BMJ Open

Ultrasound screening strategy of CAKUT in neonates based on three-level network in Shanghai, China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020634
Article Type:	Research
Date Submitted by the Author:	14-Nov-2017
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Public health, Renal medicine, Urology
Keywords:	CAKUT, Ultrasound screening, Neonate, Three-level network

Title Page

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World count: 2945

Keywords: CAKUT; Ultrasound screening; Neonate; Three-level network

Abstract

Objective: To establish an effective screening model of congenital anomalies of the kidney and urinary tracts (CAKUT) by ultrasound among neonates in Shanghai, China.

Methods: A three-level screening model for CAKUT in neonates based on child health care system was built in 2010 in Minhang District, Shanghai, China. The model was composed of the community health centers for identification of screening candidates, the district-level hospital, Minhang maternal and child health hospital for ultrasound screening of CAKUT and the tertiary hospital, Children's Hospital of Fudan University for diagnosis and intervention. Demographic and clinical data were collected from all hospitals in the model.

Results: A total of 8827 infants were screened from 2010-2015, the absolute and relative rates of different degrees of renal pelvis dilatation (RPD) classified by anterior-posterior pelvic diameter were: mild (5-9.9mm)-984(11.1%); moderate (10-14.9mm)-176(2.0%); severe (≥15mm)-20(0.2%). Of the 639 cases with RPD followed up, 11 cases were diagnosed as obstructive uropathies. Of them, 9 cases underwent surgery at a median age of 2-month-old. Meanwhile, 85.4% of mild RPD, 62.5% of moderate and 30.0% of severe resolved spontaneously (mostly within 12 months of age). Other renal and urinary morphological abnormalities were detected in 19 cases and diagnosed in 15 (0.2%). The APRPD cut-off point for significant obstructive urology and need for surgery was 9.7mm and 13.5mm, respectively.

Conclusions: The three-level screening model was an integration of medical resources, and it provides to be an effective and feasible strategy for early detection and intervention of CAKUT in early postnatal period.

Article Summary

Strengths and limitations of this study

1. Such a screening model for CAKUT based on three-level network was an integration of medical resources of community health centers, district maternal and child health hospital and tertiary children's hospitals.
2. We summarized a feasible protocol for early detection, follow-up and intervention of CAKUT in early postnatal period in developing areas.
3. We calculated the receiver operating characteristic (ROC) curve to define an appropriate APRPD cut-off point to select cases requiring further surveillance and early detect patients in need of surgery.
4. However, it was not a real population-based study due to screening candidates identified with factors, such as preterm, low birth weight and so on.

The Main Body of the Manuscript

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are common anomalies detected prenatally, which account for approximately 20%-30% of all prenatal anomalies and occur in 3-6 per 1000 live births.[1] CAKUT is considered as the leading cause of chronic kidney disease (CKD) in children[2] and even leads to end stage of renal disease (ESRD) at adult.[3]

Majority of children with CAKUT are diagnosed prenatally in most developed countries,[4, 5] largely due to the widespread use of fetal ultrasonography. Recently, postnatal ultrasound screening was reported to be a useful method in the early detection and intervention of CAKUT,[6-9] as it could not only confirm abnormalities detected in fetus, but also detect the undiscovered abnormalities during prenatal period,[5, 10] which may minimize renal damage and in turn improves the quality of life.

It was reported that the occurrence of CAKUT were associated with small gestational age, maternal gestational diabetes, oligohydramnios, maternal age and so on.[11-13] Melo BF et al[14] also identified prematurity, low birth-weight, oligohydramnios, renal involvement and associated CAKUT were independent risk factors for early mortality of CAKUT. To propose a screening strategy suitable for the developing country with large population, we carried out our ultrasound screening for CAKUT in neonates with such criteria in priority (Table 1).

Table 1 Criteria for prior screening

Criteria
Low birth weight (birth weight less than 2500 grams)
Macrosomia (birth weight more than 4000 grams)
Premature delivery (gestational weeks less than 37 weeks)
Oligohydramnios
Malposition/ Cephalopelvic disproportion
Elderly pregnancy (maternal childbearing age more than 35 years old)
Gestational diabetes mellitus
Gestational hypertension syndrome/proteinuria
Intracranial hemorrhage or infection
Neonatal hyperbilirubinemia

Health-checks of infants are obligatory according to *"The rules of systematic health check-up of 0 to 6 years-old children in Shanghai (on trial)"*, newborns would be visited at about 2 weeks of age by specialized nurses from local community health centers (CHCs) and be informed to build health records and perform their first health-check at about 1 month of age in local CHC, then systematic health checks would be performed regularly till to 6 year-old. CHCs and secondary hospitals (mostly maternal and child healthcare hospitals, MCH) play vital roles in this public child healthcare network. CHCs were considered as the basic networks of public health surveillance and medical service, such as basic health-check and health education. However, their limited medical training leads to a lack of recognition of CAKUT and CKD. Secondary hospitals are committed to guarantee the health of local children with complete equipment, However, they are short of management experience for specific pediatric diseases, like CAKUT. Hence, it is imperative to propose a useful strategy to improve the situations and make rational use of medical resources.

