

Hypertension Screening Using Blood Pressure to Height Ratio



WHAT'S KNOWN ON THIS SUBJECT: The definition of hypertension in children is complex because of the age-, gender-, and height-specific blood pressure algorithm. Blood pressure to height ratio was reported to easily identify hypertension in Chinese children living in a local area (Hebei Province).



WHAT THIS STUDY ADDS: Blood pressure to height ratio index is simple and accurate for screening for prehypertension and hypertension in Chinese children aged 6 to 17 years and can be used for early screening or treating Chinese children with hypertension.

abstract



OBJECTIVES: The definition of hypertension in children is too complex to be used by medical professionals and children and their parents because of the age-, gender-, and height-specific blood pressure (BP) algorithm. The aim of this study was to simplify the pediatric BP percentile references using BP to height ratio (BPHR, equal to BP/height) for screening for prehypertension and hypertension in Chinese children.

METHODS: Data were obtained from the China Health and Nutrition Survey, which was conducted from 1991 to 2009 and included 11 661 children aged 6 to 17 years with complete data on age, gender, height, and BP values. Receiver operating characteristic curve analysis was performed to assess the performance of systolic BPHR (SBPHR) and diastolic BPHR (DBPHR) for screening for pediatric prehypertension and hypertension.

RESULTS: The optimal thresholds for defining prehypertension were 0.81 in children aged 6 to 11 years and 0.70 in adolescents aged 12 to 17 years for SBPHR and 0.52 in children and 0.46 in adolescents for DBPHR, respectively. The corresponding values for hypertension were 0.84, 0.78, 0.55, and 0.50, respectively. The negative predictive values were much higher (all $\geq 99\%$) for prehypertension and hypertension, although the positive predictive values were relatively lower, ranging from 13% to 75%.

CONCLUSIONS: BPHR index is simple and accurate for screening for prehypertension and hypertension in Chinese children aged 6 to 17 years and can be used for early screening or treating Chinese children with hypertension. *Pediatrics* 2014;134:e106–e111

AUTHORS: Bo Xi, MD,^a Meixian Zhang, MD,^{b,c} Tao Zhang, MD,^a Yajun Liang, MD,^{d,e} Shuangshuang Li, MS,^a and Lyn M. Steffen, PhD^f

^aDepartment of Epidemiology and Health Statistics School of Public Health, Shandong University, Jinan, China; ^bDepartment of Epidemiology, Capital Institute of Pediatrics, Beijing, China; ^cGraduate School, Peking Union Medical College, Beijing, China; ^dSchool of Public Health, Jining Medical University, Jining, China; ^eAging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet–Stockholm University, Stockholm, Sweden; ^fDivision of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis

KEY WORDS

blood pressure to height ratio, high blood pressure, children, diagnostic criteria

ABBREVIATIONS

AUC—area under the curve
BP—blood pressure
BPHR—blood pressure to height ratio
CHNS—China Health and Nutrition Survey
CI—confidence interval
CVD—cardiovascular disease
DBP—diastolic blood pressure
DBPHR—diastolic blood pressure to height ratio
NPV—negative predictive value
PPV—positive predictive value
SBP—systolic blood pressure
SBPHR—systolic blood pressure to height ratio

(Continued on last page)

The prevalence of hypertension in children is increasing in China.¹ Target organ damage, including left ventricular hypertrophy and carotid intimal medial thickness, has been reported in hypertensive children.² In addition, it is well established that childhood hypertension tracks into adulthood,³ which increases the future risk of cardiovascular disease (CVD).⁴ Therefore, it is important to identify prehypertension and hypertension in childhood to prevent CVD in early adulthood.

