Profile of children diagnosed with autistic spectrum disorder managed at a tertiary child development unit

Wee Bin Lian^{1,2}, MMed, MRCP, Selina Kah Ying <u>Ho</u>^{1,2}, MMed, MRCP

INTRODUCTION There has been a rising trend in childhood developmental and behavioural disorders (CDABD). This study reports the profile of children with autistic spectrum disorders (ASD) initially referred for evaluation of CDABD. **METHODS** The CDABD database prospectively collected data of all consenting children referred in 2003 to the then Child Development Unit at KK Women's and Children's Hospital. All received medical consultation, followed by further assessments and intervention. Patients were tracked for one year.

RESULTS Among 542 referred children, 32% (n = 170) received a diagnosis of ASD one year after the first consultation. Most were male, with a male to female ratio of 4.5:1. The median age at the first consultation was 41 (19,109) months. The main presenting concern was a delay in the development of speech and language skills in 78% of the children. A significant number had behavioural (63%) and social interaction (34%) issues. Criteria for the diagnosis of ASD according to the Diagnostic Statistical Manual IV-Revised were fulfilled in almost 90%. With the remaining refusing or deferring evaluation, only 74% received a psychological assessment. ASD was assessed to be severe or moderate in 86% of the children. Three-quarters remained on follow-up one year after the first consultation. The majority were referred for either centre- or school-based intervention programmes, with 70% assessed to have improved at the one-year mark. **CONCLUSION** This is the first presentation of local data that aids programme planning and resource allocation. Children with ASD have varied outcomes. It is important to identify and intervene early in order to optimise development and functionality.

Keywords: autistic spectrum disorder, childhood development, childhood developmental and behavioural disorders, speech and language delay, social interaction Singapore Med J 2012; 53(12): 794–800

INTRODUCTION

Recent years have seen a rising trend in and a push toward earlier identification and diagnosis of childhood developmental and behavioural disorders (CDABD). In Singapore, preschoolers with such special needs are generally referred to the Department of Child Development (DCD) at KK Women's and Children's Hospital or the Child Development Unit at National University Hospital, with a smaller number referred to the Child Guidance Clinic, Institute of Mental Health, and the Department of Neonatal and Developmental Medicine, Singapore General Hospital. Other such children might not pass through the public system, but would instead be managed in the private sector.

More than a thousand children are referred to the DCD each year, which was first established as the Developmental Assessment Clinic in 1991 at the Singapore General Hospital. The CDABD database, funded by the SingHealth Cluster Research Fund in 2002,^(1,2) was formulated to facilitate prospective, systemic, standardised and complete data collection of all consenting children seen at the DCD. It was to allow the estimation of the local prevalence and incidence of childhood developmental and behavioural disorders and track the progress of these children, as well as to aid understanding of the utilisation of resources and the impact of services on their outcome.

Autism, also known as autistic spectrum disorder (ASD) or pervasive developmental disorder (PDD), is one of the more well-known among the wide range of CDABDs, with rising prevalence reportedly ranging from an incidence of one in 82 to one in 196, depending on whether the source is multiprofessional or educational in origin.⁽³⁻⁵⁾ Between 2002 to 2006, surveillance across ten United States sites revealed an increase in the average prevalence of 57%.⁽⁴⁾ This is a condition where the outcome is most positive with early diagnosis and appropriate intervention. Available literature has largely been focused on well-developed countries⁽³⁻⁶⁾ where good, and often state-paid, intervention systems are in place. There is limited data from countries such as Singapore, where developmental assessment and intervention facilities are still in a stage of advancement. This is the first report on a cohort of children who presented with varying concerns and who were diagnosed with ASD in a tertiary set-up in Singapore.

METHODS

This report focuses on a cohort of patients evaluated from January 1, 2003 to December 31, 2003. The complete methodology of data collection was detailed in the main CDABD report.⁽²⁾ This was an ethics committee-approved project. All children

¹Department of Neonatal and Developmental Medicine, Singapore General Hospital, ²Department of Child Development, KK Women's and Children's Hospital, Singapore **Correspondence**: Dr Lian Wee Bin, Senior Consultant, Department of Neonatal and Developmental Medicine, Singapore General Hospital, Outram Road, Singapore 169608. lian.wee.bin@sgh.com.sg

Table I. Demography of the cohort (n = 542).