In the current study, we established a novel three-level screening model, which was composed of CHCs for identification of screening candidates, the district Maternal and Child Healthcare Hospital (MCH) for ultrasound screening of CAKUT and the tertiary hospital, Children's Hospital of Fudan University (CHFU) for specific diagnosis and intervention. In addition, the CHFU provided training for CHCs and the district MCH. And then we practiced our postnatal urinary ultrasound screening and management for CAKUT based on the model in Shanghai, China.

Study objects and methods

The screening model

Minhang District, with a population of 2.5 million and around 30 thousand births per year, was selected to build the novel screening model. The model was based on child healthcare system and summarized in Fig.1. It consisted of the CHCs for identification of screening candidates, the district hospital, Minhang MCH for ultrasound screening of CAKUT and the tertiary hospital, Children's Hospital of Fudan University for specific diagnosis and intervention, also named as three-level network.

The study Objects

All newborns were registered in the local CHCs in Minhang District at about 28 days of age, while those met the criteria (Table 1) would be informed of a referral to Minhang MCH and ultrasound screening of CAKUT at once. Here

the ultrasound test was allowed for a delay to 3 months old to ensure that the vast majority of neonates examined.

Test methods and classification

Ultrasound test was carried out in Minhang MCH, and ultrasonographers who performed ultrasound examinations were trained uniformly and assessed regularly by CHFU.

All study objects were screened by GE-730 (USA, General Electric) scanner with a 5-7 MHz convex type transducer. The recordings consisted of six bilateral renal images,[8] including one longitudinal and two transverse images obtained in the supine position. The anterior-posterior pelvic diameter (APRPD) was measured on transverse images of the kidneys to evaluate the severity of renal pelvic dilatation (RPD). The urinary bladder was also observed in the supine position. Images were recorded when abnormalities were identified.

The following indexes were measured and obtained via ultrasonography: (1) Number, size and location of kidneys; (2) RPD and caliectasis; (3) Echogenicity; (4) Other positive findings indicating cysts or tumors. Shape and wall thickening of the urinary bladder, as well as ureterectasis (inner diameter of ureter ≥5 mm) were also recorded.

RPD was defined as APPD ≥5 mm and was further classified into three degrees: mild (5 to 9.9 mm), moderate (10 to 14.9 mm) and severe (larger than 15 mm).

Management and follow-up

When abnormalities were detected, the guardians of the affected infants were informed. Depending on the severity, we explained the situation and recommended a protocol including follow-up and further examination.

1) For cases with unilateral APPD ≥15 mm, bilateral APPD ≥10 mm whether or not caliectasis, ureterectasis or parenchyma thinning, or unilateral APPD 5-14.9 mm or bilateral APPD 10-14.9 mm with caliectasis and/or ureterectasis, or other abnormal findings of kidneys, ureters and bladder, the guardians would be recommended to transfer the infants to CHFU immediately for further examinations to obtain specific diagnosis and suitable intervention. While further examinations performed in CHFU include repeated ultrasound, urinalysis, diuretic-loaded diethylene-triamine-pentaacetic acid renography (DTPA), magnetic resonance urography (MRU), and micturating cystourethrography (MCU) or dimercaptosuccinic acid renal scintigraphy (DMSA) if necessary.
2) For cases with isolated unilateral APRPD 5-14.9 mm or bilateral APRPD 5-9.9 mm, follow-ups of ultrasound were performed in MinHang, MCH every 3-6 months combined with regular health checks, and guardians would be told to check urine test immediately if an unknown fever occurs.
3) During regular follow-up, RPD deteriorated in conditions which were listed as 1), or persistent unilateral APRPD 10-14.9mm until 1 year old, or febrile/recurrent urinary tract infection developed, would be transferred for further examinations mentioned above.

Screening of CAKUT and follow-ups of RPD in Minhang MCH was conducted by the department of Child Care, while management of severe cases in CHFU was performed by the department of nephrology and urology, together.

Data collection and statistical analysis

All demographic and clinical data were collected from Minhang MCH and CHFU in the model. Enumeration data were presented as median (P_{25}, P_{75}) and rate. In the population studied, the rate of abnormal findings was calculated, classification into basic groups was conducted according to the severity of RPD. The proportion of patients diagnosed and treated surgically was determined for individual groups of RPD.

In cases with RPD, the subsequent diagnostic and therapeutic measures were analyzed. The receiver operating characteristic (ROC) curve was plotted to enable us to define an appropriate APRPD cut-off point to select children requiring further surveillance and even detect patients in the RPD group in need of surgery. Statistical analysis was performed with Prism 6 software.

