical College of Wisconsin, Milwaukee, WI (S.K., J.N., J.A.S.); North Shore-Long Island Jewish Health System, New Hyde Park, NY (J.H.); Children’s Hospital of Pittsburgh, Pittsburgh, PA (D.K.); Morristown Memorial Hospital, Morristown, NJ (J.A.); Hasbro Children’s Hospital, Providence, RI (N.L.); Children’s Hospital of Eastern Ontario, Ottawa, Ontario, Canada (D.M.); Hospital for Sick Children, Toronto, Ontario, Canada (A.G.); Children’s Hospital, Baltimore, MD (M.D.-H.); IWK Health Centre, Halifax, Nova Scotia (A.O.); Riley Hospital for Children, Indianapolis, IN (M.P.); Columbus Children’s Hospital, Columbus, OH (W.L.); Cleveland Clinic, Cleveland, OH (R.W.); and Connecticut Children’s Medical Center, Hartford, CT (J.H.).

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children with chronic disease are not fully understood and remain understudied. We are concerned that because the weight and BMI of North American children in general has been increasing, the increased weight of children with new onset IBD might delay consideration of the correct diagnosis. The purpose of this study was to compare the BMI of all children with newly diagnosed IBD from 2 independent inception cohorts (a large multicenter North American cohort and a regional population-based Wisconsin IBD cohort) with national normative data (NHANES).

**METHODS**

**Diagnosis of IBD**

The diagnosis of CD or UC was made on the basis of clinical, biochemical, radiological, and endoscopic criteria necessitating mandatory endoscopic procedure with mucosal biopsies. The children with IBD belong to 2 independent inception cohorts, and the diagnostic criteria for the diagnosis of IBD have been published previously. Children with indeterminate colitis in whom a definitive distinction between CD and UC could not be made were excluded from further analysis.

**North American IBD Cohort**

Data for the North American cohort was generated from the database of the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry. This registry (inception cohort) was initiated in January 2002 by 18 pediatric gastroenterology centers in the United States and Canada as a method of describing the contemporary natural history of newly diagnosed IBD in patients who had not reached their 16th birthday. For each enrolled subject, clinical and demographic characteristics, including type and extent of IBD and disease activity assessment, are recorded at the time of initial diagnosis. In addition, laboratory data are recorded on standardized forms and transmitted to a central data repository. Approval for the registry was received from the human subjects review committee at each participating institution. Informed consent was obtained from all families.

**Wisconsin IBD Cohort**

All pediatric gastrointestinal physicians (n = 16) providing care at Children’s Hospital of Wisconsin voluntarily identified all new cases of IBD beginning in the year 2000, and the data were entered in a database. All children who were <16 years of age at the time of IBD diagnosis and whose residential address contained a Wisconsin ZIP postal code were eligible for inclusion in this study. All the pediatric IBD cases are from a defined geographic area in Southeast Wisconsin (18 of 72 counties in Wisconsin), therefore making this IBD cohort population-based, compared with the North American cohort which is not population-based. Although Children’s Hospital of Wisconsin is part of the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry (North American cohort), no overlap of cases in the cohorts was allowed.

**Control Patients (NHANES)**

The National Center for Health Statistics (NCHS), has been conducting the NHANES on a periodic basis since 1971. For inclusion in this study, data from NHANES 2001 to 2002 were examined. The NCHS conducted a complex, multistage design to provide a representative sample of the non-institutionalized civilian population of the United States. After an in-home interview in which participants were asked questions about their health status, disease history, and diet, a health examination including BMI measurement was performed. After applying the inclusion criteria of 4 to 16 years to the original NHANES data, 2748 subjects (823 Caucasian, 893 non-Hispanic Black, 925 Hispanic, and 107 other races) were included in this analysis as control subjects. This normative data is available publicly at www.cdc.gov/nchs/nhanes.htm.

**Data Collection**

The NHANES data was collected during a 2-year period between the years of 2001 and 2002. Data from the 2 IBD cohorts (at the time of IBD diagnosis) was also collected during approximately the same period, between 2002 and 2005 for the North American cohort and from 2001 to 2002 for the Wisconsin cohort. Height and weight were obtained on all patients with a new diagnosis of IBD before starting any treatment. Height was measured without shoes with a wall-mounted stadiometer, and weight was recorded on a standard scale by a medical technician. Weight, weight percentile for chronological age, height, height percentile for age, BMI, BMI percentile for age, age, sex, and year of diagnosis were recorded in the respective IBD databases for all children who fit our selection criteria.

BMI and BMI percentile were calculated for both children with CD and with UC at diagnosis by using CDC standards (sex-specific BMI-for-age growth chart; www.cdc.gov). Laboratory features, such as hemoglobin and serum albumin levels at presentation, were also recorded.

**Statistical Analysis**

Because the NHANES normative data were derived from a population between the ages of 4 and 16 years, only children between the ages of 4 and 16 were included from the 2 IBD cohorts for analysis. Quantitative statistics were used to describe the prevalence of normal and abnormal BMI percentiles in the respective North American and Wisconsin IBD cohorts and the NHANES controls. The $\chi^2$ test was used to test prevalence differences and the $\chi^2$ goodness of fit test was performed to examine the BMI differences in racial/ethnic groups. A univariate analysis was performed to compare the variables between North American and Wisconsin cohorts.
RESULTS

CD Cohorts

There were 456 children with CD (mean age, 11.97 ± 2.6 years) from the North American cohort and 142 children with CD (mean age, 11.75 ± 2.7 years) from the Wisconsin cohort who met the inclusion criteria (Figure 1). Most children with CD in both the North American (69%) and Wisconsin (66%) cohorts had a BMI that fell in the normative range (BMI, 5%-84 percentile). As expected, 102 of 456 children (22%) in the North American cohort had a low BMI (≤5%). Similarly, 34 of 142 children (24%) in the Wisconsin cohort had a BMI ≤5%. Forty-two of the 456 children (9%) in the North American cohort had a BMI ≥85% (at risk of overweight or overweight). The Wisconsin cohort had a similar percentage of children with CD at risk of overweight or overweight, with 14 of 142 (10%) having a BMI ≥85%.

In the control group (NHANES 2001-2002; mean age, 11 ± 3.6 years), 63% were within the reference range of BMI (5%-84%), 34% were either at risk of overweight or overweight, and only 3% were underweight, with a BMI <5%. When the BMI of NHANES was compared with the CD cohorts, a significant difference (P < .001) was found between the respective CD cohorts and NHANES normative data for overweight or underweight children (Figure 1).

UC Cohorts

There were 156 children with UC (mean age, 11.65 ± 3.1 years) from the North American cohort and 29 with UC (mean age, 11.76 ± 3.2 years) from the Wisconsin cohort who met the inclusion criteria (Figure 2). Most children with UC in both the North American and Wisconsin cohorts had a BMI percentile that fell into the reference range (BMI, 5%-84%). Fourteen of 156 children (9%) in the North American cohort had a low BMI (<5%), although 2 of 29 children (7%) in the Wisconsin cohort had a BMI <5%. We found that of the 156 children in the North American cohort, 31 (20%) of the children with UC had a BMI ≥85% (at risk overweight or overweight) at presentation. When compared with the North American cohort, the Wisconsin cohort had an even higher percentage of children with UC who were at risk for overweight or overweight, with 10 of 29 (34%), which was the same as the NHANES normative data.

Again, the normative BMI data from the NHANES cohort was used as a comparison to the UC cohorts. Significant differences (P < .003) were found between the North American and NHANES cohorts in the underweight (BMI <5%) and at risk of overweight or overweight (BMI ≥85%) categories (Figure 2). Data from the Wisconsin UC cohort were not significantly different from NHANES normative data.

There were BMI differences in children with IBD according to racial/ethnic groups: NHANES data show that when compared with Caucasian children, children in a racial/ethnic minority group (African-American and Hispanic) had significantly higher BMI percentiles. These observations led us to hypothesize that BMI differences may exist even in patients with IBD in racial/ethnic groups. We performed a χ² goodness of fit test to examine whether BMI percentile distributions in children with IBD of Caucasian and African American descent with BMI ≥85th percentile differed from the distribution observed in the NHANES sample. We elected to perform this analysis in the North American cohort only because the number of subjects in the Wisconsin cohort was small. No further analysis was undertaken in children who were Hispanic because there were only 7 patients with IBD who were of Hispanic origin. In patients with CD, the
distributions of BMI differed significantly for children who were Caucasian, but not for children who were African American. However, in patients with UC, the distributions for Caucasian and African American children did not differ from those for the NHANES sample. The number of children who were African American was small. These results suggest that racial/ethnic differences may exist with BMI distribution in populations with IBD at presentation.

Comparison of BMI in Patients with CD and UC

Next, we performed separate analysis comparing the BMI percentiles between patients with CD and patients with UC in the North American cohort and Wisconsin cohort. As expected, significantly more ($P = .0002$ for the North American cohort and $P = .04$ for the Wisconsin cohort) children with CD were in the <5% BMI group (underweight), suggesting that malnutrition is more common in children with CD than children with UC at diagnosis. Approximately 66% to 69% children with CD and 59% to 71% of children with UC fell into the reference range of BMI percentiles. A greater percentage of children with UC were in the at risk of overweight or overweight category (20% in the North American cohort and 34% in the Wisconsin cohort) compared with children with CD (9% in the North American cohort and 7% in the Wisconsin cohort; $P < .0005$).

Comparison Between North American and Wisconsin Cohorts by Univariate Analysis

Although there are no major BMI differences in North American and Wisconsin patients with CD, the BMI differences seen in patients with UC led us to perform a univariate analysis to get a better sense of the differences and commonalities between these cohorts. No significant differences were seen between the North American and Wisconsin cohorts for sex, disease location, or laboratory values. Detailed data on disease activity indices were not available for analysis.

**DISCUSSION**

The increasing weight of North American children is receiving significant attention. Very little is known about the impact of this recent phenomenon on the presentation and course of common chronic diseases such as IBD in children. With the incidence of overweight and obesity throughout North America increasing so dramatically, it is reasonable to ask whether the conditions that usually present with poor nutritional status, such as IBD, still present in that manner. Our data demonstrate that despite frequent weight loss associated with IBD, most children with newly diagnosed IBD (68%) are within the normal population distribution for weight, with BMIs ranging between the 5th and 84th percentiles. As a group, children with IBD at the time of presentation have lower BMIs than do healthy children in the general population. Our results indicate that BMI at diagnosis is dependent on the disease type (CD versus UC), but independent of disease location. In particular, CD of the small bowel does not appear to influence the BMI at diagnosis in CD. There were fewer obese children with CD and more undernourished children with CD when compared with control subjects. Similar but less pronounced findings were noted for children with UC.

Perhaps the most interesting result from our study is that at the time of diagnosis and before treatment, 9% of children with CD and 20% with UC from the North American cohort and 10% of children with CD and 34% with UC from the Wisconsin cohort are either at risk of overweight or overweight according to the Centers for Disease Control classification. On the basis of recent data by Ogden et al, 17.1% of U.S. children (surveyed on 8389 U.S. children between 1999 and 2004) and adolescents are overweight, with a BMI $\geq 95\%$. A slightly higher percentage (24%) of Wisconsin high school students are overweight (www.cdc.gov). Our data suggest that North American children in whom IBD develops are not immune to the factors promoting obesity in the general population. Although speculative, these factors are most likely environmental, because they have occurred too rapidly to be explained by changes in the gene pool. The environmental causes that have been most implicated include the increase in energy-dense food consumption caused by larger portions and “super-sizing” fast foods, and an increase in sedentary leisure time activities, particularly television viewing, internet and computer activities, and video games.

Our findings remind the clinician that children with normal or even high BMIs may have IBD. Therefore, a work-up should be initiated in any child in whom symptoms suggest possible IBD, even when the child is overweight. This is particularly true in children with UC, for whom the prevalence of being overweight appears closer to the normal population.

Whether children with IBD who are overweight will have a different disease course or are at risk for increased complications is unknown. Blain et al have reported that overweight adults with CD (3% of their 2065 patients with CD; weight data was obtained retrospectively) have a different disease course compared with adults with CD who are at normal weight, with earlier onset of fistula formation, more disease relapses, and more hospitalizations. Being at risk of overweight or being overweight may also impact therapy and complications from therapy. In particular, the decision to use corticosteroids becomes more difficult in the overweight child in whom further weight gain is problematic. If more children start out at a higher weight, they may become overweight and suffer issues related to self-esteem that may hinder compliance with treatment. Risk for hypertension and glucose intolerance, also adverse effects of steroid therapy, may also be higher in this group. Long-term natural history studies are therefore necessary to learn whether this new group of patients will be at risk for adult obesity or any of its associated complications. Many inflammatory mediators linked to obesity and adipose tissue (often referred to generally as adipocytokines) overlap with those involved...
with inflammatory bowel disease,\textsuperscript{17} including leptin.\textsuperscript{18} Future studies exploring this subgroup of overweight children with IBD and the inflammatory pathways involved are needed.

In conclusion, 68\% of all children with newly diagnosed IBD have BMI percentiles that fall within the reference range. Low BMI is more common in children with CD compared with those with UC at diagnosis. However, as many as 10\% of children with CD and 20\% to 30\% of children with UC are either overweight or at risk of overweight at the time of the initial diagnosis of IBD. Changing anthropometric data on North American youth appear to be altering the BMI of children with IBD. IBD must be considered in all children with suggestive symptoms, regardless of weight or BMI\%. Longitudinal studies of overweight children with newly diagnosed IBD will be required to define the natural history of this group and determine whether additional morbidity is observed as these patients become adults.

We acknowledge the Department of Pediatrics Section of Quantitative Health Sciences and Christine Cronk, PhD, at the Medical College of Wisconsin for statistical help in this project. We acknowledge the following study coordinators for their efforts toward this project: Miriam Lincoln (Connecticut Children's Medical Center), Kathleen Grancher (Schneider Children's Hospital), Robin McLernon (Hospital for Sick Children), Shari Huffman (Nemours Children's Clinic), Rebecca Ehlerdt (Medical College of Wisconsin), Tracey Roiff (Children's Hospital), Ruth Singleton (Children's Hospital of Eastern Ontario), Myrna Miller (Children's Medical Center), Tracey Williams (IWK Health Centre), Gail Waltz James Whitcomb ( Riley Hospital for Children), Annette Langseder (Morningside Memorial Hospital), Kelley Koslasky (The Cleveland Clinic Foundation), Vivian Abadom (The John's Hopkins Medical Institute), Ramona Bezold (Cincinnati Children's Hospital Medical Center), Janet Trotta (Hasbro Children's Hospital), Melissa Metheren (Columbus Children's Hospital), Kelly Cochlín (Children's Hospital of Philadelphia), Sandra McRandal (Children's Hospital of Pittsburgh), Sandra Hale [Study Coordinator].

\textbf{REFERENCES}

Uterine Development in Turner Syndrome

VLADIMIR K. BAKALOV, MD, THOMAS SHAWKER, MD, IRENE CENICEROS, BS, AND CAROLYN A. BONDIY, MD

Objective To evaluate uterine development of women with Turner syndrome (TS) receiving conventional medical care.

Study design In a cross-sectional study we used ultrasonography for uterine evaluation in 86 women with TS 18 to 45 years of age participating in an intramural NIH study, and who had abnormal karyotypes in >70% of white blood cells. Outcomes were uterine dimensions and shape. Information on hormone treatment was obtained by personal interview.