In 2004, the US National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents proposed the fourth report on the diagnosis, evaluation, and treatment of high blood pressure (BP) in children and adolescents.⁵ This report defined pediatric hypertension as systolic/diastolic blood pressure (SBP/DBP) above the 95th percentile specific to age, gender, and height.⁵ These diagnostic criteria are widely used in epidemiologic surveys and clinical practice. In China, 2 diagnostic criteria for childhood hypertension have been established recently, which also used the similar BP algorithm.^{6,7} This algorithm is too complex to be applied in clinical practice, and it is even more difficult for use by non-medical professionals or children and their parents or guardians. In addition, hypertension in children is usually underdiagnosed in the outpatient clinics, mainly because of the complexity of the BP algorithm.⁸ Therefore, a simple and accurate screening method to identify childhood hypertension is urgently needed. In 2011, Lu et al⁹ first reported that BP to height ratio (BPHR) can easily and accurately identify hypertension in Chinese children, and they also proposed optimal cutoffs of the BPHR index based on their study population. However, this study was based on only 3136 adolescents aged 13 to 17 years living in 1 local region (ie, Hebei

Province) of China, and the established thresholds may not be suitable for children living in other regions of China. In addition, the BPHR index was not developed to identify prehypertension in Chinese children. To overcome these limitations, we aimed to evaluate the feasibility and accuracy of the BPHR index and establish the optimal thresholds for prehypertension and hypertension among a large national representative population of Chinese children aged 6 to 17 years enrolled in the China Health and Nutrition Survey (CHNS).

METHODS

Study Design and Subjects

The CHNS is a large-scale, national, successive cross-sectional survey that was designed to explore how the health and nutritional status of the Chinese population has been affected by social and economic changes.¹⁰ Clusters of adults and children were randomly selected (the clusters of households were selected, and then all people living in the household were asked to participate) from 9 provinces (Liaoning, Heilongjiang, Jiangsu, Shandong, Henan, Hubei, Hunan, Guangxi, and Guizhou). A total of 15 492 children and adolescents aged 6 to 17 years were surveyed. However, 3831 subjects were excluded because of missing data, including SBP, DBP, or height ($n = 3464$), or <3 BP measurements ($n = 367$). Finally, a total of 11 661 children and adolescents aged 6 to 17 years with complete data on age, gender, height, SBP, and DBP values from 7 survey periods (1991, 1993, 1997, 2000, 2004, 2006, 2009) were included in the final analyses. The overall response rate was 75.3%. There were no differences in the percentage of gender (percentage male: 52.3% vs 54.8%) and mean age (12.0 ± 2.8 years vs. 11.9 ± 3.3 years) between the 11 661 included subjects and 3831 excluded ones. All children and their parents provided written informed consent, and the study was approved by

the institutional review boards from the University of North Carolina at Chapel Hill and the National Institute for Nutrition and Food Safety, China Center for Disease Control and Prevention.

Measurements

BP was measured by trained examiners using a mercury sphygmomanometer according to a standard protocol.¹¹ All BP measurements were taken by trained and certified examiners using a sphygmomanometer after children and adolescents rested quietly while sitting for 5 minutes. Appropriate BP cuff sizes were used for participants, based on measurement of midarm circumference. SBP was determined as the first Korotkoff sound (K1), and DBP was measured as the fifth Korotkoff sound (K5). Three BP values were measured at 1 visit, and the last 2 of 3 readings were averaged as the SBP and DBP values in this study. Height was measured to the nearest 0.1 cm without shoes by using a portable stadiometer. SBPHR was calculated as SBP (mm Hg)/height (cm), and DBPHR was calculated as DBP (mm Hg)/height (cm).

Definition

The definitions of prehypertension and hypertension followed the age-, gender-, and height-specific BP percentile algorithm recommended by US National High Blood Pressure Education Program Working Group.⁵ Hypertension (stages 1 and 2) was defined as SBP/DBP ≥ 95 th percentile. Severe hypertension (stage 2) was defined as SBP/DBP ≥ 99 th percentile + 5 mm Hg. Prehypertension was defined as SBP/DBP ≥ 90 th but < 95 th percentile or SBP/DBP $\geq 120/80$ mm Hg. These BP references were used as the gold standard.