Characteristic	Result
Gender (%)	
Male	81.8
Female	18.2
Race (%)	
Chinese	77.6
Malay	7.6
Indian	10.6
Others	4.1
Birth profile	00.4
Full-term* (%)	89.4
Birth Weight (g) Period of gestation among preterm	3,190 (1,420, 4,370)
infants $(n = 15)$ (w/s)	50 (51, 50)
Birth order (%)	EE O
FIISt	30.9 30 A
Third	8.8
Fourth	2.9
Apgar scores	
At 1 min	9 (3, 10)
At 5 mins	9 (6, 10)
Family profile	
Paternal age at presentation [†] (yrs)	35 (25, 55)
Maternal age at presentation [†] (yrs)	34 (20, 48)
Paternal education – university (%)	34.7
Maternal education – university (%)	28.1
Combined monthly family income (SGD)	\$4,000-\$4,999
Family history (%)	
Autistic spectrum disorder	4.7
Developmental delay	2.6
Speech delay Montal retardation	20.6
Mental retardation	2.4
Presentation profile [†]	07 (45 400)
Referral age/age at Initial	37 (15, 109)
Age at initial consultation th (mths)	/1 (19 109)
Waiting time (mths)	3.8 (0, 15)

*Gestation of at least 37 weeks. [†]Data is presented as median (min,max). **Age at presentation to primary care physician/self-referral. ⁺⁺Age at first consultation at this child development unit.

identified at the first consultation for developmental concerns were screened using parent questionnaires. Basic demographic data, as well as presentation data such as referral patterns, schooling history, childcare patterns, and medical, birth and family histories, were collected.

Diagnostic evaluation data included presenting complaints and assessment of developmental skills according to standards based on the Denver Developmental Screening Test, Singapore,⁽⁷⁾ in the following domains: motor, speech and language, social interaction, play, cognition and adaptive behaviour, as well as atypical developmental features. A clinical diagnosis, based on criteria set by the Diagnostic Statistical Manual IV-Revised (DSM-IVR),⁽⁸⁾ was formulated for each child at the first visit. Each child was tracked for a period of one year, during which investigations and referrals to other medical professionals such as geneticists, otolaryngologists and neurologists were effected, and scaled tests by specific professionals were administered. Definitive diagnoses were thus formulated at the end of one year after the initial consultation based on the DSM-IVR criteria. Management and educational placement of the children were noted.

Cases for this report were selected when the definitive diagnosis at the one year mark after the initial consultation was denoted as ASD, defined by the presence of qualitative impairments in social communication and social interaction in the presence of restricted, repetitive and stereotypic behaviour, interests and activities.^(8,9) The clinical working diagnosis at one year after the initial consultation would be accepted as the definitive diagnosis should a standardised test not be carried out, which is usually due to parental preference, provided that the DSM-IVR criteria of PDD were satisfied.

Generally, for the comparison purpose of this study, if the features of autism were severe enough to hinder the child's compliance for the cognitive assessment, or if the mental development index on the Bayley Scales of Infant Development (or other equivalent scores) fell below 50, the child was deemed to have severe ASD. When the cognitive profile was demonstrated and shown to be consistent with scores that would warrant the child's entrance to mainstream education (as locally determined by a combination of language and cognitive skills, with the latter often determined by an IQ score of \geq 70, and both verbal and nonverbal scores \geq 70), the child was deemed to have high-functioning ASD/Asperger syndrome.

Data collected were entered into a specially customised database programme. Statistical analysis was carried out using the Statistical Package for the Social Sciences for Windows version 16 (SPSS Inc, Chicago, IL, USA). Continuous variables were explored for distribution. The means and medians for continuous data were compared using *t*-tests for normally distributed data, and nonparametric tests (Mann-Whitney U test/Kruskal-Wallis test) for skewed data. Statistical significance for categorical data was explored using the Pearson's chi-square test. Statistical significance was used to compare the means of normally distributed continuous data among groups. Logistic regression was performed to determine the risk factors contributing toward ASD of at least moderate severity.