Results Twenty-five percent had a mature in size and shape uterus, and 31% had an immature uterus, with the remainder in a transitional category. Twenty percent of all participants were not taking hormone replacement therapy (HRT) in the preceding year. The majority on treatment were taking conjugated estrogens (CE) or oral contraceptives (OC). Factors associated with uterine maturity were history of spontaneous puberty and duration and type of HRT, with estradiol-based treatment being the most effective. The age at starting HRT was not a critical factor.

Conclusions Women with TS may develop a normal uterus even at a late start of HRT given adequate duration of treatment and regardless of karyotype. (J Pediatr 2007;151:528-31)

Turner syndrome (TS) is defined as deficiency of all or part of the second sex chromosome in phenotypic females and is relatively common, affecting approximately 1 in 2500 female births.1 Premature ovarian failure affects nearly 95% of girls and women with this disorder, who usually require exogenous estrogen treatment to induce puberty and maintain feminization and bone health throughout the adult years.2 Concerns about the timing of pubertal induction have related mostly to optimization of statural growth in response to pharmacological growth hormone therapy (GH Rx) because a delay in the age of estrogenization allows a longer period of longitudinal bone growth.3,4 However, several European studies have suggested that conventional pubertal induction does not produce optimal development of the uterus in TS.5-7

It is not clear from these studies whether impaired uterine development was because of delayed estrogen treatment, too low dosage, or perhaps the use of progestins with androgenic properties. There does not seem to be any inherent defect in uterine capacity in TS because development is normal in girls with TS with spontaneous puberty.8 At this time we do not have complete information on the requirements for normal uterine growth. It is not known whether there is a "window" of developmental time during childhood or adolescence when uterine growth and maturation must occur to achieve sufficient maturity for pregnancy, or whether uterine development can be induced at a later age with sufficiently high, or sufficiently long, estrogen treatment. In the present study, we addressed the pattern and type of ovarian hormone replacement and karyotype as factors involved in uterine development in adult women 18 to 45 years of age with TS.

METHODS

Study Subjects

In a cross-sectional study conducted between January 2002 and June 2006, we evaluated the uterine development of 86 women with TS, 18 to 45 years of age, who were participants in an ongoing comprehensive intramural natural history study on TS. They were recruited through NIH Web site ads. The study was NICHD Institutional Review Board approved, and all participants signed informed consents. To qualify for the study the participants had to have a karyotype by G-banding consistent with TS in more than 70% of 50 white blood cells.
METHODS

Evaluation included imaging of the uterus and gonads by transabdominal ultrasonography in 68 and by transvaginal ultrasonography in 20 of the participants. High-resolution gray-scale sonography was performed on an Accuson Sequoia scanner (Accuson, Mountain View, CA) or on an ATL scanner (Advanced Technology Laboratories, Bothell, WA) using a multifrequency transducer (5-8 MHz) for the transvaginal scans and a multifrequency transducer (3-5 MHz) for the transabdominal scans. We measured the longitudinal uterine diameter, the anterior-posterior (AP) fundal segment (upper), and the AP cervical uterine segment (lower), all in a sagittal plane, and the maximal transverse uterine diameter in a transverse plane.

Uterine development was evaluated in terms of size by the uterine length and uterine volume and in terms of shape by calculation of the upper to lower uterine ratio. We used size and shape normative data\(^6\) to characterize uterine maturity in the following way: mature uterus: length ≥6.5 cm and upper/lower segment ratio ≥1.10; transitional uterus: length 5.0 to 6.4 cm and ratio ≥1.10 or length ≥6.5 cm but ratio <1.10; and immature uterus: length <5.0 cm or length 5.0 to 6.4 cm but ratio <1.10. The uterine volume was calculated by the formula: Vol (mL) = Length (cm) × Transverse diameter (cm) × AP fundal diameter (cm) × 0.5233.\(^9\)

Each study participant filled out a questionnaire and had a detailed interview regarding pubertal development, age at initiation of hormone replacement therapy (HRT), type of estrogen used, years of estrogen use, and history of GH Rx. We calculated the years of estrogen use by adding the time intervals during which the subject was taking various estrogen-containing medications. In case of spontaneous menarche, we added the time interval from the menarche to development of amenorrhea or start of estrogen-containing medication.

Results are presented as mean values with standard deviation for continuous variables and as numbers and percent for nominal variables. We explored the contribution of the following independent variables to uterine size and maturity: age, height, body surface area (BSA), age at estrogen exposure, years of estrogen use, GH Rx, current HRT use, type of estrogen, and history of spontaneous menarche. To study the individual effect of the above variables on the uterine volume we used either simple linear regression (when the independent variables were continuous) or analysis of variance post hoc Bonferroni test (when the independent variables were nominal). We used a multiple ordinal logistic regression model to study the effect of a combination of continuous and nominal independent variables on uterine maturity (ordinal variable).

A Statistical Package for the Social Sciences statistical program (StatView and JMP, SPSS Inc., Chicago, IL) was used.

RESULTS

Study Subjects

The mean age of the study population was 31.8 ± 7.3 years, range 18 to 45. The majority participants were Cauca-.

Table I. Karyotype distribution

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X in 100% of WBC</td>
<td>49</td>
<td>57.0%</td>
</tr>
<tr>
<td>45,X/46,XX or 45,X/46,XX/47,XXX*</td>
<td>6</td>
<td>7.0%</td>
</tr>
<tr>
<td>46,XX(Xq) or 45,X/46,XX(Xq)</td>
<td>17</td>
<td>19.8%</td>
</tr>
<tr>
<td>46,Xdel(Xp) or 45,X/46,Xdel(Xp)</td>
<td>4</td>
<td>4.6%</td>
</tr>
<tr>
<td>46,Xdel(Xq) or 45,X/46,Xdel(Xq)</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td>45,X/46,Xr(X)</td>
<td>4</td>
<td>4.6%</td>
</tr>
<tr>
<td>Other: 45,X/46,X &amp; another type of abnormal X chromosome</td>
<td>3</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

\(WBC,\) white blood cells.

\(^*\)Karyotype 46,XX was found in only 2% to 14% of the peripheral WBC.

Ovarian Hormone Replacement Therapy

Fifteen percent (13/86) had experienced spontaneous menarche at an average age of 12.2 ± 1.7 years, and by their late teens they had developed amenorrhea and had started estrogen replacement. All other subjects (73/86) had not had spontaneous puberty and had started taking estrogen at an average age of 15.7 ± 4.1 years. Thirty percent (26/86) had been treated with growth hormone.

Eighty percent of the participants had been prescribed HRT at the time of study (Table II; available at www.jpeds.com). The majority (32%) were taking either oral conjugated estrogens (CE) or oral contraceptives (OC; 31%). Relatively few (12%) were using transdermal or oral estradiol. In addition to estrogen, most were taking a progestin, the preferred progestin being either medroxyprogesterone or one of the three most common components of the oral contraceptives (norethindrone, levonor/desogestrel, or norgestimate). One fifth of the participants were not taking HRT, the reasons being concern about side effects, experience of discomfort, or financial constraints.

Uterine Size and Maturity

Approximately one quarter of the women with TS (21/86; 24.4%) had fully developed in size and shape uterus (Table III). Most (38/86; 44.2%) had somewhat smaller in size uterus (transitional) and almost one third had an immature “cylindrical shaped” uterus (27/86; 31.4%). Women who had developed mature uteri were as likely to have ”pure” 45,X karyotype as were women with immature uteri (Table III).
Factors Influencing Uterine Maturity

In separate regression analyses uterine size (volume) was influenced significantly by age, years of estrogen use, current use of HRT, history of spontaneous menarche, and type of estrogen medication (Table IV). Notably, women who were taking OC had uterine size similar to that of those who were not currently taking HRT, although those who were taking estradiol-based hormone replacement had significantly larger uterus (Table IV). There was no correlation between the age at first exposure to estrogens and the size of the uterus. In addition, none of the measures of body size (height, weight, and BSA) were correlated to the size of the uterus.

We explored the combined influence of several independent variables (age at first exposure to estrogens, years of estrogen use, type of HRT, and history of spontaneous menarche) on the degree of uterine maturity in an ordinal multiple logistic regression analysis. The uterine maturity was expressed as an ordinal dependent variable in the following way: immature uterus = 0, transitional uterus = 1, mature uterus = 2. We did not include age in the model because it was strongly correlated to years of estrogen use (r = 0.59, P < .00001). The overall χ² of the model was 17.5 with a P value of .0077. The degree of uterine maturity was positively associated with years of estrogen use (χ² = 4.0, P = .045), estradiol-based HRT (χ² = 4.1, P = .044), and with history of spontaneous menarche (χ² = 5.3, P = .021), and it was negatively associated with the lack of current HRT (χ² = 4.3, P = .038). The age at first exposure to estrogen, again, had no influence over the uterine maturity (χ² = 0.15, P = .701).

**DISCUSSION**

This study shows that women with TS treated with oral or transdermal estradiol or oral CE, in combination with oral medroxyprogesterone or micronized progesterone for several years, may attain a normal, mature uterine size and configuration. The age of pubertal induction was not critical. Stature and history of GH Rx did not impact the degree of uterine development. Karyotype was not a contributing factor, and 45,X women did have normal uterine development given adequate treatment (Table IV). A recent study from Germany found that only 45,X/46,XX mosaic females developed normal uterine proportions, although none with 45,X did.7 In fact, karyotype was the only significant predictor of normal uterine development in this study, with age at estrogen initiation and age at start of cyclic progestin or duration of estrogen showing no correlation to the uterine development.7 The different findings in our study (12/21 or 57% of the subjects with mature uterus had 45,X karyotype) may be explained by the longer average duration of estrogen treatment in our subjects. The mere currency of HRT is not enough in itself to guarantee a normal uterine size if it has not been administered long enough—as illustrated in Table III, the majority of the women with TS who had immature uterus (70%) had been taking HRT at the time of the study.

The optimal age for pubertal initiation and the safest and most effective protocol for pubertal development and maintenance HRT in girls and young women with premature ovarian failure are important issues that lack strong, evidence-based support at present. According to some studies, age at pubertal induction was an important factor in achieving a normal uterine size.5,6,8 In previous years, expert opinion recommended pubertal induction with low-dose estrogen

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**Table III. Immature vs mature uterus in Turner syndrome**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Immature uterus (n = 27)</th>
<th>Mature uterus (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (cm) ± SD (range)</td>
<td>5.0 ± 0.9 (2.8-6.4)</td>
<td>7.2 ± 0.7 (6.5-8.1)</td>
</tr>
<tr>
<td>AP (cm) ± SD (range)</td>
<td>1.7 ± 0.7 (0.7-4.8)</td>
<td>2.5 ± 0.5 (1.5-3.8)</td>
</tr>
<tr>
<td>Transverse (cm) ± SD (range)</td>
<td>2.8 ± 0.7 (1.8-4.0)</td>
<td>3.7 ± 0.9 (1.5-5.0)</td>
</tr>
<tr>
<td>Volume (mL) ± SD (range)</td>
<td>12.8 ± 7.2 (3.1-35.2)</td>
<td>35.2 ± 12.3 (17.2-69.6)</td>
</tr>
<tr>
<td>Uterine ratio ± SD (range)</td>
<td>1.08 ± 0.16 (0.93-1.78)</td>
<td>1.44 ± 0.21 (1.12-1.85)</td>
</tr>
<tr>
<td>Age (years) ± SD (range)</td>
<td>28.9 ± 6.6 (28.0-10)</td>
<td>34.8 ± 6.8 (25.0-17)</td>
</tr>
<tr>
<td>45,X karyotype in 100% of the cells</td>
<td>14/27 (52%)</td>
<td>12/21 (57%)</td>
</tr>
<tr>
<td>Spontaneous puberty (n, %)</td>
<td>1/27 (3.7%)</td>
<td>5/21 (24%)</td>
</tr>
<tr>
<td>Currently taking HRT (n, %)</td>
<td>19/27 (70%)</td>
<td>19/21 (90%)</td>
</tr>
</tbody>
</table>

**Table IV. Variables influencing uterine volume**

<table>
<thead>
<tr>
<th>Continuous independent variables</th>
<th>R²</th>
<th>F value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.24</td>
<td>5.08</td>
<td>.027</td>
</tr>
<tr>
<td>Height</td>
<td>0.008</td>
<td>0.68</td>
<td>.411</td>
</tr>
<tr>
<td>Weight</td>
<td>0.017</td>
<td>1.46</td>
<td>.230</td>
</tr>
<tr>
<td>BSA</td>
<td>0.016</td>
<td>1.40</td>
<td>.240</td>
</tr>
<tr>
<td>Age at estrogen exposure</td>
<td>0.022</td>
<td>1.85</td>
<td>.177</td>
</tr>
<tr>
<td>Years of estrogen exposure</td>
<td>0.161</td>
<td>15.94</td>
<td>.0001</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Nominal independent variables</th>
<th>Level</th>
<th>Volume (mL) Mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of GH use</td>
<td>Yes (n = 26) 18.3 ± 12.0</td>
<td>.066</td>
<td></td>
</tr>
<tr>
<td>No (n = 60) 22.8 ± 12.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current HRT</td>
<td>Yes (n = 69) 23.0 ± 12.6</td>
<td>.0019</td>
<td></td>
</tr>
<tr>
<td>No (n = 17) 15.0 ± 8.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous menarche</td>
<td>Yes (n = 13) 30.0 ± 16.9</td>
<td>.014</td>
<td></td>
</tr>
<tr>
<td>No (n = 73) 19.9 ± 10.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of estrogen</td>
<td>E2 (n = 10) 28.0 ± 10.0</td>
<td>E2 vs None, P = .0015</td>
<td></td>
</tr>
<tr>
<td>CE (n = 28) 25.0 ± 14.6</td>
<td></td>
<td>E2 vs OC, P = .045</td>
<td></td>
</tr>
<tr>
<td>OC (n = 27) 19.7 ± 11.0</td>
<td></td>
<td>CE vs None, P = .0032</td>
<td></td>
</tr>
<tr>
<td>None (n = 20) 15.4 ± 8.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BSA, body surface area; E2, estradiol; CE, conjugated estrogens; OC, oral contraceptives.
treatment beginning between 12 and 15 years of age, with gradual increases in dose until feminization is adequate, and the addition of a cyclic progestin on a regular basis after 12-24 months. The average age of initiation in our group of community-treated patients was rather late, at almost 16 years of age. This may be because of a trend in recent years to delay the start of estrogen treatment to promote additional statural growth under GH Rx. Our study suggests that age at estrogen initiation is not critical to adequate uterine development.

Previous studies have found that the dose of estrogen is an important contributor to uterine size and maturity. Our study indicates that, in addition, the type of HRT may play an important role. The real test of adequate uterine development is successful pregnancy, and although initial reports on assisted reproduction outcomes in TS did suggest a potential uterine problem, a recent review of women with TS participating in oocyte donation programs in the US found that of 146 women treated, 101 (69%) became pregnant; 94 of these pregnancies resulted in the birth of a live baby, for a miscarriage rate of only 6.4%. This important observation indicates that given adequate hormonal treatment, women with TS may develop a uterus able to sustain a term pregnancy. Although the uterus may sustain a pregnancy, the cardiovascular system of the mother with TS may not, so the parent's risk factors for pregnancy complications.

Our study has certain limitations. As with every cross-sectional study, it may have unsuspected bias. Unexplained remained the fact that when compared with historic reference data, women with TS in our study had smaller uterine volumes even when they fulfilled the criteria for uterine maturity. In addition, the small number of women taking transdermal estrogen therapy (n = 5, Table II) did not allow valid conclusions regarding the effect of different modes of estrogen administration, that is, oral versus transdermal. Future studies are needed to compare uterine size and maturity of girls with TS who have had the currently recommended “optimal” pubertal induction and HRT with a group of age-matched girls with normal karyotypes and normal pubertal development.