Statistical Analysis

Quantitative variables are expressed as mean \pm SD, and categorical data are

expressed as numbers and percentages. The area under the curve (AUC) and 95% confidence interval (CI) for the BPHR index, calculated by receiver operator characteristic curve analysis, were used to assess the discriminatory power of a test. The AUC typically ranges from 0.5 to 1, representing a test that has poor discrimination to 1 that has perfect discrimination. An AUC <0.5 indicates that the test is inversely associated with the outcome (eg, the criteria for “normal” and “abnormal” should be reversed). To determine the optimal thresholds of the BPHR index for identifying elevated BP, the values corresponding to the maximum of Youden’s index (sensitivity + specificity – 1) were selected.¹² Prehypertension and hypertension were then redefined by the determined optimal thresholds of the BPHR index and were used as predictive variables to compare with the gold standard. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and AUC (95% CI) were calculated to assess the performance of determined optimal thresholds. SPSS version 13.0 (IBM SPSS Statistics, IBM Corporation) was used for data analyses. A *P* < .05 was considered statistically significant.

RESULTS

A total of 11 661 children and adolescents were included in the current study, including 5882 children (3119 boys and 2763 girls) aged 6 to 11 years and 5779 adolescents (2983 boys and 2796 girls) aged 12 to 17 years. The prevalences of prehypertension and hypertension using the gold standard (the fourth US BP references) were 8.5% and 4.4%, respectively. Table 1 shows the characteristics of the study population, including SBP, DBP, height, systolic BPHR (SBPHR), and diastolic BPHR (DBPHR) by age and gender.

TABLE 1 Characteristics of Chinese Children by Age and Gender, *n* = 11 661

	<i>N</i> (%)	SBP (mm Hg)	DBP (mm Hg)	Height (cm)	SBPHR	DBPHR
6–11 y						
Boys	3119 (53.0)	92.01 ± 11.65	60.65 ± 9.18	130.30 ± 10.61	.71 ± .09	.47 ± .07
Girls	2763 (47.0)	91.72 ± 11.81	60.26 ± 9.38	130.30 ± 11.56	.71 ± .10	.46 ± .07
Total	5882 (100)	91.87 ± 11.73	60.47 ± 9.28	130.30 ± 11.07	.71 ± .09	.47 ± .07
12–17 y						
Boys	2983 (51.6)	103.02 ± 12.39	67.19 ± 9.16	156.58 ± 11.47	.66 ± .07	.43 ± .06
Girls	2796 (48.4)	101.54 ± 11.35	66.77 ± 8.57	152.68 ± 8.03	.67 ± .07	.44 ± .05
Total	5779 (100)	102.30 ± 11.92	66.99 ± 8.88	154.70 ± 10.15	.66 ± .07	.43 ± .06

Quantitative variables were expressed as mean ± SD.

Selection of optimal thresholds of SBPHR for identifying elevated SBP is shown in Table 2. Because the optimal thresholds of SBPHR between boys and girls were very similar in each subgroup of elevated SBP, results were reported for all individuals in each subgroup. Among children aged 6 to 11 years, 0.81 was selected as an optimal threshold for SBP ≥90th percentile but <95th percentile, 0.84 was selected as an optimal threshold for SBP ≥95th percentile, and 0.90 was selected as

an optimal threshold for SBP ≥99th percentile + 5 mm Hg. Accordingly, the values for adolescents aged 12 to 17 years were 0.70, 0.78, and 0.86, respectively.

Selection of optimal thresholds of DBPHR for elevated DBP is shown in Table 3. Among children aged 6 to 11 years, 0.52 was the optimal threshold for DBP ≥90th percentile but <95th percentile, 0.55 was the optimal threshold for DBP ≥95th percentile, and 0.64 was the optimal threshold for

TABLE 2 Selection of Optimal Thresholds of SBPHR for Identifying Elevated SBP in Chinese Children Aged 6–17 y, *n* = 11 661