The study was approved by the Research Ethical Committee of Children's Hospital of Fudan University, and informed consents were obtained from all parents or guardians before all procedures in this study.

Results

The overall condition

Between Sept.2010 and Sept.2015, 12350 consecutive newborns met the

criteria, which accounted for about 8% of all births during the study period. Of these, 10858 neonates actually transferred to Minhang MCH on schedule and urinary ultrasound screening was performed in 8827 infants [(Female: Male=1.3:1), the mean screening rate was 81.3% (8827/10858), which was increased over years and reached 96% in 2015 (Fig. 2). The median age at screening was 40 (33,60) days. Infants with factors such as premature delivery and/or low birth weight accounted for 61.4%, and then followed by macrosomia (23.7%).

RPD was found in 1180 (13.4%) with an approximate male to female ratio of 2.2:1. Classified by APRPD, the incidence rates of RPD in individual groups were as follows: mild (5-9.9 mm), 984 (11.1%); moderate (10-14.9 mm), 176 (2.0%); severe (larger than 15 mm), 20 (0.2%).

The follow-up data of RPD

Among cases with RPD, 70 cases were in accordance with the referral criterion for further examinations. 36 of them followed according to the previous procedure to CHFU, another 30 patients were still under observation mainly in Minhang MCH, so the total case-management rate of severe patients reached 94.3% based on the three-level network. 575 cases with isolated mild-moderate RPD were followed up in Minhang MCH, approximately 51.8% in general.

Combining all followed-up data of RPD, 11 (16.7%) of the 36 patients

transferred to CFHU obtained specific diagnosis, 6 cases of ureteropelvic junction obstruction (UPJO), 3 cases of renal duplication with ipsilateral RPD, and 2 cases of megaureter. Surgery was performed in 9 cases at a median age of 2 month-old (Supplement 1). As to others RPD cases (Table 2, Fig 3A), 85.4% of mild, 62.5% of moderate and 30.0% of severe resolved spontaneously, mainly within 12 months of age (Fig 3B). And persistent pelvic dilatation continued significantly longer in moderate and severe cases than in mild ones (P=0.0134).

Table 2 The outcome of RPD followed up

	Mild	Moderate	Severe	Total
No. followed-up (% No. RPD)	507 (51.5)	113 (64.2)	20 (100.0)	640 (54.2)
No. of diagnosed (% No. followed-up)	2 (0.6)	3 (2.7)	6 (30.0)	11 (1.7)
Diagnosis	MU (1) RD (1)	UPJO (1) RD (2)	UPJO (5) MU (1)	UPJO (6) RD (3) MU (2)
No. remission (% No. followed-up)	433 (85.4)	70 (62.5)	6 (30.0)	509 (79.5)

MU: Megaureter; RD: Renal duplication

Of all RPD followed up, 85.4% were mild RPD, 62.5% of moderate RPD and 30.0% of severe RPD resolved spontaneously, while others were either still under follow up or only followed for a period.

Other abnormal findings of renal and urinary system

Nineteen cases were detected with other findings, and 15(0.2%) were confirmed, 7 cases with unilateral renal aplasia (URA), two with renal duplication, two with renal dysplasia, one with multicystic renal dysplasia (MCDK), one with renal ectopia, one with ureterectasia (diagnosed as

ureterovesical junction obstruction, UVJO), one with renal cyst. One case with URA combined with ipsilateral VUR staging V, developed renal damage and was operated at 11-month-old, preventing further kidney injury.

Data of the ROC curve

The ROC curve for postnatal ultrasound screening was plotted, and the area under the curve (AUC = 0.901, 95% CI：0.813~0.990) was calculated (Fig. 4). Based on the ROC, the ideal APRPD cut-off point for the detection of significant obstructive urology appears to be 9.7 mm and more, the sensitivity was 81.8% (95%CI: 48.2%~97.7%), the specificity was 80.3% (95%CI: 77.0%~83.3%), +LR and –LR were 4.13 and 0.23.

When to indicate the need for surgery intervention, the area under the curve was AUC = 0.9334 (95% CI: 0.850~1.017) (Fig. 5), and ideal APRPD cut-off point appears to be 13.5 mm and more, the sensitivity was 77.8% (95%CI: 40.0%~97.2%), the specificity was 96.5% (95%CI: 94.8%~97.8%), +LR and –LR were 22.3 and 0.2, respectively.