The definitions of the terminologies used are as follows: (a) normal development – normal history of milestones and development, with normal physical examination; (b) global developmental delay – child < 4 years of age with delays in speech and language domains, and in \geq 1 other developmental domain; (c) ASD – qualitative impairments in social communication and interaction, together with the presence of restricted, repetitive and stereotypic behaviour, interests and activities; (d) attention deficit/hyperactivity disorder – the presence of hyperactivity, inattention and impulsivity presenting prior to seven years of age, of sufficient degree to impair social, academic or occupational functioning, and present for \geq 6 months across \geq 2 environments; (e) speech and language (S&L) disorder/motor delay – delays/ difficulties in these specific developmental domains (inappropriate for age level) not explained by any of the above diagnoses; and











Fig. 3 Bar graph shows distribution by parental education. Upp: upper

(f) learning disability – achievement substantially below the expected, given the child's age, intelligence and appropriate education.

RESULTS

Of the 542 children referred for the assessment of CDABD



 $\ensuremath{\textit{Fig. 4}}$ Venn diagram shows the distribution of languages spoken at home.

concerns in 2003, 170 (32%) were given a diagnosis of ASD one year after consultation. Table I shows the demographics of the cohort. Most of the children were male (81.8%), full-term infants (89.4%) and firstborn (55.9%). The male to female ratio was 4.5:1. While the majority of the children were Chinese, Indians were more common (10.6%) than Malays (7.6%). The majority of the children came from lower to middle-income families (Fig. 1), although about 90% had purchased their own homes. A minority of 3.6% hailed from single-parent families. Parental demographics are shown in Figs. 2 and 3. Fig. 4 depicts the language culture of the children. About 78% spoke English. The care provider patterns are shown in Table II. Parents were directly involved in childcare in the majority of the families. Family history was positive for ASD in eight cases, S&L delay in 35 and mental delay in four of the cohort.

Referrals were made at the median age of 37 (min, max: 15, 109) months with the first evaluation carried out at the median age of 41 (19, 109) months. The median duration of waiting time was of 3.8 (0, 15) months. In the majority of the cases, concerns

Table II. Care provider patterns.

Care provider	Frequency (%)
Parents only	35.9
Parents and grandparents	11.8
Parents and childcare	7.6
Parents and maid	11.1
Parents and babysitter	0.6
Grandparents only	6.5
Grandparents and maid	10.0
Grandparents and childcare	1.7
Childcare only	8.2
Childcare and maid	2.9
Maid only	2.9
Maid and other relatives	0.6

Table III. Presenting concerns.

Presenting concern	Frequency of occurrence (%)	As an isolated concern (%)
Speech and language (S&L)	77.6	22.9
Behavioural (B)	62.9	12.1
Social interaction (SI)	31.1	0.0
S&L, B and SI	18.2	-
S&L and B	14.1	-
S&L and SI	10.0	-

Table IV. Concerns identified at initial evaluation.

Identified concern at evaluation	Frequency (%)
Impaired social communication (delays and/or atypicalities in S&L development)	157 (92.4)
Impaired social interaction, impaired and/ or atypical play patterns, and/or atypical developmental features	151 (88.8)
Atypical developmental features/behaviour	135 (79.4)
Total with combined concerns	133 (78.2)

S&L: speech and language

were raised by parents (93.5%), with contributing concerns from schools (43.5%) and by medical professionals in a small percentage of cases (11.2%). Table III shows the types of presenting concerns. S&L concerns were the main complaints in the majority of cases and were either isolated (23%) or in coexistence with other concerns. No child presented with an isolated concern in the domain of social interaction, but 12% were deemed to have isolated behavioural concerns by the caregivers or referring party. In contrast to the presentation profile, the clinician at the first consultation identified only seven (4.1%) children with isolated S&L delays and three (1.8%) children with isolated social interaction concerns. None had isolated behavioural or motor difficulties. Table IV shows the combination of features at presentation. Almost 90% had identified concerns in the social interaction domain.

Of the 170 diagnosed with ASD, 126 (74%) achieved a definitive diagnosis of ASD. Two had visual impairment that required aids. Only four had recognisable genetic syndromes (Goldenhar syndrome, congenital hydrocephaly, Rubinstein-Taybi syndrome and suspected Rett syndrome). Among those who received a psychological evaluation, this was carried out at

a median age of 42 (19, 112) months. Assuming that diagnosis is defined by the administration of a standardised assessment, the median age at diagnosis was 42 (19, 112) months. By this criteria, the median age at diagnosis was significantly different among those with high-functioning/Asperger-type, moderately severe and severe ASD (p < 0.001), and those with severe ASD were picked up at a younger age (Table V).