	Threshold	Sensitivity	Specificity	AUC (95% CI)
90th percentile ≥ SBP < 95th percentile				
6–11 y				
Boys	.82	0.846	0.932	0.958 (0.938–0.977)
Girls	.80	0.900	0.860	0.947 (0.927–0.967)
Total	.81	0.863	0.897	0.953 (0.939–0.967)
12–17 y				
Boys	.69	0.926	0.782	0.907 (0.896–0.919)
Girls	.72	0.967	0.879	0.964 (0.957–0.972)
Total	.70	0.911	0.801	0.921 (0.912–0.930)
SBP ≥ 95th percentile				
6–11 y				
Boys	.85	1.000	0.951	0.990 (0.987–0.994)
Girls	.84	0.982	0.937	0.989 (0.983–0.994)
Total	.84	0.992	0.941	0.990 (0.987–0.993)
12–17 y				
Boys	.77	1.000	0.954	0.987 (0.982–0.992)
Girls	.78	1.000	0.957	0.993 (0.989–0.996)
Total	.78	1.000	0.952	0.990 (0.987–0.993)
SBP > 99th percentile + 5 mm Hg				
6–11 y				
Boys	.90	1.000	0.983	0.997 (0.993–1.002)
Girls	.92	1.000	0.992	0.999 (0.997–1.000)
Total	.90	1.000	0.983	0.998 (0.996–1.000)
12–17 y				
Boys	.87	1.000	1.000	1.000 (1.000–1.000)
Girls	.86	1.000	0.999	1.000 (0.999–1.000)
Total	.86	1.000	0.999	1.000 (1.000–1.000)

TABLE 3 Selection of Optimal Thresholds of DBPHR for Identifying Elevated DBP in Chinese Children Aged 6–17 y, *n* = 11 661

	Threshold	Sensitivity	Specificity	AUC (95% CI)
90th percentile \geq DBP < 95th percentile				
6–11 y				
Boys	.52	0.935	0.868	0.956 (0.944–0.967)
Girls	.52	0.945	0.829	0.945 (0.931–0.959)
Total	.52	0.935	0.847	0.951 (0.942–0.960)
12–17 y				
Boys	.45	0.974	0.794	0.937 (0.927–0.946)
Girls	.48	0.966	0.901	0.972 (0.967–0.978)
Total	.46	0.943	0.825	0.946 (0.940–0.953)
DBP \geq 95th percentile				
6–11 y				
Boys	.56	1.000	0.939	0.989 (0.985–0.992)
Girls	.55	0.982	0.903	0.973 (0.966–0.981)
Total	.55	0.967	0.921	0.981 (0.977–0.985)
12–17 y				
Boys	.49	0.982	0.901	0.979 (0.973–0.985)
Girls	.51	0.986	0.937	0.989 (0.984–0.994)
Total	.50	0.946	0.930	0.981 (0.976–0.985)
DBP > 99th percentile + 5 mm Hg				
6–11 y				
Boys	.64	1.000	0.998	1.000 (1.000–1.000)
Girls	.64	1.000	0.995	0.998 (0.996–1.000)
Total	.64	1.000	0.997	0.999 (0.998–1.000)
12–17 y				
Boys	.58	1.000	1.000	1.000 (1.000–1.000)
Girls	.59	1.000	0.999	1.000 (1.000–1.000)
Total	.58	1.000	0.999	1.000 (1.000–1.000)

DBP \geq 99th percentile + 5 mm Hg. Accordingly, the values for adolescents aged 12 to 17 years were 0.46, 0.50, and 0.58, respectively.

Prehypertension, hypertension (stages 1 and 2), and severe hypertension (stage 2) were redefined using the optimal thresholds of BPHR index and compared with the gold standard (Table 4). Performance of the optimal thresholds of the SBPHR/DBPHR index for detecting hypertension and severe hypertension was better than that for

detecting prehypertension based on sensitivity, specificity, PPV, NPV, and AUC (95% CI), regardless of age group. The NPVs were much higher (all \geq 99%) for prehypertension and hypertension, although the PPVs were lower (ranging from 13% to 75%).

DISCUSSION

To our knowledge, our study is the first establishing the optimal thresholds of the BPHR index for detecting prehypertension, and it confirms that this

index is suitable for identifying hypertension in a large national sample of Chinese school-aged children (*n* > 10 000). Our results suggest that the BPHR index is a simple and accurate index for screening for prehypertension and hypertension in Chinese youth.