REFERENCES
<table>
<thead>
<tr>
<th>Medication/dose</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>29</td>
<td>33.7%</td>
</tr>
<tr>
<td>≤20 mcg</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>25-30 mcg</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>≥35 mcg</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Conjugated estrogens</td>
<td>28</td>
<td>32.6%</td>
</tr>
<tr>
<td>≤0.3 mg</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>0.625-0.9 mg</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>≥1.25 mg</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>10</td>
<td>11.6%</td>
</tr>
<tr>
<td>Oral estradiol</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Transdermal estradiol</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2.3%</td>
</tr>
<tr>
<td><strong>Progestins</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>26</td>
<td>30.2%</td>
</tr>
<tr>
<td>Continuous</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Intermittent</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>5</td>
<td>5.8%</td>
</tr>
<tr>
<td>Continuous</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Intermittent</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Norethindrone</td>
<td>12</td>
<td>13.9%</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>9</td>
<td>10.5%</td>
</tr>
<tr>
<td>Nor-/desogestrel</td>
<td>10</td>
<td>11.6%</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2.3%</td>
</tr>
<tr>
<td>Unopposed estrogens</td>
<td>5</td>
<td>5.8%</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>27</td>
<td>31.4%</td>
</tr>
<tr>
<td>Total number taking some form of HRT</td>
<td>69</td>
<td>80.2%</td>
</tr>
<tr>
<td>No current HRT</td>
<td>17</td>
<td>19.8%</td>
</tr>
</tbody>
</table>
Parental Opinions about Clinical Research

Marilyn C. Morris, MD, Deborah Besner, BA, Hector Vazquez, MD, Robert M. Nelson, MD, PhD, and Ruth L. Fischbach, PhD

Objective To characterize parental perception of clinical research, particularly in emergency settings. To identify specific aspects of clinical research that concern parents and to discuss how these concerns can be addressed.

Study design Quantitative and qualitative survey in tertiary care children’s hospital and affiliated clinics.

Results Family caregivers (n = 136) participated in this study; 81% of study participants agreed or strongly agreed that physicians should do research involving children, with 5% disagreeing. However, 18% felt that researchers care more about the research than about the patient, and 13% believed that when a child is in a research study, physicians must follow the research protocol even if it is not in the best interest of the child. Participants were significantly less likely to endorse the conduct of research in an emergency setting than in a nonspecified setting (P < .001). Parents’ foremost concern about emergency research was that it could delay therapy or distract physicians’ attention from the child’s needs.

Conclusion Parents largely support pediatric clinical research, but they have specific concerns that should be addressed in research planning and in communicating with parents about clinical research. (J Pediatr 2007;151:532-7)

The traditional informed consent process allows one-on-one conversations, during which investigators can respond to specific parental questions or concerns. Notwithstanding this process, data show that many individuals and parents who consent to research participation have serious misconceptions about the research process.1-8 An ability to communicate effectively with parents about clinical research depends upon an understanding of their fears and concerns, yet little is known about how the parents of potential research participants perceive risk in medical research.

In emergency settings, opportunities for communication are limited, making it all the more important to understand what concerns regarding clinical research are common among parents. In the most extreme cases, obtaining meaningful prospective informed consent may not be possible. The need for pediatric emergency research exists in many different settings, including but not limited to the pre-hospital setting, the emergency department, the delivery room, and neonatal or pediatric intensive care units. Federal regulations allow for some emergency research to take place with an exception from informed consent, but only after a process of community consultation and public disclosure of the proposed study.9 Institutional review boards are instructed to take into account the findings during the community consultation process when determining whether to approve emergency research with an exception from informed consent. A better understanding of parental perception of emergency research will allow investigators to address those concerns prospectively in the process of study design, and in the process of community consultation and public disclosure.

We conducted a survey with quantitative and qualitative components, designed to characterize parental perception of the risk of participating in resuscitation research. We first examined caregivers’ general impression of clinical research, then their impression of specific types of research, with a focus on emergency research. We hypothesized that parents would be less supportive of research in the emergency setting than of research in the general medical setting. Further, we hypothesized that parents who perceived their children to be sicker would be more supportive of medical research in general and of medical research in the emergency setting than parents who perceived their children to be healthier.
This investigation was approved by the institutional review board. Survey participants were recruited from among parents of children receiving medical care in the pediatric emergency room, the pediatric and neonatal intensive care units, and pediatric outpatient clinics of a major, urban, tertiary care children’s hospital. Participants were also recruited at a private primary care pediatrics practice several miles from the hospital. In all of these settings, a convenience sample of all parents present when the investigator was available to administer the survey was asked to participate. Surveys occurred predominantly during weekday working hours, all between May 8 and August 29, 2006. We included in the study parents of persons of any age receiving medical care in a pediatric setting. We did not exclude parents of adolescents over 18 years of age because we believed that their input as consumers of past and current pediatric care would be valuable.

The institutional review board determined that study participation posed no more than minimal risk and waived the requirement for written informed consent. Verbal consent to participate was obtained. Parents who agreed to participate were given an age-appropriate book for their child as thanks for participation.

Participants completed a brief self-administered written survey, in which they reported demographic information and a brief assessment of their child’s baseline health. Next, a verbal survey was administered, first assessing parental opinions about clinical research and then measuring parental perception of risk in specific different types of medical research. Responses were recorded on a 5-point Likert scale (1 = “strongly agree,” 5 = “strongly disagree”). Parents were given a card showing the Likert scale to refer to throughout the survey process. The survey also contained open-ended questions, the responses to which were recorded verbatim. To assess parental perception of risk inherent in different types of research, brief descriptions of hypothetical studies in lay terms were read to the parents. Parents were also given a 5- × 9-inch index card on which the same study description was written. Parents were then asked to rate the risk inherent in each study on a 5-point Likert scale (1 = “not at all risky,” 5 = “extremely risky”). After each numeric response, parents were asked why they chose that response; these responses were written down verbatim. The complete survey instrument is available in the Appendix (available at www.jpeds.com).

Two interviewers (DB and HV) administered the surveys. The text of the survey was fully scripted, as were all prompts used to elicit more detailed information from parents. After several test-surveys by each interviewer, the text of the interview was reviewed word by word to ensure comparability of survey administration. Face validity of the survey was evaluated during these test-surveys as well; parents were asked to elaborate on their reasons for answering questions in a given manner, and their responses were examined to ensure that the questions were consistently interpreted. Following these test-surveys, minor changes to the wording of several questions were made for clarification, and several questions were dropped as they did not yield consistently interpretable responses. Face validity was further assured by review of the survey instrument by senior investigators with extensive experience in qualitative research. Because only one interviewer (HV) was fully bilingual, interviews with Spanish-speaking parents were all conducted by that interviewer. Parents who were not fluent in English or Spanish were excluded from the study, as were Spanish-speaking parents when the bilingual interviewer was not available. Only one parent of any given child participated in the survey.

Categorical data were analyzed using χ² or Fisher’s exact tests where appropriate. Continuous data were compared using student’s t test or Wilcoxon’s rank sum test where appropriate. Likert scale responses are reported as median and interquartile range (IQR). Bonferroni correction was used for multiple comparisons where appropriate. Qualitative data were stored, organized, and retrieved using the NVivo qualitative analysis software package (QSR International Pty Ltd, Doncaster, VIC, Australia). A coding scheme to categorize comments according to relevant concepts and themes was developed based upon the content analysis of the comments and the prospectively designed research questions. The NVivo software was used to compile and review all statements relevant to each specific code. Answers to the question “What does the term ‘clinical research’ mean to you?” were categorized as positive, negative, or neutral. This categorization was performed independently by two investigators (MM and DB). The two raters agreed on 106 of 119 (89%) responses initially. All nonconcordant categorizations were resolved to the satisfaction of both investigators. Qualitative data were separated from demographic and other patient-specific data before analysis.

RESULTS

Caregivers (n = 136) participating in this study included 119 mothers (88%), 14 fathers (10%), and three other family caregivers (2%) (Tables I and II). Twenty-five caregivers were asked to participate but declined (84% participation). The reasons for nonparticipation were: time constraints or needing to care for child/sibling (n = 12), lack of interest (n = 10), and concern about child (n = 3). Fourteen interviews were interrupted before completion, either because the child was called in for an appointment (n = 9) or because of a need to tend to a child (n = 5). Sixty surveys (44%) were conducted in an outpatient setting, 55 (40%) in an intensive care unit, and 21 (15%) in the pediatric emergency department. Characteristics of study participants and their children are presented in Tables I and II.

Initial Perception of Medical Research

Of 119 parents who answered the question, “What does the term ‘medical research’ mean to you?” 58 (49%) made a statement with a positive connotation (eg, “performing stud-
ies to bring about better medical care”), 7 (6%) made a statement with negative connotations (“a lot of money,” or “guinea pigs”), and 54 (45%) made a neutral statement (“studying illnesses,” or “I don’t know”). To the question “Do you think it is good for a patient to be in medical research?” 83 of 136 (61%) parents responded yes, 7 of 136 (5%) no, and 46 of 136 (34%) didn’t respond or stated that it depends on the situation. Reasons given why it is not good to be in medical research included “Maybe someone else’s kid, but not mine,” and “It’s safer to go with what they know.” Race, sex, age, past research participation on the part of the child or parent, and parental education level were not associated with negative impressions of research, or with the response to whether it is good to be in medical research.

### Table I. Characteristics of survey participants. Data are reported as n (%), or median (range)

<table>
<thead>
<tr>
<th>Relationship to child</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>119 (88%)</td>
<td></td>
</tr>
<tr>
<td>Father</td>
<td>14 (10%)</td>
<td></td>
</tr>
<tr>
<td>Other (eg, grandparent)</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Age in years of survey participant</td>
<td>35 (20-64)</td>
<td></td>
</tr>
<tr>
<td>Race of participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian/European Non-Hispanic</td>
<td>59 (44%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>42 (31%)</td>
<td></td>
</tr>
<tr>
<td>African-American/Black</td>
<td>15 (11%)</td>
<td></td>
</tr>
<tr>
<td>Asian/Indian/Pacific Islander</td>
<td>9 (7%)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Was participant born in the United States?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>92 (68%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>44 (32%)</td>
<td></td>
</tr>
<tr>
<td>Religion of participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catholic</td>
<td>60 (44%)</td>
<td></td>
</tr>
<tr>
<td>Protestant</td>
<td>14 (10%)</td>
<td></td>
</tr>
<tr>
<td>Jewish</td>
<td>20 (15%)</td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other religion</td>
<td>13 (10%)</td>
<td></td>
</tr>
<tr>
<td>Does not identify with a specific religion</td>
<td>18 (13%)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Education level of participant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not complete high school</td>
<td>10 (7%)</td>
<td></td>
</tr>
<tr>
<td>High school degree/GED</td>
<td>31 (23%)</td>
<td></td>
</tr>
<tr>
<td>Associate’s degree or some college</td>
<td>31 (23%)</td>
<td></td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>27 (20%)</td>
<td></td>
</tr>
<tr>
<td>Graduate or professional degree</td>
<td>36 (26%)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Has survey participant ever participated in clinical research?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (16%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>113 (83%)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>2 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table II. Characteristics of the patient child of the survey participants. Characteristics of other children in the family were not collected. Data are reported as n (%), or median (range)

<table>
<thead>
<tr>
<th>Location within the healthcare system at the time of the survey</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediatric Intensive Care Unit</td>
<td>45 (33%)</td>
</tr>
<tr>
<td>Neonatal Intensive Care Unit</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Emergency Room</td>
<td>21 (15%)</td>
</tr>
<tr>
<td>Subspecialty outpatient clinic</td>
<td>30 (22%)</td>
</tr>
<tr>
<td>Primary care pediatrician’s office</td>
<td>30 (22%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age of child</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 (1 day-24 years)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parental assessment of the child’s general health</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>57 (42%)</td>
</tr>
<tr>
<td>Good</td>
<td>51 (38%)</td>
</tr>
<tr>
<td>Fair</td>
<td>21 (15%)</td>
</tr>
<tr>
<td>Poor</td>
<td>7 (5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of lifetime hospitalizations (excluding routine stay at birth)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50 (37%)</td>
</tr>
<tr>
<td>1</td>
<td>31 (23%)</td>
</tr>
<tr>
<td>2</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>3 or more</td>
<td>40 (29%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Has the child ever received CPR?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>17 (12%)</td>
</tr>
<tr>
<td>No</td>
<td>119 (88%)</td>
</tr>
</tbody>
</table>

### Perceived Value of Research and of Emergency Research

Participants were asked how strongly they agreed or disagreed with the following two statements: “Doctors should do medical research involving children,” and “Doctors should do medical research involving children in emergency situations.” The median response for research on the unspecified setting was 2 (“agree,” IQR 1-2; Likert scale 1-5 with 1 = “strongly agree” and 5 = “strongly disagree”; see Figure, A), and the median response for emergency research was 3 (“neither agree nor disagree”) with an IQR of 2 to 4 (Figure, B; \( P < .0001 \)). The ambivalence that parents expressed about emergency research is summarized by one mother’s comment: “You have to do research to learn how to treat kids in an emergency, but the kids should not be in research when the emergency is happening.”

The extent to which participants endorsed the conduct of emergency research differed according to educational level of the participants. Among those with at least a bachelor’s degree, the median value reported was 3 (“neither agree nor disagree” IQR 2-4), and among those with less than a bachelor’s degree, the median reported value was 2 (“agree” IQR 2-4; \( P = .006 \); significance value of .008 to correct for multiple comparisons). Analysis of qualitative data did not further elucidate this finding. The extent to which participants endorsed the conduct of emergency research was not associated with the perceived health status of the child, whether the child had previously received cardiopulmonary

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resuscitation (CPR), or with the medical setting in which the survey took place. Further, it was not associated with the age, race, or sex of the participant.

We have previously found that parents of critically ill children find it very unsettling to hear that physicians do not already know the best way to resuscitate a child.12,13 This finding was reconfirmed in this study, exemplified by the comment: “I don’t understand why you would want to do research during an emergency. Haven’t you figured that all out with monkeys already?” It is not clear from the data obtained in this study the extent to which the lower level of support for emergency research than general research reflects a perception that such research is not valuable and the extent to which it reflects a perception that such research is not appropriate.

Perceived Morality of Clinical Researchers

Participants were asked how strongly they agreed or disagreed with the following statement: “Medical research is almost always done in a way that is morally right.” (Likert scale, 1 = “strongly agree,” 5 = “strongly disagree”). The median response was 2 (“agree”), IQR 2-3 (Figure, C). Twenty-five caregivers (19%) disagreed or strongly disagreed with the statement. All participants were then asked why they gave their response. Reasons given why research may not be conducted in a way that is morally right were diverse, including references to stem cell research, disparities in how the potential benefits of research are distributed, and fear that physicians use research subjects primarily to advance their careers.

Parents were also asked to state how strongly they agreed or disagreed with the following two statements about clinical research: “When a child is in a research study, the doctors care more about the research than about the patient,” and “When a doctor takes care of a patient who is in a research study she has to do what the research says, even if she thinks it might not be best for the patient.” The median response to the first question was 3 (“neither agree nor disagree”; Figure, D), and the median response to the second was 4 (“disagree”; Figure, E). Twenty-four of 131 respondents (18%) agreed or strongly agreed that physicians care more about the research than about the patient, and 17 of 126 (13%) agreed or strongly agreed that physicians must do what the research says, even if it is not in the best interest of the child.