At the one-year mark after the initial consultation, ASD was assessed to range from moderately severe to severe in > 85% of the entire cohort as well as among those with a psychological assessment. High-functioning ASD children, generally deemed to be potentially capable of mainstream ability, comprised 14% (10% among those who received a psychological assessment) of our study cohort. Logistic regression revealed that the only contributory factor for the diagnosis of moderate to severe ASD (as opposed to a high functioning ASD/Asperger syndrome profile) was a younger referral age. The younger the child at presentation, the higher the likelihood of a diagnosis of at least a moderately severe variant of ASD (odds ratio 0.959; confidence interval 0.933-0.986; p = 0.003). Factors included for logistic regression were gender, ethnicity (non-Chinese), preterm status, birth order, paternal age, maternal age, birth weight, a low Apgar score of < 7 at 5 minutes, gestation and a family history of developmental disorders.

At first consultation, 26 cases within the entire cohort were not given a clinical diagnosis of ASD. The majority of these (n = 15) were deemed to have S&L delay with or without atypicalities, with five deemed to have global developmental delay, two with attention deficit/hyperactive disorder, two with cognitive delay and two with behavioural disorders.

The allied healthcare team that was most taxed for service provision was the psychological team (72.4%), which provided assessment with administration of standardised tests as well as intervention and implementation of ASD-specific programmes such as picture exchange communication system, structured teaching and Social Stories. S&L and occupational therapists also received significant referrals at 61.8% and 56.5%, respectively. These team members provided assessments of needs and profiles as well as intervention. A small number of children required behavioural intervention (5.3%) and physiotherapy (3.5%).

Eight children were discharged and another eight were transferred. A total of 128 (75.3%) remained on follow-up, with a defaulter rate of 14.7%. In general, 70% of the children were deemed to have improved after one year. Referral for special education placement was recommended in 47%. At the oneyear mark after initial evaluation, only 7.1% were placed while 4.7% refused placement. The rest were either on the wait-list or the referral process was still in progress. The referrals then were predominantly to the Structured Teaching for the Exceptional Pupils (STEP) programme located at Rainbow Special School. Agency referral for early intervention (TOUCH, Autism Association, Singapore, or Autism Resource Centre) were made in 18.8% of cases.

Table V. Timing of presentation according to severity of condition.

	Total	Group			p-value
		High functioning ASD/ Asperger syndrome	Moderately- severe ASD	Severe ASD	
No. (%) of entire cohort	170 (100)	24 (14)	69 (41)	77 (45)	-
Age of entire cohort at time of referral (mths)	37 (15, 109)	43 (21, 78)	39 (15, 74)	32 (18, 109)	p < 0.001
Age of entire cohort at 1st evaluation (mths)	41 (19, 109)	48 (32, 81)	42 (21, 78)	37 (19, 109)	p < 0.001
No. (%) of patients with only clinical diagnosis at 1st evaluation	44 (100)	11 (25)	23 (52)	10 (23)	-
Age of patients with only clinical diagnosis at 1st evaluation (mths)	42 (20, 74)	45 (35, 71)	40 (21, 74)	40 (20, 74)	0.201
No. (%) of patients with definitive diagnosis	126 (100)	13 (10)	46 (37)	67 (53)	-
Age of patients with definitive diagnosis (mths)	42 (19, 112)	52 (31, 83)	48 (31, 80)	38 (19, 112)	p < 0.001

Note: Age of patients is presented as median (min,max).

ASD: autistic spectrum disorder

DISCUSSION

The CDABD database is the first such database in the region. Its importance lies in being able to provide profile information on all children presenting to the largest national tertiary centre, which essentially sees preschool children with developmental concerns. There has been little forthcoming data from Asian countries, whereas ASD has been well described in Western countries, although a recent Chinese paper quoted the prevalence of ASD to be 0.9% –2.6%.⁽¹⁰⁾ Despite being among the better known and more common CDABD, data on ASD in Singapore is limited and its prevalence in the country is still unclear. Although support services have improved over the last few years, the seemingly increasing number of children diagnosed with ASD has resulted in an increase in the demand for such services. This study, which is the first local report on ASD children, is thus timely as the government has sought to increase the community and school support services for ASD in recent years.