Prevention of childhood hypertension is feasible and effective to reduce the risk of developing hypertension or slowing down the progression to hypertension and CVD during adulthood. Therefore, early identification of pediatric prehypertension and hypertension is important. The gender, age, and height percentile–specific BP references have been widely accepted as the main tool for diagnosis of pediatric hypertension.^{5–7} However, this method is too complicated and time-consuming to be used by clinicians, nonclinical health professionals, and children or their parents or guardians. In addition, the complicated tables often lead to undiagnosed hypertension in pediatric population.⁸ Thus, the need for a simple, inexpensive, and acceptable tool for detecting hypertension in children was urgent. The BPHR index was suggested as a simple and accurate index for identifying childhood hypertension in a local area of China⁹ and has been replicated in Italian,¹³ Nigerian,¹⁴ US,¹⁵ and Iranian children.¹⁶ The BPHR index, standardized for height, is strongly and positively associated with SBP and DBP but is not related to

TABLE 4 Performance of Optimal Thresholds of SBPHR/DBPHR for Identifying Prehypertension and Hypertension in Chinese Children Aged 6–17 y, *n* = 11 661

	Threshold (SBPHR/DBPHR)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	AUC (95% CI)
Prehypertension						
6–11 y						
	.81/.52	0.783	0.885	0.216	0.990	0.834 (0.784–0.883)
12–17 y						
	.70/.46	0.938	0.726	0.342	0.987	0.832 (0.817–0.846)
Hypertension (stages 1 and 2)						
6–11 y						
	.84/.55	0.982	0.894	0.309	0.999	0.939 (0.928–0.950)
12–17 y						
	.78/.50	0.959	0.895	0.286	0.998	0.927 (0.912–0.942)
Severe hypertension (stage 2)						
6–11 y						
	.90/.64	1.000	0.980	0.131	1.000	0.990 (0.987–0.994)
12–17 y						
	.86/.58	1.000	0.999	0.751	1.000	0.999 (0.999–1.000)

age, so it is not dependent on height or age.⁹ Our results confirmed the previous findings and established nationwide cutoffs for the BPHR index for detecting hypertension in Chinese children.

The AUC of 0.93 to 0.99 suggested the robust discriminatory performance of the BPHR index to identify hypertension in Chinese children, but the AUC of 0.83 in both age groups was less satisfactory for identifying prehypertension. The much higher NPVs of optimal cutoffs of the BPHR indicated that this method is unlikely to omit people with prehypertension or hypertension. The low PPVs of optimal cutoffs showed that many people with normal blood pressure would be misclassified as having prehypertension, or those with prehypertension would be misclassified as having hypertension. Thus, the BPHR index cannot be used to replace the existing age-, gender-, and height-specific BP percentiles for diagnosing elevated BP, but it can be easily used to screen people at high risk of pre-

hypertension or hypertension in large-scale epidemiologic surveys or mobile clinic checkups or by children and their parents or guardians. The screened children with potential hypertension should be assessed by medical professionals.

The strength of this study includes the large, nationally representative sample of children with wide age range; thus, our conclusions can be credibly applied to all Chinese school-aged children. In addition, the standardized BP protocols were used in the continuous surveys, and health care workers were trained and certified to take BP measurements for each survey. However, several limitations should be noted. First, even though the study population is a nationally representative sample of Chinese children, the results may not be generalizable to other populations. Second, only 9 of 31 provinces of China were surveyed. However, they were selected based on their economic and social representativeness of China.¹⁰

CONCLUSIONS

The BPHR is a simple and accurate index for screening for prehypertension and hypertension in Chinese children aged 6 to 17 years. It can prevent the underdiagnosis of childhood hypertension and can be used to screen children before the development of pediatric prehypertension and hypertension and to manage hypertension in Chinese children, ultimately reducing the risk of developing hypertension and related CVD in adulthood.

ACKNOWLEDGMENTS

This research uses data from CHNS. We thank the National Institute of Nutrition and Food Safety, China Center for Disease Control and Prevention, the Carolina Population Center, the University of North Carolina at Chapel Hill, and the Fogarty International Center. We also thank the National Institutes of Health for financial support for the CHNS data collection and analysis files from 1989 to 2011 and future surveys, and the China–Japan Friendship Hospital, Ministry of Health, for support for CHNS 2009.