Perceived Risk of Medical Research

In qualitative analysis of parents’ explanations of research risk, we identified 87 statements indicating either a specific way in which research has the potential to harm a child or a specific objection to research. (Table III; available at www.jpeds.com.)

The most common objection relevant to nonemergency research was that novel medications may lack efficacy or may have unanticipated side effects. Parents also feared that medications developed for adults may harm children. The most common objection specific to emergency research was that conducting clinical research in the emergency setting may delay medical intervention or divert physician attention from the child.

Parents rated the risk inherent in two hypothetical studies that would take place during CPR. One hypothetical trial compared two commonly used medications to help restart the heart, and one compared a standard medication to an experimental medication. Parental perception of the risk level for the trial comparing two standard-of-care medications versus the perceived risk level for the trial comparing a standard medication with an experimental medication did not differ significantly. However, 40 statements were made specifically indicating a perceived increase in risk when an experimental medication is introduced. For example: “The unknown is always risky. You don’t have the history of a treatment,” and “It is risky when there are no known long-term outcomes because procedures are new.” Along similar lines, 18 statements were made suggesting a decrease in risk when only standard therapies are included in the trial, for example: “It is the same medicine that is being prescribed. The risk is the same, especially in emergency medicine when you don’t even know what doctor you are getting,” or “If doctors use both of them, then both must be ok.” Only one statement was made indicating the possibility for additional benefit from receiving experimental therapy.

DISCUSSION

We found that parents in diverse medical settings value clinical research, but that a substantial minority of parents has serious concerns about how clinical research is conducted. Further, we found that parents endorse the conduct of clinical...
research involving children significantly more strongly in the nonspecified setting than in the emergency setting. An examination of parents’ specific concerns suggests ways in which communication with parents about clinical research can be optimized, both in the nonemergency and in the emergency setting.

Substantive concerns should be addressed prospectively when communicating with parents about clinical research. In the process of seeking consent for study participation, investigators should emphasize that treating physicians retain the final authority in caring for the patient and that the patient’s well-being will always be prioritized above the research. When possible, parents should be approached first by a trusted physician and asked whether they are interested in discussing clinical research with an investigator. When seeking consent for research participation, investigators should be cognizant that parents want to protect their children and may not assume that adequate measures exist to protect research participants from harm.

Clinical Research in Emergency Situations

Parents perceive clinical research in emergency settings as riskier than research in nonemergency settings and are less likely to endorse its conduct. The foremost reported concern specific to emergency research was that conducting research in an emergency setting may delay medical care or divert physician attention from the child to the requirements of the research project. Clearly, ethically conducted emergency research must not delay medical care. This proviso must be ensured in the study design and clearly communicated to actual or potential research subjects. Concerns that emergencies are “not the time for research” are harder to address. Emergency researchers need to be aware that this is a prevalent concern among parents. Ensuring that research is designed in such a way as to not interfere with patient care is paramount. Communicating this priority to families may ease some of this concern.

We found that parents with a bachelor’s degree or higher level of education were less likely to endorse research in the emergency setting than were parents with less than a bachelor’s degree. Published literature varies in terms of the effect of education on research understanding and participation. Higher socioeconomic status has been correlated with better parental understanding of pediatric clinical research, yet the impact of socioeconomic status on research participation varies. In studies involving adults with AIDS and cancer, a higher level of education was positively associated with research participation, yet in a randomized pediatric oncology study, parents with higher income and higher levels of education were more likely to refuse participation. We posit that the interplay between education and risk assessment is complex and dependent on the type of research proposed. Persons with an incurable disease may perceive experimental medication as their best chance for a cure. Those with more economic means and a more sophisticated understanding of the medical system may be more successful in seeking out these trials. The impact of educational level on participation in a randomized trial may differ. We speculate that the “therapeutic misconception,” in which research participants believe that research protocols are designed to benefit them directly rather than to test or compare treatment methods, may be less prevalent among more educated parents, accounting for their lower level of acceptance of this type of research.

The specific words used to communicate with families must be chosen with care. In the description of one hypothetical study, parents were told that in adults, a novel medication had been proven to be more effective than standard therapy, but that the novel therapy had not been tested in children. We were surprised by the large number of parents who expressed strong concern that adult medications are “too strong” or “too big a dose” for children. This finding underlines the importance of involving parents when designing tools or scripts used to communicate about emergency research. When referencing studies with medications given to adults, pediatric researchers should clarify that the medications will be given in child-appropriate doses. This finding also highlights the need for pharmacokinetic and pharmacodynamic studies involving children.

When it is not possible to obtain prospective informed consent for participation in emergency research, an institutional review board may choose to grant the study an exception from informed consent for emergency research. For a study taking place with an exception from informed consent, a community consultation and public disclosure process must take place demonstrating support of the community for the research project. In designing the community consultation process, researchers should specifically address parental concerns about emergency research. Because parents may learn about an emergency research study via a newspaper advertisement or article, without an immediate opportunity to ask questions, researchers should take great care to communicate key points, for example that research participation will not delay definitive care (or if it will, by how much), that children will not become research participants if their physicians feel that it is contrary to their best interest, and that children will be removed from a study when appropriate. To protect against inadvertent messages, such communications should be designed with input from nonmedical personnel from varying backgrounds.

Study Limitations

Study participants were chosen on the basis of which family caregivers were present with their children when the study was conducted. Although this method achieved significant racial, educational, and age diversity, only 10% of study participants were fathers. The study size was insufficient to determine whether the concerns of fathers differ from those of mothers. Substantially more fathers may participate in actual decisions about clinical research participation, making a
more complete understanding of paternal perception of clinical research desirable. Interviews were conducted largely on weekdays during working hours, therefore, parents who tended not to be present during these hours are not fully represented. The population involved in this study may not be representative of that seen in other medical settings. We have little information about the socioeconomic status of our participants (aside from educational level). Half of the children of the study participants were characterized by their parents as having fair or poor general health. Although this is certainly not representative of the general public, we do not know the extent to which it is representative of potential pediatric research participants.

We limited the number of items in the survey to minimize the demands on caregivers’ time. As such, we did not ask parents to rate the risk level of a trial in a nonemergency setting that included the use of a novel medication. Doing so would have better allowed us to separate concerns about novel medications from concern about research conducted in emergency settings.

REFERENCES

APPENDIX

Parental opinions about medical research involving children
Thank you for participating in this survey.
Please feel free to leave items blank if you choose.

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>In what year were you (parent) born?</td>
<td></td>
</tr>
<tr>
<td>How old is your child?</td>
<td></td>
</tr>
<tr>
<td>Are you:</td>
<td>Male Female</td>
</tr>
<tr>
<td>What is your relationship to the child being seen here today?</td>
<td>Mother Father Grandmother Grandfather Other blood relative Step-mother Step-father Other non-blood relative</td>
</tr>
<tr>
<td>Would you describe yourself as:</td>
<td>Caucasian/European Non-Hispanic African-American/Black Hispanic/Latino Asian/Indian/Pacific Islander Mixed Other</td>
</tr>
<tr>
<td>Does your child have a chronic (long-term) illness?</td>
<td>Yes No</td>
</tr>
<tr>
<td>If yes, what diagnosis has s/he received?</td>
<td></td>
</tr>
<tr>
<td>For how long has s/he had this illness?</td>
<td></td>
</tr>
<tr>
<td>In general, would you say that your child’s health is: (please circle one)</td>
<td>Excellent Good Fair Poor</td>
</tr>
<tr>
<td>How many times has your child been hospitalized (overnight) in his/her life?</td>
<td>0 1 2 3 or more</td>
</tr>
<tr>
<td>Has your child ever needed cardiopulmonary resuscitation or “CPR”? (this is when a person’s heart stops beating and someone pushes on the chest and gives medicines to restart the heart)</td>
<td>Yes No</td>
</tr>
</tbody>
</table>

Thank you!
When you have completed this information, please give the papers to the interviewer who will then ask you questions about what you think and know about medical research. Feel free to not answer any questions if you choose.

(Given to parents as a reference)

<table>
<thead>
<tr>
<th>“How strongly do you agree with this statement”</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly agree</td>
<td>Agree</td>
<td>Neither Agree nor Disagree (Neutral)</td>
<td>Disagree</td>
<td>Strongly Disagree</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>“How risky do you think something is”</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all risky</td>
<td>A little bit risky</td>
<td>Moderately risky</td>
<td>Very risky</td>
<td>Extremely risky</td>
<td></td>
</tr>
</tbody>
</table>

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Verbally administered items (note verbatim pertinent statements made by parents)

What does the term “medical research” mean to you?
Do you think it is good for a patient to be in medical research? ____________ Why?

Let me clarify how we define medical research.

Medical research is when doctors try to learn more about diseases and how to better take care of people. It can be just reading old medical charts, or it can be comparing two medicines to see which works better. I will give you some examples as we go through.

1. To your knowledge, have you or your child ever participated in medical research?
   0 No
   1 Yes: child
   2 Yes: parent

If yes, please describe ______________________________________
   child: ________________________________________________
   parent:________________________________________________

Now I’ll make some statements, and I’d like you to tell me on a scale of 1 to 5 how strongly you agree or disagree with a statement, according to this sheet. 1 means that you strongly agree, and 5 means that you strongly disagree. (Give the response sheet)

Using the answer scale on the sheet I gave you, could you tell me how strongly you agree or disagree with the following statements: If you aren’t sure, just give me your best estimate.

2. Doctors should do medical research involving children.
   1 Strongly agree
   2 Agree
   3 Neither agree nor disagree
   4 Disagree
   5 Strongly disagree

Why do you think that?

3. Sometimes, children have emergency situations, for example, drowning or being hit by a car. How strongly do you agree or disagree with this statement: Doctors should do medical research involving children in emergency situations.
   1 Strongly agree
   2 Agree
   3 Neither agree nor disagree
   4 Disagree
   5 Strongly disagree

Why do you think that?

4. How strongly do you agree or disagree with this statement: Medical research is almost always done in a way that is morally right.
   1 Strongly agree
   2 Agree
   3 Neither agree nor disagree
   4 Disagree
   5 Strongly disagree

Why do you think that?

5. How strongly do you agree or disagree with this statement: When a child is in a research study, the doctors care more about the research than about the patient.
   1 Strongly agree
   2 Agree
   3 Neither agree nor disagree
4 Disagree
5 Strongly disagree

Why do you think that?

6. How strongly do you agree or disagree with this statement: When a doctor takes care of a patient who is in a research study she has to do what the research says, even if she thinks it might not be best for the patient.
   1 Strongly agree
   2 Agree
   3 Neither agree nor disagree
   4 Disagree
   5 Strongly disagree

Why do you think that?

7. How strongly do you agree or disagree with this statement: It is risky to let your child participate in medical research.
   1 Strongly agree
   2 Agree
   3 Neither agree nor disagree
   4 Disagree
   5 Strongly disagree

Why do you think that?

What specific things are risky about being part of research?

Vignettes/Scenarios

Sometimes, different doctors use different medicines for the same disease, and no one knows whether one is better. Researchers may want to compare these two different medicines to determine which is better so everyone can use the better medicine. In this type of research, patients may be randomly assigned to get one or the other medicine. This means that it’s like a coin toss: if you get heads, you get one treatment, and if you get tails, you get the other. After a number of children have gotten each treatment, researchers compare them to see which group does better. After that, doctors can all use the better treatment. Do you have questions about how that works? (Clarify)

8. How risky do you think it is for a child to participate in this type of research?
   1 Not at all risky
   2 A little bit risky
   3 Moderately risky
   4 Very risky
   5 Extremely risky

Why do you think this?

9. Children with urine infections get treated with antibiotics. Right now, some doctors give antibiotics for 7 days and some give antibiotics for 10 days. We do not know whether 7 or 10 days is better. How risky is it for a child with a urine infection to be part of a study where half of the kids get treated for 7 days and the other half get treated for 10 days? The decision is random, based on the flip of a coin. How risky is it for a child to be in this study, do you think?
   1 Not at all risky
   2 A little bit risky
   3 Moderately risky
   4 Very risky
   5 Extremely risky

Why do you think this?

10. Sometimes children come to the emergency room while having a seizure. There are two different medicines that doctors use to stop seizures. Some use medicine A and some use medicine B. We do not know which is better. In this study, half of the children will get medicine A and half will get medicine B, based on a coin toss. How risky is it for a child to participate in this research study?
11. Sometimes a child’s heart stops and the doctors do CPR, which is when they push on the chest and give medicines to try to restart the heart. If a child’s heart stops and the child needs CPR, there are two different medicines that may help restart the heart. Some doctors use medicine A and other doctors use medicine B. We do not know which is better. How risky is it for a child to participate in a research study where half of the children get medicine A and the other half get the other medicine B, based on the flip of a coin?

   1. Not at all risky
   2. A little bit risky
   3. Moderately risky
   4. Very risky
   5. Extremely risky

Why do you think this?

12. Again, imagine a situation involving kids whose heart stops so they need CPR. The medicine that doctors use now doesn’t always work to restart the heart. Imagine there is a new medicine that works better than the usual medicine in adults. Researchers think it will be better for kids, too, but it hasn’t been tried in kids. How risky is it for a child to participate in a research study where half of the children get the medicine that has only been used in adults and the other half get the usual medicine, based on the flip of a coin? If either medicine was not successful, the child would get the other choice 2 minutes later.

   1. Not at all risky
   2. A little bit risky
   3. Moderately risky
   4. Very risky
   5. Extremely risky

Why do you think this?

13. How risky do you think it is for a child to get a routine blood test?

   1. Not at all risky
   2. A little bit risky
   3. Moderately risky
   4. Very risky
   5. Extremely risky

Why do you think this?

Do you have any other thoughts about medical research and children that you would like to share? (Note responses verbatim)

Do you have any questions about this project? (Note questions)

Thank you very much for participating!