As seen in this report (consistent with Western figures), ASD knows no age, racial or economic barriers.^(3,4,6) In this study, the median ages of presentation and initial consultation leading to diagnosis were slightly younger than that described in other studies, which ranged from 45 months in Williams et al's study⁽⁵⁾ to 58 months as reported by Rhoades et al.⁽¹¹⁾ Notably, the definition of time of diagnosis may be different, be it by clinical assessment based on DSM-IV criteria⁽⁷⁾ versus the administration of standardised tests, for example, Autism Diagnostic Interview-Revised (ADI-R)⁽¹²⁾ and Autism Diagnostic Observation Schedule (ADOS)⁽¹³⁾ may have different definitions.

Both the care provider and parental profile did not form any clear patterns. In his 1943 paper, Leo Kanner had called attention to what came to be known as the 'refrigerator mother' theory of autism, where the genuine lack of maternal warmth was deemed to be a causative factor.⁽¹⁴⁻¹⁶⁾ This was unfortunately further propagated by Bruno Bettleheim.⁽¹⁷⁾ This propagation continued till it was directly attacked by Rimland in 1964.⁽¹⁸⁾ Subsequent studies

indicated that there was a huge genetic component. This was reviewed by Muhle et al⁽¹⁹⁾ in 2004, and in a recent Chinese paper by Xu et al.⁽¹⁰⁾

Interestingly, contrary to Russell et al's theory that mothers of firstborn children were significantly less likely to have children diagnosed with ASD,⁽²⁰⁾ this study reflected that more than half were firstborns. The male to female ratio in our study was consistent with the report by Renty et al,⁽²¹⁾ although most epidemiologic studies reported a male to female ratio of 3:1.^(4,20) The highest male to female ratio of 6.8:1 was reported by Williams et al.⁽²²⁾

Consistent with reports from foreign centres, young children with ASD most frequently present with S&L difficulties.^(3,4,9) However, few would come forward with the triad of impairments that is classical of ASD. It is only with careful history taking and experienced, detailed clinical observation that more subtle differences in social interaction/play profiles and atypical behavioural patterns emerge. Even then, some may be missed if long-term follow-up is not carried out, as seen by the 22% of subsequently diagnosed children who, at first consultation, did not present with the classic triad. Follow-up cannot be overemphasised. Hence, the disorder burden increases over each new year with new cases added to existing ones.

The severity of ASD or PDD in any child has often been difficult to determine. For the purpose of this study, the cognitive profile was taken into account in relation to the presentation. It appeared that the more severe the profile, the more likely that the diagnosis would be picked up earlier. It must be kept in mind that people look at severity in various different ways. The more obvious the traits of autism, the more severe the autism is deemed to be. The more atypical the features, which may mean exceptional skills (better skilled than the typical individual), the more severe the degree of autism is deemed to be. There is at present no instrument to measure the degree of severity. ADI-R⁽¹²⁾ and ADOS⁽¹³⁾ are nowadays considered standardised scales tests to augment the diagnosis of ASD. Although they were not developed

to measure the severity of ASD, researchers have however more recently been looking at using the raw scores from these standardised tests as a guide.^(23,24) More studies should be done to look at the feasibility of using these scores as standardised measures of the severity of ASD, and if found suitable, there would be meaningful comparison for international collaboration.

Service utilisation is an ongoing load on existing resources. This has been recognised and significant changes have already been made to the system with the implementation of the nationwide EIPIC (Early Intervention Programme for Infants and Children) centres. Now, ASD children can be referred at first consultation for EIPIC in ASD-specific programmes while awaiting further assessment. EIPIC, which should occur separately but concurrently with an integrated school programme, provides regular and intensive intervention in a cost-effective way for local children aged 0-6 years of age. A reassessment is often called at the age of six years for long-term educational placement. Children recognised as requiring more intensive intervention during those early years will be referred to EIPIC, whereas those deemed to require some, though not as intensive, intervention will then be referred for intervention within the hospital or to community support services, such as the Society for the Physically Handicapped. Parents who are financially able might choose to tap private intervention services due to logistics and time constraints.