REFERENCES

1. Xi B, Liang Y, Mi J. Hypertension trends in Chinese children in the national surveys, 1993 to 2009. *Int J Cardiol*. 2013;165(3):577–579
2. Stergiou GS, Giovas PP, Kollias A, et al. Relationship of home blood pressure with target-organ damage in children and adolescents. *Hypertens Res*. 2011;34(5):640–644
3. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation*. 2008;117(25):3171–3180
4. Rapsomaniki E, Shah A, Perel P, et al. Prognostic models for stable coronary artery disease based on electronic health record cohort of 102 023 patients. *Eur Heart J*. 2013;35(13):844–852.
5. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents. *Pediatrics*. 2004;114(suppl 2):555–576
6. Mi J, Wang TY, Meng LH, et al. Development of blood pressure reference standards for Chinese children and adolescents. *Chin J Evid Based Pediatr*. 2010;5(1):4–14
7. Yan W, Liu F, Li X, et al. Blood pressure percentiles by age and height for non-overweight Chinese children and adolescents: analysis of the China Health and Nutrition Surveys 1991–2009. *BMC Pediatr*. 2013;13:195
8. Hansen ML, Gunn PW, Kaelber DC. Underdiagnosis of hypertension in children and adolescents. *JAMA*. 2007;298(8):874–879
9. Lu Q, Ma CM, Yin FZ, Liu BW, Lou DH, Liu XL. How to simplify the diagnostic criteria of hypertension in adolescents. *J Hum Hypertens*. 2011;25(3):159–163
10. Popkin BM, Du S, Zhai F, Zhang B. Cohort profile: The China Health and Nutrition Survey—monitoring and understanding socio-economic and health change in China, 1989–2011. *Int J Epidemiol*. 2010;39(6):1435–1440
11. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560–2572
12. Zou KH, O'Malley AJ, Mauri L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. *Circulation*. 2007;115(5):654–657
13. Rabbia F, Rabbone I, Totaro S, et al. Evaluation of blood pressure/height ratio

- as an index to simplify diagnostic criteria of hypertension in Caucasian adolescents. *J Hum Hypertens*. 2011;25(10):623–624
14. Ejike CE. Blood pressure to height ratios as simple, sensitive and specific diagnostic tools for adolescent (pre)hypertension in Nigeria. *Ital J Pediatr*. 2011;37:30
 15. Galescu O, George M, Basetty S, et al Blood pressure over height ratios: simple and accurate method of detecting elevated blood pressure in children. *Int J Pediatr*. 2012;2012:253497
 16. Kelishadi R, Heshmat R, Ardalan G, et al. First report on simplified diagnostic criteria for pre-hypertension and hypertension in a national sample of adolescents from the Middle East and North Africa: the CASPIAN-III study. *J Pediatr (Rio J)*. 2014;90(1):85–91

(Continued from first page)

Drs Xi and Steffen conceptualized and designed the study and drafted the initial manuscript; Drs M. Zhang and Li carried out the initial analyses and reviewed and revised the manuscript; Drs T. Zhang and Liang designed the data collection instruments, coordinated data collection, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-0643

doi:10.1542/peds.2014-0643

Accepted for publication Mar 28, 2014

Address correspondence to Bo Xi, MD, Department of Epidemiology and Health Statistics, School of Public Health, Shandong University, 44 Wenhuxi Road, Jinan 250012, China. E-mail: xibo2010@sdu.edu.cn or Lyn M. Steffen, PhD, Division of Epidemiology and Community Health, University of Minnesota, 1300 South 2nd Street, WBOB 300, Minneapolis, MN 55454. E-mail: steffen@umn.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2014 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This work was partially supported by National “Twelfth Five-Year” Plan for Science & Technology Support Program (2012BAI03B03), the Outstanding Young Scientist Foundation in Shandong Province (grant BS2011YY026), the Scientific Research Organization Construction Project of Shandong University (grant 21320074615021) and Shandong Province Natural Science Foundation of China (grant ZR2012HQ033). This work was also supported by the NIH (grants R01-HD30880, DK056350, R24 HD050924, and R01-HD38700). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.