Interviewer: Please note any relevant perceptions you have about the survey process.
<table>
<thead>
<tr>
<th>Category of statement</th>
<th>No. of statements</th>
<th>Representative statement from this category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research may delay treatment/Focus should not be on research</td>
<td>29</td>
<td>“In emergencies, deal with the patient. There is no time to deal with research.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Research shouldn’t be done if it will cause a delay in emergency care.”</td>
</tr>
<tr>
<td>Potential for unknown effects or lack of efficacy of a novel medication</td>
<td>21</td>
<td>“You never know how they’ll react.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“In an emergency, you can’t use things that haven’t been tried.”</td>
</tr>
<tr>
<td>Medications that have been proven effective in adults may be inappropriate for children</td>
<td>13</td>
<td>“Our bodies are different. You don’t use child medicines on adults or adult medicines on children.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“There’s a very good chance that it might not work in kids, or that it may even kill them to give the adult the medications.”</td>
</tr>
<tr>
<td>Using patients to advance careers or to otherwise benefit the researchers</td>
<td>10</td>
<td>“You need research, but some doctors just want to make discoveries. I’ve seen it in the movies where doctors jeopardize patients’ lives because they are passionate about their research.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“There is a big influence that drug companies have over research. There are a lot of incentives for doctors, which blurs the lines and weakens the state of research.”</td>
</tr>
<tr>
<td>Following protocol may not be in the interest of the patient</td>
<td>5</td>
<td>“Once the family has consented, you follow the protocol even if you don’t believe in the study.”</td>
</tr>
<tr>
<td>Potential to receive a placebo or a less-effective treatment</td>
<td>5</td>
<td>“As long as someone’s not getting a placebo then it’s ok.”</td>
</tr>
<tr>
<td>Patient as guinea pig</td>
<td>4</td>
<td>“They want to see how a treatment works, and we are just rats or specimens.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“The risky thing is they could mess with your heart, look inside your brain, and then when they’re done, they don’t need you anymore.”</td>
</tr>
</tbody>
</table>
Metabolic Cardiomyopathy and Mitochondrial Disorders in the Pediatric Intensive Care Unit

JASON M. KANE, MD, FAAP, JANET ROSSI, MD, FAAP, SABRINA TSAO, MBBS, MRCP (UK), AND BARBARA K. BURTON, MD, FAAP

Our patient, a 10 year-old boy with a past medical history significant for Pearson’s anemia, Addison’s disease, retinitis pigmentosa, ataxia, and sensoryneural hearing loss, came to the pediatric intensive care unit with cardiogenic shock. He was born at 34 weeks gestational age with an uneventful delivery and had mild developmental delay. There was no family history for cardiac or genetic abnormalities. Pearson’s anemia was diagnosed when he was 4 months old, and he required chronic transfusion therapy and monthly erythropoietin injections until age 3 years, when his disorder went into spontaneous remission. When he was 4 years old, Addison’s disease was diagnosed after a hospitalization for diarrhea and hyponatremia. With the exception of an appendectomy for acute appendicitis, he had no other surgical history. His home medications included sodium bicarbonate, magnesium, calcium, potassium, enalapril, and spironolactone for his renal disorder; he was maintained on physiologic doses of prednisone for his Addison’s disease.

On the day of admission, he was found unresponsive in his bed with labored breathing and generalized pallor. Paramedics found the child unresponsive to painful stimuli. Rhythm strip revealed bradycardia and complete heart block. He was started on an isoproterenol infusion because of bradycardia and was then transported to the pediatric intensive care unit. On arrival, he was found to be tachypneic with a Kussmaul breathing pattern and bradycardic. His skin was pale and lips were dry. Results of an abdominal examination were significant for hepatomegaly with liver edge palpable 4 cm below the right costal margin. Capillary refill time was prolonged to 4 seconds with weak distal pulses. His mental status was significant for intermittent moaning, asking for his mother, and requesting water.

Mildly enlarged cardiac shadow with bilateral alveolar infiltrates was demonstrated with chest radiography. An electrocardiogram was performed (Figure), and moderate left ventricular dilation with reduced systolic function and mild tricuspid and mitral valve regurgitation were demonstrated. Laboratory evaluation results were significant for arterial blood gas pH of 7.22, PaCO₂ 5.2 torr, with a base deficit of −25. The serum chemistry results showed a serum bicarbonate level of 5.3 mEq/L, a glucose level of 245 mg/dL, a lactate level of 12 meq/L, and an ammonia level of 53 μmol/L. Urine testing results were positive for ketones and glucose. The results of the remainder of laboratory studies, including complete blood count, liver enzymes, bilirubin, and coagulation studies, were normal.

In the next several hours, he progressed to respiratory failure from pulmonary edema, requiring intubation and mechanical ventilation. He was started on stress-dose steroids because of home steroid use and multiple inotropic agents to augment cardiac output. Transcutaneous pacing was attempted, and intermittent capture was achieved at ventricular rates of 80, 90, and 100 beats per minute; however, there was no significant improvement in his hemodynamic condition. With further titration of his cardiac medications, including isoproterenol, milrinone, epinephrine, and dobutamine, his hemodynamics improved in the subsequent 24 hours of hospitalization.

Temporary transvenous ventricular pacing was initiated, which facilitated weaning off all inotropes, and he was successfully extubated. Coenzyme Q10 and carnitine supplementations were added, and a muscle biopsy was sent for mitochondrial analysis. Despite being metabolically stable, he remained in complete heart block, requiring placement of a permanent transvenous dual-chamber pacemaker. His home medications were resumed, and he was discharged to home at his neurologic baseline.

DIFFERENTIAL DIAGNOSIS

Our patient had cardiomyopathy, acute cardiogenic shock, and a history of multiple seemingly unrelated medical problems. Applying the tenet of Occam’s razor, “Pluralitas non est ponenda sine necessitate” (“the simpler the explanation, the better”), we sought a single metabolic etiology that would explain not only his acute cardiac decompensation, but also tie-together his other underlying medical conditions.
The etiologies of metabolic cardiomyopathy include amino acid, lipid, and mitochondrial disorders and storage diseases. Disorders of lipid metabolism include primary carnitine deficiency and abnormalities of carnitine palmitoyltransferase and defects in long chain fatty acid oxidation. In addition, cardiomyopathy is frequently seen as part of the storage disorders, including mucopolysaccharidosis, mucolipidosis, Fabry disease, or glycogen storage disease. Many of these disorders are accompanied by a characteristic physical appearance and often present early in infancy. Mitochondrial diseases are a heterogeneous group of disorders affecting function of the respiratory chain and frequently involve multiorgan system dysfunction. These may cause either hypertrophic or dilated cardiomyopathy and cardiac conduction defects. A number of specific clinical syndromes have been identified in association with mitochondrial defects, including myoclonic epilepsy with ragged red fibers, chronic progressive external ophthalmoplegia, Kearns-Sayre syndrome, myoclonic epilepsy with lactic acidosis and stroke like episodes, and Leigh’s disease.1-5

**Diagnosis and Discussion**

The constellation of Pearson’s syndrome, sensorineural deafness, endocrine dysfunction, recent onset of ataxia, retinitis pigmentosa, and complete heart block, suggested an underlying mitochondrial disorder in our patient. The findings were similar to those observed in patients with Kearns-Sayre Syndrome, who typically exhibit age of onset <20 years, progressive external ophthalmoplegia, and pigmentary retinopathy. In addition, patients with that disorder often have cardiac conduction defects, proteinorachia, and cerebellar signs.6 In patients with Kearns-Sayre Syndrome, cardiac conduction abnormalities may progress to complete atrioventricular block. Our patient was found by Southern blot analysis to have a large mtDNA deletion in muscle tissue, similar to that observed in patients with typical Kearns-Sayre syndrome, supporting the clinical diagnosis of a mitochondrial disorder.

Mitochondrial diseases represent a new challenge to the pediatric intensivist. An understanding of the genetic basis for these disorders was not elucidated until 1989. Since then, >200 individual mutations of the mitochondrial genome have been described.1 Many other patients with mitochondrial respiratory chain defects have mutations in 1 of the nuclear-encoded genes that affect the oxidative phosphorylation pathway. Although the ability to establish a diagnosis of certain mitochondrial disorders has improved, there have been limited advances in the treatment of these disorders.

Diagnosing a previously unrecognized mitochondrial disorder in the pediatric intensive care unit requires a high index of suspicion. Some patients may have findings indicative of a known clinical syndrome. Other patients have multiorgan system failure as the presenting sign of an underlying mitochondrial disorder. When concern for a mitochondrial cytopathy is raised, consultation with experts in genetic and metabolic disorders is warranted to ensure a comprehensive diagnostic evaluation, appropriate outpatient follow-up, and genetic counseling to other family members.

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**Figure.** Electrocardiogram showing third-degree heart block with ventricular rate 38 beats per minute, atrial rate 140 beats per minute; QRS morphology with left axis deviation and right bundle branch block.
Organ-System Dysfunction and Pediatric Intensive Care Unit Management

Respiratory failure is common in patients with mitochondrial cytopathies. Studies in adults indicate that the 2 most common presentations of respiratory dysfunction in patients with mitochondrial disorders are respiratory muscle fatigue leading to increased dyspnea or hypoventilation. The use of either non-invasive or mechanical ventilation to treat respiratory failure is a mainstay of care. Although there are no data that describe long-term pediatric outcomes, adults with underlying mitochondrial disorders often have interval improvement but recurrent episodes of respiratory failure and may develop partial or full mechanical ventilator dependency. Tracheostomy may play a role in the chronic treatment of pediatric patients with mitochondrial cytopathies; however, this approach remains controversial.

Cardiac abnormalities often accompany many mitochondrial cytopathies and may be the presenting manifestation. The most commonly encountered cardiac problems include hypertrophic or dilated cardiomyopathy and cardiac conduction defects. The incidence of cardiomyopathy may be as high as 40% in patients with respiratory chain disorders. The most severe cases can have heart failure from either pure cardiac muscle dysfunction or from complete heart block. Resultant lactic acidosis and organ dysfunction from poor tissue perfusion often occurs and is best managed by aggressive treatment of underlying arrhythmias and reversal of low cardiac output. Inpatient treatment will depend on the specific cardiac abnormality. In the acute setting, inotropic support, afterload reduction, and cardiac pacing may all be required.

Transition to oral medications to treat chronic heart failure including beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics may all be indicated to ameliorate chronic cardiac insufficiency. The major life-threatening complication of metabolic induced cardiomyopathy is the occurrence of arrhythmias. When conduction abnormalities and arrhythmias continue, prophylactic implantation of permanent pacemaker may be warranted to prevent sudden cardiac death.

Neurologic complications including strokes and seizures may occur in patients with certain mitochondrial disorders. Strokes often involve the occipital or parietal lobes and do not follow a typical vascular pattern. Thromboembolism from dilated cardiomyopathy or arrhythmia may lead to critical central nervous system events. Seizures may be difficult to control, and phenytoin should be the drug of choice when not otherwise contraindicated. Phenobarbital and valproic acid may inhibit oxidative phosphorylation and subsequently lower the seizure threshold. L-arginine infusions have been used in patients who manifest signs of stroke, and preliminary evidence suggests that they may improve the outcome in patients with myoclonic epilepsy with lactic acidosis and stroke like episodes and other mitochondrial disorders.

Renal abnormalities are common in patients with mitochondrial disease, but rarely manifest as glomerular dys-

function. Pediatric patients frequently have severe renal tubular dysfunction with non-selective loss of amino acids, glucose, phosphate, and bicarbonate. Unlike in adults with mitochondrial disorders, overt renal failure is uncommon in pediatric patients.

Both invasive and non-invasive monitoring may be helpful in achieving goal-directed therapy. Continuous electroencephalogram monitoring can allow for titration of drug dosage against seizure and burst suppression activity. Hemodynamic monitoring of arterial and central venous pressure can ensure adequate fluid resuscitation and allow for titration of inotropic support. The use of newer technologies such as near-infrared spectroscopy for the management of shock and as a measure of tissue oxygenation is promising.

Mitochondrial disorders, although genetically diverse, share the common cellular consequences of decreased adenosine triphosphate production, increased reliance on anaerobic energy sources, and increased production of reactive oxygen species. Long-term therapy is typically directed at these consequences by using a variety of nutritional supplements. For a few of these supplements, there have been limited studies demonstrating efficacy, but in many cases the data to support specific benefits are lacking. Nutritional support and prompt attention to intercurrent illnesses is extremely important. The agents most commonly used include coenzyme Q10, L-carnitine, creatine, B-vitamins, vitamin C, Vitamin E, magnesium orotae, lipoic acid, and zinc picolinate.

Patients with mitochondrial disease can develop severe and profound lactic acidosis because of the underlying mitochondrial defect and the secondary impairment of hepatic lactate metabolism. Maintaining a high glucose infusion rate can halt catabolism in these patients, and boluses of 5% or 10% dextrose in patients with lactic acidosis in spite of euglycemia is often helpful. Also, because many patients waste bicarbonate because of renal tubular impairment, bicarbonate replacement has been recommended.

CONCLUSIONS

Patients with underlying disorders of the mitochondrial oxidative phosphorylation pathway often come to the pediatric intensive care unit with multi-organ system dysfunction requiring advanced monitoring and management techniques. Unfortunately, treatment of the precipitating illness and providing supportive care to patients with mitochondrial cytopathies remains the mainstay of therapy. In the case presented, the suspicion of Kearns-Sayre syndrome was made early after a characteristic pattern of clinical symptoms, including complete heart block, was recognized. In evaluating a case of cardiomyopathy in childhood, a thorough investigation for the possibility of a metabolic disorder should be made. Maintaining a high index of suspicion and a low threshold for genetic testing can aid practitioners in diagnosis and management of previously unrecognized mitochondrial disorders. Consultation with experts in pediatric genetic and metabolic diseases can facilitate long-term outpatient management after hospital discharge.
REFERENCES

Ethnic Differences in Extreme Obesity

AILSA GOULDING, PHD, FACN, ANDREA M. GRANT, MSc, RACHAEL W. TAYLOR, PHD, SHEILA M. WILLIAMS, DSc, WINSOME R. PARNELL, PHD, NOELA WILSON, PHD, AND JIM MANN, DM, PHD, FRACP

A nationwide representative survey of New Zealand schoolchildren showed a 2.7% incidence of extreme obesity (versus 4% in the United States) but revealed worrying ethnic differences in prevalence. Prevalence percentages (95% CI) were 0.8 (0.4 to 1.9), 5.1 (3.6 to 7.1), and 10.9 (8.9 to 13.3) in New Zealand European, Māori, and Pacific Island groups, respectively. These findings warrant remedial action. (J Pediatr 2007;151:542-4)

It was recently reported that 4% of children and adolescents in the United States now have extreme obesity (defined as having body mass index [BMI] values >99th percentile for age and sex from the Center for Disease Control data), with this condition affecting more than 2 million American children in 2005. This high prevalence is regarded as a major public health concern, because a high proportion of individuals with such extreme adiposity develop biochemical abnormalities during their pediatric years. Furthermore, longitudinal investigations from the Bogalusa Heart Study demonstrated that obesity persisted into adult life in all such children, with their average young adult BMI values being 43 kg/m².

Childhood obesity is a current concern in New Zealand, particularly among Māori and Pacific Islanders, two groups with high adult levels of type 2 diabetes and cardiovascular disease. The aim of the present analysis was to assess the prevalence of extreme obesity among children in New Zealand and evaluate differences among ethnic groups within this population, by examining BMI values obtained in a representative national sample of school children conducted in 2002.

METHODS

The National Children’s Nutrition survey was a cross-sectional survey of a national sample of New Zealand children ages 5 to 14 years drawn from 172 schools that was conducted in 2002 and was funded by the New Zealand Ministry of Health. The protocol was approved by all participating regional health ethics committees (n = 13). Full details of the study design are described elsewhere. Although only 22% of the NZ population of this age are identified as Māori and 9.9% as Pacific Islanders, oversampling of Māori and Pacific children was performed to enable ethnic-specific analyses to be undertaken. Briefly, the study aim was to recruit 3000 participants, with 1000 from each of 3 ethnic groups: Māori, Pacific, and New Zealand European and Others (NZEO). Informed written consent was obtained from every participating child and their parents or guardians. When participants indicated that they belonged to more than one ethnic group, ethnicity was assigned to a single category, using recommended procedures: if Māori was one of the groups reported, the participant was assigned to the Māori group. If Māori was not reported but Pacific ethnicity was reported, the participant was assigned to the Pacific group. All remaining participants were assigned to the NZEO group.