Regardless of intervention and placement, children identified to be at risk for developmental and learning disorders at a young age will require close follow-up and serial tracking into their school-going years. Therefore, with earlier identification and intervention, more children with ASD can be assisted toward functionality and be able to contribute to society, although some degree of educational support may be required in the bulk of ASD children. Primary schools in Singapore now have the services of counsellors, allied educators and educational psychologists supported by the Ministry of Education, and are better equipped to support children with ASD who are cognitively able to access mainstream education. Much still needs to be done to provide appropriate training for all teachers, who would at some point in their teaching careers find themselves having to manage and support special needs children.

It would be useful for the children in this study to be further tracked into their school-going years. This is presently ongoing and the outcomes can be further measured. Databases such as the CDABD are therefore helpful in facilitating long-term tracking of patients with developmental conditions, which are often lifelong in nature.

ACKNOWLEDGEMENT

The authors would like to acknowledge the SingHealth Cluster Research Funding 2003, Ministry of Health, for the funding of this study.

REFERENCES

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008; 371:75-84.

- 2. Lemons JA, Bauer CR, Oh W, et al. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics 2001; 107:E1.
- Ford GW, Doyle LW, Davis NM, Callanan C. Very low birth weight and growth into adolescence. Arch Pediatr Adolesc Med 2000; 154:778-84.
- 4. Hack M, Merkatz IR, McGrath SK, Jones PK, Fanaroff AA. Catch-up growth in very-low-birth-weight infants. Clinical correlates. Am J Dis Child 1984; 138:370-5.
- 5. Hack M, Fanaroff AA. The outcome of growth failure associated with preterm birth. Clin Obstet Gynecol 1984; 27:647-63.
- 6. Hack M, Schluchter M, Cartar L, et al. Growth of very low birth weight infants to age 20 years. Pediatrics 2003; 112 (pt 1):30-8.
- Kelleher KJ, Casey PH, Bradley RH, et al. Risk factors and outcomes for failure to thrive in low birth weight preterm infants. Pediatrics 1993; 91:941-8.
- Olsen IE, Richardson DK, Schmid CH, Ausman LM, Dwyer JT. Intersite differences in weight growth velocity of extremely premature infants. Pediatrics 2002; 110:1125-32.
- 9. Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. Pediatrics 1999; 104 (pt 1):280-9.
- Datar A, Jacknowitz A. Birth weight effects on children's mental, motor, and physical development: evidence from twins data. Matern Child Health J 2009; 13:780-94.
- 11. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001; 107:270-3.
- 12. Koo WW, Hockman EM. Posthospital discharge feeding for preterm infants: effects of standard compared with enriched milk formula on growth, bone mass, and body composition. Am J Clin Nutr 2006; 84:1357-64.
- 13. Cooke R. Postnatal growth in preterm infants: have we got it right? J Perinatol 2005; 25 (Suppl 2):12-4.
- 14. Ehrenkranz RA. Growth outcomes of very low-birth weight infants in the newborn intensive care unit. Clin Perinatol 2000; 27:325-45.
- 15. Barker DJ. Fetal origins of coronary heart disease. BMJ 1995; 311:171-4.
- 16. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986; 1:1077-81.
- Williams SP, Durbin GM, Morgan ME, Booth IW. Catch up growth and pancreatic function in growth retarded neonates. Arch Dis Child Fetal Neonatal Ed 1995; 73:F158-61.
- Horta BL, Gigante DP, Osmond C, Barros FC, Victora CG. Intergenerational effect of weight gain in childhood on offspring birthweight. Int J Epidemiol 2009; 38:724-32.
- 19. Das UN. Pathophysiology of metabolic syndrome X and its links to the perinatal period. Nutrition 2005; 21:762-73.
- Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med 2005; 353:1802-9.
- 21. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? Lancet 2004; 363:1642-5.
- 22. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ 1989 4; 298:564-7.
- 23. Barker DJ. The malnourished baby and infant. Br Med Bull 2001; 60:69-88.
- Dodrill P, Cleghorn G, Donovan T, Davies P. Growth patterns in preterm infants born appropriate for gestational age. J Paediatr Child Health 2008; 44:332-7.
- 25. Lucas A, Fewtrell MS, Cole TJ. Fetal origins of adult disease-the hypothesis revisited. BMJ 1999; 319:245-9.
- Forsén T, Eriksson JG, Tuomilehto J, Osmond C, Barker DJ. Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. BMJ 1999; 319:1403-7.
- 27. Law C. Adult obesity and growth in childhood. BMJ 2001; 323:1320-1.
- Martorell R, Stein AD, Schroeder DG. Early nutrition and later adiposity. J Nutr 2001; 131:874S-880S.
- 29. Cooke RW, Foulder-Hughes L. Growth impairment in the very preterm and cognitive and motor performance at 7 years. Arch Dis Child 2003; 88:482-7.
- 30. WHO Child Growth Standards: Growth velocity based on weight, length and head circumference: Methods and development [online]. Available at: www.who.int/childgrowth/standards/velocity/tr3chap_2.pdf. Accessed September 30, 2009.
- Hu YM, Jiang ZF. Zhu Futang Parctice of pediatrics. 7th ed. Beijing: People's Medical Publishing House, 2006.
- 32. The Division of Maternal and Child Health and Community Health of the