In total, 4728 children were invited to participate and 3275 did so. Response rates were 74% in Pacific Islanders, 69.8% in NZEO, and 65.3% in Māori. Anthropometry was performed on 3049 children (51.3% male) whose age distribution is shown in Table I. Trained personnel measured height (portable stadiometer to the nearest 0.1 cm) and body weight (to the nearest 0.1 kg), with the children wearing light clothing and no shoes. BMI (kg/m²) was calculated and converted to a z-score, using the US LMS constants. Children with z-scores ≥1.65 and ≥2.33 (equivalent to ≥95th and 99th US CDC percentiles for age and sex) were classified as overweight, or as having extreme obesity, respectively. Socioeconomic status was evaluated using the New Zealand Index of Deprivation, which has 10 categories and is assigned from the residential address of participants and 8 dimensions of deprivation.
The statistical analysis was carried out using STATA 9.0, using the survey procedures to adjust for the complex sampling design. Schools were the primary sampling unit. Sampling weights, based on the inverse probability of selection, were used. Because the prevalence of extreme obesity was low, Poisson regression was used to obtain the prevalence estimates (95% CI) for the groups of interest.

Estimates of nationwide numbers of children exhibiting extreme obesity were calculated by applying our ethnic prevalences to the New Zealand nationwide 2001 Census data.7

RESULTS

The prevalence of extreme obesity countrywide in New Zealand children ages 5 to 14 years was calculated to be 2.7% (95% CI, 1.9 to 3.8), indicating that approximately 15,000 of the 576,900 children ages 5 to 14 years in New Zealand (2001 Census)7 have this condition. We estimate that of these about 3000 will be NZEO, 6000 Māori, and 6000 of Pacific Island ethnicity.

The ethnic differences in the prevalences of overweight and extreme obesity we observed were substantial in all age brackets (Tables I and II), with children of Māori and Pacific Island ethnicity having higher prevalences than the NZEO group in both sexes. In Pacific Islanders, about one third of the overweight children displayed extreme obesity (Table II), which is a higher proportion than occurred among NZEO or Māori. Extreme obesity was more common among children having low socioeconomic status. The relative risk was 7.2 (95% CI, 3.7, 14) when the 4 most disadvantaged categories were compared with the remaining 6 categories.

Table I. Number of children surveyed, age- and sex-specific cut-points of body mass index (kg/m²) used to identify overweight (BMI ≥ 95th percentile) and extreme obesity (BMI ≥ 99th percentile), and prevalence (95% CI) of extreme obesity found in boys and girls of different ethnicity

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>n</th>
<th>Boys (kg/m²)*</th>
<th></th>
<th></th>
<th>Girls (kg/m²)*</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BMI ≥ 95</td>
<td>BMI ≥ 99</td>
<td></td>
<td>BMI ≥ 95</td>
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<tr>
<td>5</td>
<td>285</td>
<td>18.1</td>
<td>20.1</td>
<td></td>
<td>18.5</td>
<td>21.5</td>
</tr>
<tr>
<td>6</td>
<td>333</td>
<td>18.8</td>
<td>21.6</td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>321</td>
<td>19.6</td>
<td>23.6</td>
<td></td>
<td>20.2</td>
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<td>316</td>
<td>20.6</td>
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<td>9</td>
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<td>22.4</td>
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<tr>
<td>10</td>
<td>344</td>
<td>22.7</td>
<td>29.3</td>
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<td>26.4</td>
<td>33.2</td>
<td></td>
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</tr>
<tr>
<td>5-14 y</td>
<td>3049</td>
<td></td>
<td></td>
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</table>

Table II. Prevalence (95% confidence intervals) of overweight and extreme obesity at different ages

<table>
<thead>
<tr>
<th>Age group</th>
<th>5-6 y (n = 618)</th>
<th>7-10 y (n = 1335)</th>
<th>11-14 y (n = 1096)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Overweight (BMI ≥ 95th percentile for age and sex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZEO*</td>
<td>6.9 (3.9-12.2)</td>
<td>7.6 (5.5-10.6)</td>
<td>10.6 (7.6-14.6)</td>
</tr>
<tr>
<td>Māori</td>
<td>21 (15.8-27.9)</td>
<td>19.2 (16.1-22.8)</td>
<td>17.4 (13.1-23.1)</td>
</tr>
<tr>
<td>Pacific</td>
<td>32.7 (25.5-42)</td>
<td>33.7 (20.4-38.6)</td>
<td>34.4 (31.2-38.1)</td>
</tr>
<tr>
<td></td>
<td>% With extreme obesity (BMI ≥ 99th percentile for age and sex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NZEO</td>
<td>1.1 (0.3-4.5)</td>
<td>0.2 (0.03-1.7)</td>
<td>1.2 (0.4-3.8)</td>
</tr>
<tr>
<td>Māori</td>
<td>8.3 (5.4-13)</td>
<td>4.5 (2.9-7.2)</td>
<td>4 (2.4-6.6)</td>
</tr>
<tr>
<td>Pacific</td>
<td>11.8 (7.6-18.4)</td>
<td>10.7 (7.6-14.9)</td>
<td>10.7 (8.1-14.1)</td>
</tr>
</tbody>
</table>

*New Zealand European and other.
DISCUSSION

The present findings that extreme obesity affects 1 Pacific Island child in 10 and 1 Māori child in 20, versus 1 NZEO child in 100, draws attention to the need for identification and remedial treatment of affected individuals. More research into reasons underlying these ethnic disparities is warranted and ways to implement successful strategies to curb severe adiposity in young children are urgently needed. Ethnic differences in severe obesity may originate from genetic factors, different patterns of eating, and physical activity or low socioeconomic status. Earlier sexual maturity is not a likely explanation because ethnic differences were evident in participants as young as 5 to 6 years. Given that diabetes and metabolic syndrome are prevalent in obese Māori and Pacific adults with type 2 diabetes occurring in these groups in adolescence, we consider children with extreme obesity are at high risk for current and later comorbidities.

We thank the children and parents who participated in the Children’s Nutrition Survey 2002. The principal investigators for this survey were from the University of Otago (Winsome Parnell, Noela Wilson), University of Auckland (David Schaaf, Robert Scragg), and Massey University (Eljon Fitzgerald).

REFERENCES

Ratio of High-, Medium-, and Low-Molecular Weight Serum Adiponectin to the Total Adiponectin Value in Children

RIMEI NISHIMURA, MD, MPH, AYA MORIMOTO, MD, TORU MATSUDAIRA, MD, YUMI MIYASHITA, MD, HIRONARI SANO, MD, TAKAKO SHIRASAWA, ME, EIKO TAKAHASHI, MD, PHD, AND NAOKO TAJIMA, MD

In 760 children age 9 to 10 years, the serum adiponectin composition (high molecular weight [HMW], hexameric medium molecular weight [MMW], and trimeric low molecular weight [LMW]) was found to vary markedly depending on whether the total adiponectin value was high or low. A lower total adiponectin value was associated with a lower ratio of HMW adiponectin. (J Pediatr 2007;151:545-7)

Adiponectin is a hormone released from adipocytes. Previous studies have indicated that serum adiponectin levels were lower in obese subjects compared with nonobese subjects.\textsuperscript{1,2} Adiponectin is classified mainly as high molecular weight (HMW), hexameric medium molecular weight (MMW), or trimeric low molecular weight (LMW) adiponectin.\textsuperscript{3-5} Clinical findings on the HMW adiponectin isoform reported in 2006 indicated that HMW is superior to total adiponectin level for predicting the development of insulin resistance, metabolic syndrome, and coronary artery disease.\textsuperscript{3-5} In the current study, all 3 adiponectin isoforms were examined for their relative ratio to the total adiponectin value in a population-based cohort of children age 9 to 10 years.

METHODS

In the past, a number of health-promoting activities have been conducted in Ina-machi, Saitama Prefecture, Japan (a town located on the outskirts of Tokyo with a population of approximately 38,000). In the present study, which formed part of these activities, a total of 760 children (374 male and 386 female fourth-graders age 9 to 10 years), participated in the study in 2005 and 2006. These study subjects represented a nearly perfect population-based cohort, accounting for 98.7% of the male and 99% of the female fourth-graders in the area.

Blood samples were drawn from the subjects at the time of routine health checkup to measure adiponectin isoform values using a commercially available enzyme-linked immunosorbent assay kit (Daiichi Pure Chemical Co Ltd, Tokyo, Japan).\textsuperscript{5,6} Intraassay coefficients of variations for total, HMW + MMW, and HMW adiponectin were reported to be 5.3%, 4.1%, and 3.3%, respectively.\textsuperscript{6} Most children had their blood collected between 2 and 3 hours after eating breakfast, following the recommendation of the Institutional Review Board.

The correlations among HMW, MMW, and LMW adiponectin and total adiponectin and among HMW, MMW, and LMW adiponectin and body mass index (BMI) were assessed using Spearman’s correlation coefficient. Changes in the ratio of HMW, MMW, and LMW adiponectin to the total adiponectin value were plotted to demonstrate how these ratios varied with changes in total adiponectin value. Statistical analyses were done using SPSS (SPSS Inc, Cary, NC).

The study protocol was approved by 2 independent Institutional Review Boards at Jikei University School of Medicine and Showa University School of Medicine. All of the participants and their guardians gave their written consent to participate in the study.

RESULTS

The medians (intraquartile ranges) of HMW, MMW, LMW, total adiponectin (μg/mL), and BMI (kg/m\textsuperscript{2}) were 2.5 (1.7 to 3.5), 1.8 (1.5 to 2.3), 1.5 (1.2 to 1.9), 5.9 (4.7

<table>
<thead>
<tr>
<th>BMI</th>
<th>Body mass index</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMW</td>
<td>High molecular weight</td>
</tr>
<tr>
<td>LMW</td>
<td>Low molecular weight</td>
</tr>
<tr>
<td>MMW</td>
<td>Medium molecular weight</td>
</tr>
</tbody>
</table>

From the Division of Diabetes, Metabolism, and Endocrinology, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan (R.N., A.M., T.M., Y.M., H.S., N.T.); Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA (R.N.); and Department of Public Health, Showa University School of Medicine, Tokyo, Japan (T.S., E.T.).

Supported by grants from the Ministry of Education, Culture, Sports, Science and Technology, Japan (Basic Research A2 #14207020, 2002-2004 and Basic Research A #17209024, 2005-2008). The Ministry of Education, Culture, Sports, Science and Technology, Japan had no direct input into the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

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to 7.6), and 16.8 (15.6 to 18.8) for males and 2.7 (1.7 to 3.8), 1.8 (1.5 to 2.3), 1.6 (1.2 to 2), 6.4 (4.8 to 7.8), and 16.4 (15.3 to 17.9) for females, respectively. No statistical differences by sex were noted in any of these values except BMI ($P < .002$).

HMW, MMW, and LMW adiponectin values were all found to be positively significantly correlated with the total adiponectin value for both male and female subjects (Figure 1 and Figure 3A,B,C; available at www.jpeds.com). HMW and MMW adiponectin showed a significant negative weak correlation with BMI; however, LMW adiponectin showed no significant relationship with BMI (Figure 4A,B,C; available at www.jpeds.com). The correlation coefficient for BMI and HMW adiponectin was slightly larger than that for total adiponectin ($r = .169$ for males and $r = .225$ for females).

HMW adiponectin accounted for approximately 60% of the total adiponectin value in the subjects with a higher total adiponectin value; these ratios became significantly smaller as the total adiponectin value decreased (Figure 2 and Figure 3D; available at www.jpeds.com). MMW and LMW adiponectin each accounted for about 40% of the total adiponectin value in the subjects with a lower total adiponectin value; these ratios became significantly smaller as the total adiponectin value increased (Figure 3E,F; available at www.jpeds.com). The HMW/total ratio showed a significant negative correlation and the LMW/total ratio a significant positive correlation with BMI. (Figure 4D,E,F; available at www.jpeds.com).

**DISCUSSION**

This study examined the relative ratio of HMW, MMW, and LMW adiponectin isoforms to the total adiponectin value using a childhood population-based cohort. In adult and adolescent subjects, total and HMW adiponectin values have been reported to be higher in females than in males, due to the higher androgen and testosterone levels in males.7-11 No sex-related differences in HMW, MMW, and LMW adiponectin levels were observed, because most of the study participants were prepubertal. The findings were consistent with the findings of a study of total adiponectin levels in prepubertal children.1,2

Previous studies have indicated that HMW, LMW, and HMW adiponectin have different biological activities.7,12 Although biological activities among these 3 isoforms are a matter of controversy; recent studies have indicated that HMW adiponectin may be the active form of adiponectin.3-5,13 The present study found a significant negative correlation between HMW adiponectin and BMI, which was not applicable to LMW adiponectin. Total and MMW adiponectin also showed a significant negative correlation with BMI; however, the associations were weaker than that observed for HMW adiponectin. These results are consistent with those from previous studies.3-5,13 Because earlier reports have indicated that levels of circulating adiponectin do not change in response to a high-fat meal or a 75-g glucose load,14,15 the results of the current study are not likely to be affected by postprandial status.

Our results demonstrate that the adiponectin composition varies markedly depending on whether the total adiponectin value is high or low. Of particular note, subjects with a lower total adiponectin value are associated with a lower ratio of HMW adiponectin to total adiponectin. Further in-depth research is needed to clarify whether or not this variation in the adiponectin composition has any pathophysiological implications or any affect on clinical outcomes when the study participants become adolescents or adults.

*The authors thank all the participants, all the members of the Board of Education, Ina, Saitama Prefecture; the Ina Conference for the Promotion and Operation of Childhood Lifestyle–Related Disease Prevention Examination (Chairman, Yoshibito Toriyama, MD); Michio Sato, MD; and Takeshi Kawaguchi, MD.*

**REFERENCES**


Figure 3. (A-C) Scatterplots showing the relationship between HMW, MMW, and LMW adiponectin values and total adiponectin value. (D-F) Scatterplots showing the relationship between the ratios of HMW, MMW, and LMW adiponectin values and total adiponectin value, and the total adiponectin value in a childhood population-based cohort age 9 to 10 years (n = 760). r: Spearman’s correlation coefficient, *P < .001; ●, male; ○, female.
Figure 4. (A-C) Scatterplots showing the relationship between HMW, MMW, and LMW adiponectin values and BMI. (D-F) Scatterplots showing the relationship between the ratios of HMW, MMW, and LMW adiponectin values and total adiponectin value, and BMI in a childhood population-based cohort age 9 to 10 years (n = 760). r: Spearman’s correlation coefficient, *P < .001; **P < .01; ●, male; ○, female.

Anne Louise Svendsen, PhD, Maria Feychting, PhD, Lars Klæboe, PhD, Frøydis Langmark, MD, and Joachim Schüz, PhD

We studied the incidence of childhood acute lymphoblastic leukemia in Denmark, Finland, Norway, and Sweden during 1976-2002, on the basis of data from national cancer registries. The incidence of acute lymphoblastic leukemia increased with the calendar period until 1983, and with the birth cohort until 1980, but incidence has been stable thereafter. (J Pediatr 2007;151:548-50)

In a large European study covering the time period 1970 to 1999, the incidence of childhood acute lymphoblastic leukemia (ALL) was found to increase by around 0.7% per year.1 However, concerns regarding the completeness of some of the cancer registries during the study period have been raised.2 Hence, improved registration might be at least partially responsible for the increase of ALL, as well as of other childhood cancers, for which an increase was also found.1 We investigated time trends in childhood ALL with data from the high-quality population-based Nordic cancer registries over a 27-year period.

METHODS

The study is based on data from Denmark, Finland, Norway, and Sweden during the period 1976-2002. Data on incident cases of childhood leukemia (age 0-14 years) were obtained from the national cancer registries, together with information about year of diagnosis, age at diagnosis, sex, and subtype of leukemia. Originally the subtype classification varied by country, so we regrouped all leukemias according to a slight modification of the Birch-Marsden classification,3 namely: ALL, other lymphoblastic leukemia, acute nonlymphoblastic leukemia, chronic myeloid leukemia, other and unspecified leukemia/possibly ALL, and other and unspecified leukemia/definitely not ALL. Population figures were obtained from the respective national statistics offices.

We modeled the incidence rates as a log-linear function of the variables age (by 1 year), sex, and country, along with first-order interactions of these, while investigating the effect of the calendar year as a (log-linear) spline, with Poisson regression.4 The model allowed the effect of the calendar year to vary for the age groups 0-1 (children less than 2 years of age), 2-5 (children at least 2 years and less than 6 years of age), and 6+ years (children at least 6 years of age). The dependence of incidence on the birth cohort was modeled similarly.

RESULTS

The trend in incidence for the 6 different subtypes of leukemia is illustrated in the Figure. There seems to be an increasing trend for ALL, which appears to occur in the early years of the study period, but there is no clear pattern for the other subgroups.

Modeling the ALL incidence rate as a function of the calendar year resulted in a statistically significant change of course in 1983 (P = .006), indicating that the effect of the calendar year is best modeled with trends with different slopes before and after 1983. The ALL incidence rate increased by 3.3% (95% confidence interval [CI] 1.5%-5.2%) per year before 1983, and by 0.2% (95% CI, −0.3%-0.8%) per year after 1983. Applying the model to leukemia groups 1 and 5 combined slightly attenuates the increase in the incidence before 1983 to 2.4% (95% CI, 0.6%-4.3%) per year, whereas after 1983 it remained similar to group 1 alone (0.3% per year). Modeling the incidence rate as a function of the birth cohort resulted in a change in the year 1980 (P < .001); an increase of 2.5% (95% CI, 1.4%-3.6%) was seen per birth cohort in children born before 1980, and of 0.1% (95% CI, −0.5%-0.6%) in children born after 1980. Age group–specific results are shown in the Table.

<table>
<thead>
<tr>
<th>ALL</th>
<th>Acute lymphoblastic leukemia</th>
<th>CI</th>
<th>Confidence interval</th>
</tr>
</thead>
</table>

From the Institute of Cancer Epidemiology, Danish Cancer Society (A.S., J.S.), Copenhagen, Denmark, the Institute of Environmental Medicine, Karolinska Institutet (M.F.), Stockholm, Sweden, and The Cancer Registry of Norway (L.K., F.L.), Montebello, Oslo, Norway.

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DISCUSSION

We found a statistically significant annual increase of 3.3% in the incidence of childhood ALL in the Nordic countries until 1983, but thereafter the incidence has been stable. Including the group of other and unspecified leukemias that are possibly ALL somewhat attenuated this increase. This suggests that some of the increase may be due to changes in coding practices, improved accuracy of reporting, or improvement in diagnostics of subtypes, that is, some of the increase in ALL is explained by a decline in unspecified leukemias. The incidence by birth cohort displayed an effect similar to the one for the calendar period, but with a rise only to 1980. This was in good accordance with the change found until the calendar year 1983 because children born in 1980 turned 3 years old in 1983, and this is the peak age of diagnosis. It could not be determined whether the increase in the incidence was mainly an effect of the calendar period or of the birth cohort. A similar pattern in the incidence rate was seen for all age groups.

There have been other recent national investigations of childhood ALL incidence trends. In the United Kingdom, a statistically significant annual increase of precursor B-cell ALL of 1.4% (95% confidence interval for increase, 0.8%-2%) was reported for the period 1980-1996; previously, restricted to the area of Yorkshire, this increase was reported to be 2.4%. In Northern Italy, ALL increased annually by 1.2% in 1967-2001. On the basis of the clinical registry of the Nordic Society of Paediatric Haematology and Oncology, the incidence of precursor B-cell ALL remained stable between 1982 and 2001, with an annual change of 0.3%. Our results are similar in that we only observed an increase in the earlier time period. Compared with the United Kingdom and Italy, both with a continuous small increase, it seems that in the Nordic countries the increase was stronger before the mid 1980s and flattened thereafter.

One strength of our study is that we only used data from established cancer registries that were built decades before the study period. A limitation of the study is that childhood ALL is a rare disease. The total childhood population in the 4 Nordic countries is 4.4 million, so our rates are based on small numbers (overall 4403 ALL cases). We have examined possible artifacts caused by changes in the classification or registration procedure, but although we found some evidence for bias, this only explains part of the ALL incidence increase found in the early study period. Moreover, early diagnosis because of improved diagnostic techniques is unlikely to explain this increase because ALL progresses rather quickly.

We conclude that the incidence rate of ALL in the Nordic countries increased with the calendar period and birth cohort until around 1983, respectively 1980, but was relatively stable thereafter, and that this increase is unlikely to be a registration artifact. This pattern is seen for all age groups and needs to be considered when trying to identify causes of the disease.
Table. Annual percent change of incidence* of childhood acute lymphoblastic leukemia (total and by age group†)

<table>
<thead>
<tr>
<th></th>
<th>By calendar year</th>
<th>By birth cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual change</td>
<td>P value</td>
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<tr>
<td></td>
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<td>for change of</td>
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<td>0.2% (-0.3%-0.8%)</td>
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<td>Age 0-1 years</td>
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<td>Age 2-5 years</td>
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*Incidence rates are modeled as a spline function of the calendar year with a knot in the year 1983 and of birth cohort with a knot in the year 1980.
†Age groups are defined to approximate a grouping by biologically heterogeneous subtypes of ALL in children, because these subtypes may be associated with different causal pathways and therefore might display unique incidence patterns; during infancy an ALL with pro-B cell phenotype outweighs other subtypes, whereas the marked age peak at ages 2 to 5 years is associated with common precursor-B cell ALL.12
‡The annual change over the whole period (1976-2002) is calculated only when the spline function was not statistically significant.

Thanks to the Danish Cancer Registry, the Finnish Cancer Registry, the Norwegian Cancer Registry, and the Swedish Cancer Registry for providing the data.

REFERENCES

A 18-year-old girl suffered from a slight foreign-body sensation during swallowing for a number of years. Three-dimensional reconstructed images from the left anterior oblique view using contrast-enhanced cardiac computed tomography with volume rendering and color encoding of variable tissue segmentation (Figure) revealed a complete vascular ring (red) enwrapping the trachea (green) and upper esophagus (blue) (video; available at www.jpeds.com). This vascular ring consisted of the aortic arch on the right side, Kommerell’s diverticulum (K) on the dorsal side, and the ascending aorta (AAo) plus pulmonary trunk (PT) bifurcation plus the bilateral central pulmonary artery on the ventral side, together with a calcified ligamentum arteriosum (arrow) on the left lateral side. The middle esophagus was directly compressed by the ventral trachea against the dorsal Kommerell’s diverticulum, limiting lateral escape by the ligamentum arteriosum and producing her symptoms. Division of this ligamentum relieved her symptoms.

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Figure. Three-dimensional computed tomography image of this complete vascular ring.
Children with first urinary tract infection may not benefit from antibiotic prophylaxis

Question Among children with a first urinary tract infection (UTI), what risk factors predict recurrent UTI, is there an association between antimicrobial prophylaxis and recurrent UTI, and what risk factors predict antimicrobial resistance in recurrent UTIs?

Design Cohort study, with a nested case-control study for children diagnosed with recurrent UTI.

Setting Twenty-seven primary care pediatric practices in urban, suburban, and semi-rural areas spanning 3 states.

Participants From a primary care cohort of children aged ≤6 years (n = 74,974), 611 children diagnosed with a first UTI were identified; 83 of these children had recurrent UTI during the study period.

Outcomes Time to recurrent UTI and antimicrobial resistance of recurrent UTI pathogens.

Main Results Of the children in the network, 611 (0.007 per person-year) had a first UTI, and 83 (0.12 per person-year after first UTI) had a recurrent UTI. In multivariable Cox time-to-event models, factors associated with increased risk of recurrent UTI included white race (0.17 per person-year; hazard ratio [HR], 1.97; 95% CI, 1.22-3.16), age 3 to 4 years (0.22 per person-year; HR, 2.75; 95% CI, 1.37-5.51), age 4 to 5 years (0.19 per person-year; HR, 2.47; 95% CI, 1.19-5.12), and grade 4 to 5 vesicoureteral reflux (0.6 per person-year; HR, 4.38; 95% CI, 1.26-15.29). Sex and grade 1 to 3 vesicoureteral reflux were not associated with risk of recurrence. Antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI (HR, 1.01; 95% CI, 0.5-2.02), even after adjusting for propensity to receive prophylaxis, but was a risk factor for antimicrobial resistance in children with recurrent UTI (HR, 7.5; 95% CI, 1.6-35.17).

Conclusions In the children in this study, antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.

Commentary This study adds to a growing body of literature that challenges the need for prophylactic antibiotics and voiding cystourethrogram (VCUG) in children who have sustained their first UTI, an approach felt to reduce the rate of recurrent infections, especially in children with associated vesicoureteral reflux (VUR), who may be at risk for development of reflux nephropathy. Using an electronic medical record covering numerous primary care practices affiliated with the Children's Hospital of Philadelphia, the investigators demonstrated that prophylactic antibiotics not only did not reduce the rate of recurrent infections, they increased the risk of the development of a resistant organism. Additionally, the risk of recurrent infections did not seem to increase in the presence of reflux, especially for grades 1 to 3 VUR. So should we throw out the prescription pad and stop ordering studies to detect VUR? Not so fast. As the authors state, the rate of performance of VCUGs was relatively low in the children included in the study, despite many recommendations to the contrary. There were also very few children with higher grades of reflux, and no analysis of renal scarring/reflux nephropathy was conducted. Therefore, this study does not provide sufficient rationale to stop performing VCUGs. Furthermore, although detailed prescribing data were available to the investigators, resistance patterns were not analyzed on the basis of the antibiotic prescribed. This is important because certain
antibiotics, specifically amoxicillin and the cephalosporins, are incompletely absorbed in the upper gastrointestinal tract and therefore do get into the colon, where they can cause the gut flora to become resistant. Nitrofurantoin and trimethoprim/sulfamethoxazole, however, are better absorbed, so relatively little of them get into the colon, thereby reducing the likelihood of increased antibiotic resistance. If the practices in the Children’s Hospital of Philadelphia network were in a habit of using amoxicillin or cephalosporins for prophylaxis, this could explain the increased risk of antibiotic resistance. Finally, and perhaps most importantly, these data highlight the need for a properly conducted, randomized controlled trial of antimicrobial prophylaxis in the prevention of recurrent UTIs and renal scarring. The National Institutes of Diabetes and Digestive and Kidney Diseases is currently sponsoring such a trial, the Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR) trial (Clinical trials.gov #NCT00405704). Until the results of RIVUR are available, practitioners should have thoughtful discussions with patients’ families before prescribing prophylaxis, at least in those children without known high-grade VUR. When prophylaxis is prescribed, it is probably wise to only prescribe those antibiotics that have the lowest likelihood of inducing resistance. 

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REFERENCES

Prophylactic fluconazole decreases incidence of invasive candidiasis in preterm infants

Question In very low birth weight (VLBW) infants, does fluconazole prevent fungal colonization and infection?

Design Multicenter, randomized, controlled trial.

Setting Eight tertiary Italian neonatal intensive care units.

Participants All neonates weighing <1500 g at birth (n = 322).

Intervention Infants were randomly assigned to receive either fluconazole (either 6 mg or 3 mg per kilogram of body weight) or placebo from birth until day 30 of life (day 45 for neonates weighing <1000 g at birth).

Outcomes Incidence of colonization and incidence of invasive fungal infection.

Results In infants receiving fluconazole, fungal colonization occurred in 9.8% in the 6-mg group and 7.7% in the 3-mg group, as compared with 29.2% in the placebo group (P < .001 for both fluconazole groups versus the placebo group, number needed to treat [NNT] = 6 for the 6 mg dose and 5 for the 3 mg dose). The incidence of invasive fungal infection was 2.7% in the 6-mg group and 3.8% in the 3-mg group, as compared with 13.2% in the placebo group (P = .005 for the 6-mg group, NNT = 10, and P = .02 for the 3-mg group versus the placebo group, NNT = 11). The use of fluconazole did not modify the relationship between colonization and the subsequent development of invasive fungal infection. Overall mortality was similar among groups, as was the incidence of cholestasis. No evidence for the emergence of resistant candida species was observed, but the study did not have substantial power to detect such an effect.

Conclusions Prophylactic fluconazole reduces the incidence of colonization (NNT = 5–6) and invasive candida infection (NNT = 10–11) in neonates weighing <1500 g at birth. The benefit of treating candida colonization is unclear.

Commentary This study offers the strongest support for fluconazole prophylaxis of invasive candidiasis in preterm neonates to date. Despite these apparently encouraging findings, caution remains warranted before embracing this strategy as standard for care. It took 15 months for the 8 participating Italian neonatal intensive care units to identify 363 VLBW infants (although 27 were excluded from enrollment and another 14 from analysis) and enroll 141 extremely low birth weight (ELBW; birth weight ≤1000 grams) infants. This suggests that each neonatal intensive care unit admitted slightly >3 VLBW and 1 ELBW infant per month, totals much lower than would be seen in most neonatal intensive care units in the United States. This may be an important factor, because development of antimicrobial resistance in a discrete care unit (such as an intensive care unit) is often dependent on the frequency and intensity of exposure of flora to the antimicrobial agent in question. The larger the number of VLBWs and ELBWs present in a neonatal intensive care unit and receiving a specific antimicrobial agent, the greater is the likelihood that resistance to that agent will develop (although the speed at which such a development occurs varies with the family of antimicrobial). The absence of induced fluconazole resistance in this study may reflect the relatively short duration of the study and the apparently limited exposure to the agent within each neonatal intensive care unit.

The reported lack of improvement in overall mortality and duration of neonatal intensive care unit hospitalization in this...
Most patients with a moderate ventricular septal defect will not require intervention


Question In children and adolescents with moderate to large pressure-restrictive ventricular septal defect (VSD), what is the natural history of the left ventricular (LV) dilation associated with this defect? Is interventional management of such defects warranted?

Design Cohort study.

Setting Single cardiology division at a university hospital.

Participants Patients (n = 70) with a moderate to large VSD were identified. Thirty-three of these patients had LV dilation (LV end-diastolic dimension [LVED] z score ≥2) at the time of enrollment and had serial clinical and echocardiographic follow-up for >2 years.

Outcomes Evidence of persistent or progressive LV dilation; signs or symptoms of congestive heart failure (CHF), failure to thrive (FTT), or pulmonary hypertension (PAH); and acquired ventricular outflow obstruction or aortic regurgitation. LVED z scores at enrollment were compared with those at the latest follow-up.

Results Mean age at enrollment was 4.6 ± 3.2 years, and mean duration of follow-up was 7.8 ± 4 years (range, 2.8-22 years), during which the mean LVED z score decreased from 3 ± 0.6 to 1.2 ± 1.3 (P < .01). LVED z score decreased in 29 of the 33 patients and decreased to <2 in 26 of these 29 patients (79%).

Conclusions Most patients with pressure-restrictive VSD with moderate-to-severe LV dilation without CHF, FTT, or PAH will experience spontaneous resolution of LV dilation and can avoid cardiac surgery or catheter-based intervention.