People's Republic of China, Capital Institute of Pediatrics, Coordinating Study Group of Nine Cities on the Physical Growth and Development of Children, eds. Growth standards and growth charts for Chinese Children: Children's physical development and nutrition assessment software. Shanghai: The Second Military Medical University Press, 2009.

- 33. Santos IS, Matijasevich A, Domingues MR, et al. Late preterm birth is a risk factor for growth faltering in early childhood: a cohort study. BMC Pediatr 2009; 9:71.
- 34. Rah JH, Shamim AA, Arju UT, et al. Difference in ponderal growth and body composition among pregnant vs. never-pregnant adolescents varies by birth outcomes. Matern Child Nutr 2010; 6:27-37.
- 35. Sices L, Wilson-Costello D, Minich N, Friedman H, Hack M. Postdischarge growth failure among extremely low birth weight infants: Correlates and consequences. Paediatr Child Health 2007; 12:22-8.
- Madden J, Kobaly K, Minich NM, et al. Improved weight attainment of extremely low-gestational-age infants with bronchopulmonary dysplasia. J Perinatol 2010; 30:103-11.
- 37. Knops NB, Sneeuw KC, Brand R, et al. Catch-up growth up to ten years of age in children born very preterm or with very low birth weight. BMC Pediatr 2005; 5:26.
- Belfort MB, Martin CR, Smith VC, Gillman MW, McCormick MC. Infant weight gain and school-age blood pressure and cognition in former preterm infants. Pediatrics 2010; 125:e1419-26.
- 39. Franz AR, Pohlandt F, Bode H, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics 2009; 123:e101-9.
- 40. Sun XJ, Yu XT, Wang DH, Research Group for the Nutrition of Premature

Infants in China. Growth assessment with z score of weight for age in premature infants during hospital stay. Chin J Neonatal 2010; 25:263-7. Chinese.

- Powers GC, Ramamurthy R, Schoolfield J, Matula K. Postdischarge growth and development in a predominantly Hispanic, very low birth weight population. Pediatrics 2008; 122:1258-65.
- Sullivan MC, McGrath MM, Hawes K, Lester BM. Growth trajectories of preterm infants: birth to 12 years. J Pediatr Health Care 2008; 22:83-93.
- 43. Saigal S, Stoskopf BL, Streiner DL, Burrows E. Physical growth and current health status of infants who were of extremely low birth weight and controls at adolescence. Pediatrics 2001; 108:407-15.
- 44. Morley R, Brooke OG, Cole TJ, Powell R, Lucas A. Birthweight ratio and outcome in preterm infants. Arch Dis Child 1990; 65(1 Spec No):30-4.
- Martin CR, Brown YF, Ehrenkranz RA, et al. Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics 2009; 124:649-57.
- 46. Radmacher PG, Looney SW, Rafail ST, Adamkin DH. Prediction of extrauterine growth retardation (EUGR) in VVLBW infants. J Perinatol 2003; 23:392-5.
- 47. Wood NS, Costeloe K, Gibson AT, et al. The EPICure study: growth and associated problems in children born at 25 weeks of gestational age or less. Arch Dis Child Fetal Neonatal Ed 2003; 88:F492-500.
- 48. Ehrenkranz RA, Dusick AM, Vohr BR, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006; 117:1253-61.
- 49. Ru XF, Feng Q, Wang Y, et al. [Dynamic evaluation on body weight gain in premature infants and its significance]. Zhonghua Er Ke Za Zhi 2010; 48:661-7. Chinese.