Commentary Natural history studies provide a foundation that supports the development of medical and surgical therapies. A therapeutic intervention is judged worthwhile (that is, effective, safe, and beneficial) when its outcomes are superior to outcomes that occur without treatment. Seminal natural history studies of congenital heart disease were published in 1977 and 1993 and are required reading for any physician or surgeon who cares for children with heart disease. Kleinman et al now provide important, new natural history data to guide our treatment of children with a ventricular septal defect (VSD). They reported 70 patients with a moderate VSD (60 membranous defects and 10 muscular-type defects) who were observed without intervention for an average of 7.8 years. At presentation, all children had LV volume overload consistent with at least a moderate shunt, but none had symptoms or pulmonary hypertension that might mandate an early intervention. During follow-up, virtually all children experienced spontaneous diminution in VSD size and improvement in LV volume overload. Of particular interest was a subgroup of 33 children whose initial LV diastolic dimension was >2 SDs higher than the mean. In these children, LV volume overload improved spontaneously by 60% during the follow-up period. Kleinman et al conclude that children with a moderate-sized VSD and volume overload, who do not have symptoms or pulmonary hypertension, are best treated conservatively and rarely require intervention. As the field of pediatric cardiology continues its rapid movement toward earlier surgical repairs and aggressive transcatheter interventions, it becomes even more essential that surgeons and interventional cardiologists be keenly aware of natural history data. The report by Kleinman and et al will help guide our therapies in the future. Certainly, not all children with a moderate VSD require surgery or device implantation. In many children, the natural history of the defect is preferable to the consequences of either therapy. Just because we can close a VSD does not mean we should.
Antibiotics of short-term benefit for children with chronic active otitis media


Question In children with chronic active otitis media (COM), does prolonged outpatient treatment with trimethoprim/sulfamethoxazole result in less otorrhea?

Design Randomized, placebo-controlled trial.

Setting Pediatric otorhinolaryngology department of the University Medical Center, Utrecht, The Netherlands.

Participants 101 children (1-12 years of age) with COM (defined as otorrhea for ≥12 weeks).

Intervention All children were given a short course of steroid and antibiotic eardrops. They were then assigned randomly to 6 to 12 weeks of orally administered trimethoprim/sulfamethoxazole (18 mg/kg, 2 times per day) or placebo.

Outcomes The primary end point was otomicroscopic signs of otorrhea in the presence of a tympanostomy tube or tympanic membrane perforation. Secondary outcome measures included use of medication other than the study medication for ear disease, adverse effects of the study medication, health-related quality of life, pure-tone hearing levels, and bacteriologic findings for the otorrhea samples.

Results At 6 weeks, 28% of children in the trimethoprim/sulfamethoxazole group and 53% of children in the placebo group had otomicroscopic signs of otorrhea (number needed to treat [NNT] = 4). At 12 weeks, these values were 32% and 47%, respectively, which were not significantly different. At 1 year, the numbers of children with otorrhea were similar in the 2 groups (25% and 20%, respectively). In 1 child in the trimethoprim/sulfamethoxazole group, a skin rash developed. Vomiting or diarrhea was reported for 9% of the trimethoprim/sulfamethoxazole group and 2% of the placebo group. Pure-tone hearing levels and health-related quality of life improved during the study, but did not differ between the trimethoprim/sulfamethoxazole group and the placebo group. Pseudomonas aeruginosa was the most frequently isolated bacteria in the otorrhea samples from both groups.

Conclusions A 6- to 12-week course of high-dose, orally administered trimethoprim/sulfamethoxazole therapy is beneficial for children with COM. The treatment effect is most pronounced with the shorter course and disappears when the medication is discontinued.

Commentary COM is frequently difficult to treat. P aeruginosa and Staphylococcus aureus are the most commonly isolated species. Aggressive medical management with topical antibiotic/steroid preparations, aural toilet, and oral or intravenous antibiotics can fail to provide long-term disease control. Surgical intervention may ultimately be required. The role of biofilms, fungal entities and resistant bacteria have also been described, especially in the context of tympanostomy tubes and prolonged antimicrobial usage. van der Veen et al document better disease control in the treatment group after 6 weeks (72% resolution versus 47% resolution in control subjects). This study provides encouraging evidence that in the short-term, an inexpensive, well-tolerated oral antibiotic may provide relief from COM in some patients. Several factors should be considered in interpreting the study results. The use of antimicrobial medications is carefully regulated in the Netherlands, raising the possibility that these results may not be generalizable to settings with less restricted use of broad spectrum antibiotics. Moreover, at the 1-year follow-up evaluation, there were no significant differences seen between the treatment and control groups in the rate of persistent COM, quality of life, or hearing. The similarity in long-term outcomes between the treatment and control groups questions the usefulness of long-term administration of even a relatively well-tolerated antibiotic, unless the goal is short-term disease management before surgical intervention. Finally, after a year, nearly one-fourth of the patients in both groups had persistent otorrhea despite continued treatment by their physicians after study participation. That high rate of persistent disease underscores the recalcitrant nature of COM and further reinforces the need for continued investigation into optimal treatments for long-term disease resolution.

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ALSO NOTED


Necrotizing enterocolitis (NEC) is a common serious complication for preterm infants. It is associated with high morbidity and mortality. A number of investigators have observed an increased incidence of neurodevelopmental impairment (NDI) in children who have survived NEC. This increased incidence is felt to be related to the increased proinflamma-
tory cytokines that are released during the NEC episode. Schulzke et al undertook this meta-analysis to examine whether there was an increased risk and whether the risk was higher in surgically managed NEC. Although there was significant heterogeneity in the studies, and variation in how NDI was defined, the investigators did find that the risk of long-term NDI was significantly higher for those children with at least stage II NEC versus no NEC (odds ratio, 1.82; 95% CI, 1.46-2.27). In addition, infants with NEC who required surgery were at higher risk for NDI compared with infants treated medically (odds ratio, 1.99; 95% CI, 1.26-3.14). Physicians who provide follow-up care for preterm infants should be aware of these risks and include them when counseling parents of children who have had NEC.
Factors influencing capillary refill time

To the Editor:

Following their research into prolonged capillary refill time (CRT) as a prognostic indicator in severe and complicated malaria, Evans et al.1 concluded that it is justified to include prolonged CRT (defined as > 2 seconds) as a defining criterion for severe and complicated malaria. The authors measured CRT after applying pressure on a finger. They did not discuss the factors influencing CRT in healthy people, however. These factors are important for future studies to validate their findings and to enhance the applications of this tool in research and clinical practice.

The site of CRT assessment has important implications for its ability to reflect cardiovascular status. This was noted in neonates, in whom the data points of CRT of the periphery (heel) showed a wide scatter even though those of CRT of the head and chest approached normality.2 This may be related to the strong influence of environmental and axillary temperature on peripheral CRT in the hands and feet.3 The influence of ambient temperature on CRT in the fingertips of healthy children was also demonstrated in older children, who in a room with an ambient temperature of 19.4°C were found to have a mean CRT of 2.39 seconds, as opposed to those in a warmer room (25.7°C) who had a mean CRT of 0.85 seconds.4 Using the head or chest for CRT may improve the specificity of this assessment tool.

The authors’ findings cannot be transferred to adults and should be analyzed stratified for sex, because normal CRT is age- and sex-dependent. Application of the 2-second upper limit of normal in a previous study resulted in false-positive rates of 4.0% in children and adult males, 13.7% in adult females, and 29.0% in elderly persons.5

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10.1016/j.jpeds.2007.06.016

REFERENCES

Reply

To the Editor:

The comments of Eisenhut about the assessment of capillary refill time are well taken. The study was clearly one of severe malaria in children, and the findings cannot be extrapolated to adults. There are well-documented differences in the presentation of severe malaria in adults compared with children.5

The role of pCRT in all forms of severe malaria will continue to be investigated, as will its use as a triage tool and in guiding interventions. A comparison of the site used to assess capillary refill should be incorporated, as suggested, in forthcoming studies.

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REFERENCE

Neurologic complications in children hospitalized with influenza: Comparison between USA and Hong Kong

To the Editor:

We read with interest the report by Newland et al.1 on the influenza-related neurologic complications (INC) in hospitalized children with laboratory confirmed influenza infection (LCI). In their study, 8.5% developed INCs. The estimated incidence of INCs was 4 cases per 100,000 person-years in USA.

We have also examined the INC in our unit, which is a university-affiliated hospital and the only public pediatric service for a population of 100,000 infants, children, and adolescents <16 y.o. in Hong Kong, where public sector provides >90% of inpatient and outpatient medical service.

Our retrospective review from March 1998 to February 2003 showed 20% of children developed INCs which is higher than that reported by Newland (Figure). The majority were febrile seizure (90%). Five INCs (0.6%) were encephalopathy and 2 died; 1 case had underlying methylmalonic aciduria and developed metabolic acidosis, shock and then renal failure. The other was a previously healthy 6 year-old girl progressing in a devastating course with shock and consumption coagulopathy who died on day 2 of fever. Com-
puted tomography showed generalized cerebral edema with hypodense lesions in thalamus, brainstem and basal ganglia, and was compatible with acute necrotizing encephalopathy. There was no case of acute disseminated encephalomyelitis (ADEM) during this 5 year period but there was one case of influenza A in 2004 from our database.

Influenza-related hospitalization for children in Hong Kong was reported as approximately 120 per 10,000 in 1998 and 1999. This is 3-10 times higher than that of USA. Additionally, the incidence of INCs was about 240 per 100,000 person-years in Hong Kong. This discrepancy is at least partly attributable to a lower threshold for admission for influenza-related illnesses and febrile seizure. Similar data from Japan will be of great interest if underlying ethnic difference in the neurotropic effect of influenza is to be explored.

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REFERENCES

Reply

To the Editor:

We thank Chung et al for their comments related to our recently published study on influenza-related neurologic complications (INC) in hospitalized children. The rate of INCs in Hong Kong of 240 per 100,000 person-years was markedly higher than we observed in our study of urban children in Philadelphia. We agree with Chung et al that the difference in the overall rate of INCs in children hospitalized with influenza might be due to different thresholds for admission.

Similar to our study, Chung et al noted that the majority of patients with INCs suffered febrile seizures and a small number of children experienced encephalopathy/encephalitis. These data suggest that the risk of influenza-related encephalopathy might differ substantially in Asia. Additional population-based studies are needed to define the rate and spectrum of INCs in various populations.

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Letters to the Editor

An important finding was that the VLBW infants in the NIMV group that failed nasal support had significantly higher initial ventilatory settings but spent less time on mechanical ventilation than the NCPAP group. Tolerating higher initial ventilatory settings and early extubation from mechanical ventilation might have helped decrease the incidence of BPD. There is a group of VLBW infants in the preterm population who, despite all efforts, will inevitably need mechanical ventilation; strategies to decrease BPD in this group need to be identified.

Our neonatal unit has been using NIMV for initial respiratory support in preterm infants with RDS. As part of an ongoing study, we are finding that NIMV does reduce the need for mechanical ventilation compared with NCPAP, especially in conjunction with surfactant therapy. Further analysis of the data will show whether this trend will appear in the group of infants with birth weight <1000 g and, if so, whether it will influence the incidence of BPD.

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REFERENCES

Reply

To the Editor:

We appreciate the comments of Dr Meneses on our recent article. It is true that surfactant was not administered to infants in whom nasal respiratory support was successful and was given only as rescue therapy. On the other hand, our policy was that those infants who failed nasal respiratory support for respiratory distress syndrome (RDS) and needed endotracheal ventilation got surfactant. Because this policy was similar in those infants treated initially with nasal continuous positive airway pressure (NCPAP) and those treated initially with nasal intermittent mandatory ventilation (NIMV), the rate or surfactant administration did not differ between the failing infants in the 2 methods. Individualized intubation strategy in delivery room was found to be safe. Several centers administer surfactant, immediately extubate the infants, and then use NCPAP to shorten the course of mechanical ventilation. The best option for treatment of RDS in respect to gestational age and RDS severity should be investigated further.

The significant decrease in bronchopulmonary dysplasia (BPD) in infants treated initially with NIMV was surprising when taking into account the complexity of causes leading to

REFERENCE

Benefits of nasal intermittent mandatory ventilation for preterms

To the Editor:

We read with interest the report by Kugelman et al that demonstrated that preterm infants with respiratory distress syndrome (RDS) treated initially with nasal intermittent mandatory ventilation (NIMV) needed less mechanical ventilation and had a decreased incidence of bronchopulmonary dysplasia (BPD) compared with preterm infants treated with nasal continuous positive airway pressure (NCPAP).

Observational studies have shown that surfactant administration followed by extubation to NCPAP or NIPPV decreases the need for mechanical ventilation in preterm infants. Kugelman et al reported that surfactant was given as a rescue therapy in their study. This leads us to determine the rate of surfactant use in each group and to evaluate whether surfactant use was higher in the NIMV group.

There was a 50% reduction in the need for mechanical ventilation and a significant decrease in the incidence of BPD (33% vs 5%; P = 0.04) in the very low birth weight (VLBW) infants in the NIMV group. This substantially decreased incidence of BPD is very surprising even when the lower need for mechanical ventilation is taken into account, because BPD is such a complex disorder. However, as the authors point out, the study does not have statistical power for these outcome measures. In addition, the number of infants with birth weight <1000 g in each group was small. It is important to determine whether these ventilatory strategies to decrease mechanical ventilation and BPD would be effective with in the extremely preterm infants, who are more vulnerable.

An important finding was that the VLBW infants in the NIMV group that failed nasal support had significantly
NIMV is safe and is the preferred mode of nasal support for the decreased rate of BPD in the NIMV group could result, at least in part, from the reduced rate of endotracheal ventilation in this group in our study. A trend toward a lower rate of BPD in NIMV compared with NCPAP (but not reaching statistical significance) was reported in studies comparing the 2 modes at the postextubation period.7-9 Yet, as we pointed out, our results in VLBW infants regarding the incidence of endotracheal ventilation and BPD in the NIMV group should be viewed with caution, because our study does not have statistical power for these outcome measures in this group of infants. Furthermore, the number of infants with birth weight <1000 g in our cohort was small.

The reported experience of Meneses et al of a decreased rate of mechanical ventilation in infants supported initially with NIMV, especially in conjunction with surfactant therapy, is interesting and supports our initial findings. However, larger trials and long-term follow-up data are warranted in the target population of infants with birth weight <1500 g to conclude that NIMV is safe and is the preferred mode of nasal support in preterm infants with RDS.

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REFERENCES

The importance of avoiding head flexion in preterm infants

To the Editor:

We were delighted to read the very important article from Salhab et al reporting that the rate of hypoxic events in preterm infants ready for discharge was similar in a car bed and an infant car seat. This concern is not confined to preterm infants; some term infants also have been reported to experience episodes of cyanosis while confined to car seats.2 The key question now is: What factor in these 2 environments compromises respiration in infants compared with simply lying in a cot?

We have shown that when a preterm infant is confined to a car seat, the infant’s head is flexed forward on the neck so that the chin presses on the chest, leading to narrowing of the upper airway.3 This occurs because (as shown in the Figure), unlike in an adult, in an infant, the occiput protrudes behind the spinal line,4 and thus when the infant's body is held firmly on a flat surface, the head must flex forward. We found that modifying the infant car seat with a simple insert to keep the infant’s head upright and in a neutral position on the spine led to an increased upper airway size and a significantly reduced rate of oxygen desaturation.5 We speculate that a limitation of the present car bed design is that although the infant is recumbent, he or she is still being restrained against a flat surface, leading to some degree of forced flexion.

Head flexion was clinically associated with at least one event in the car bed in the report of Salhab et al,1 but we
cannot determine from the data provided how much this mechanism contributed to other events. Have the authors assessed the effect of these environments on infants’ upper airway dimensions?

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REFERENCES