Discussion

Our rationale of CAKUT screening was to perform the screening before the occurrence of renal damage and as many as neonates could be screened. In Japan, health checks at 1 month-age were very popular because public health plans cover the fee. Junko Yoshida et al[8] proposed that mass screening for

CAKUT at 1-month-old health check was timely and technically appropriate, and more than 90% of infants born at their hospital received renal ultrasound screening as part of their routine health checks during the study period. What's more, Masami Tsuchiya et al[9] also advocated an established ultrasonographic screening system for CAKUT in Japan. Similarly in Italy, Vito Antonio Caiulo et al[6] conducted their ultrasound screening at the age of 2 months, combined with routine health check. According to *The management of infants (low-birth-weight) in Shanghai (on trial)*, routine health checks after birth are performed by the CHCs at the age of 1 month, which are supervised by the district MCH. Furthermore, the district MCH should monitor all newborns, especially those with factor of preterm, low birth weight and so on. In the present study, we conducted our screening combined with public Child Healthcare in Shanghai, urinary ultrasound screening was part of routine health checks based on the three-level network during the study period. More than 80% candidate neonates were examined in their first 3 months of life, what was remarkable that the screening rate increased gradually and reached to 96% in 2015, indicating the raising awareness regarding the importance of early detection of CAKUT in CHCs, MCH and guardians. Moreover, the district hospital, Minhang MCH was actually the central hub of the screening model, screening candidates identified in CHCs, conducting follow-up of cases with mild-moderate RPD and transferring cases with severe findings to tertiary hospital. At the same time, it played a significant role in medical and social

education, which reflected from the increasing screening rates over years. Otherwise, CHFU was not only used for diagnosing and treating cases with CAKUT, but also used for designing, training and quality supervision. Such a screening model was an example of integration of the original child healthcare delivery system and tertiary children's hospital, practicing hierarchical management model and making medical resource more rationally. When considering follow-up, almost all severe cases, who met the referral criteria, were transferred or followed up under the cooperation of CHFU and Minhang MCH. Although the number of cases with mild-moderate RPD followed-up was not as high as other studies mentioned previously, however, most of them had favorable outcomes. It was a better and more expended utilization of child healthcare service.

Junko Yoshida et al[8] indicated that a pelvic dilatation of ≥ 5 mm was sufficient to find all dilated systems. However, evaluation was made certainly easier by increasing the specificity of setting the criterion for abnormal RPD of APPD ≥ 10 mm according to the recent multidisciplinary consensus of urinary tract dilation (UTD) classification system, which proposed that renal pelvis was considered to be normal when the APRPD <10 mm postnatally.[15] With APRPD greater than 5mm as the criterion of RPD in our study, 1180 infants (13.4%) were classified as having RPD. While several studies used an APRPD ≥ 10 mm as the threshold, the frequency ranged from 1.1%-2.8%,[6, 16, 17] and some other studies chose SFU stage 2 or higher to judge, like Masami

Tsuchiya et al[9] screened 5700 1-month-old infants, yielding 114 RPD cases (2.0%). What's more, all these studies showed similar diagnostic rate of 12%-13% in cases with RPD, which mainly consists of UPJO (20%-70%), VUR (30%-60%) and other obstructive uropathies (20%-30%). In our study, the incidence rate of RPD was decreased to 2.2% if the criterion of APRPD changed to ≥ 10 mm consequently, close to the studies mentioned above. However, we had only 9 cases (4.6%) diagnosed specifically. Compared with the study by Masami Tsuchiya et al,[9] they reported that 8 (53.3%) out of 15 cases were operated on severe uropathies, while that of our study was 88.9%. The relative low diagnosed rate might attribute to the serious indications for further examination we designed and low parents' compliance to some extent. In addition, we totally detected 0.2% cases with other types of CAKUT, which was similar with others.[7, 9] So as to the follow-up data of mild-moderate RPD,[17] we found that cases with APRPD 5-9.9mm, 85% of cases had undergone a spontaneous normalization as demonstrated on renal US within 12-month-old, even in APRPD≥10mm, about 60% got remission.

Based on the ROC curve, we calculated that the ideal APRPD cut-off point for the detection of significant obstructive urology and indicator of the need for surgical intervention was 9.7mm and 13.5mm, which is in contradiction to such analyses in some studies.[7, 18] In the case of a screening test, the most important parameter is its sensitivity. If we wish to promote ultrasound screening for CAKUT in all neonates, high specificity without decreasing the

sensitivity are very important criteria, as well. In fact, we diagnosed two cases with CAKUT in an APRPD of 5-9.9mm, one was diagnosed with renal duplication with mild ipsilateral RPD and ectopic ureteral orifice, the other one was detected with remarkable ureterectasia on following ultrasounds. Therefore, we proposed to select APPD ≥10mm as criterion of RPD who required follow-up and further examinations if necessary, as well as APRPD 5-9.9mm with ureterectasia or other abnormal findings. While for cases with isolated APRPD ≥5-9.9mm, education of UTI was even more important in case of pathological abnormalities, such as VUR.

In a study from Sheih et al,[19] they estimated that renal ultrasound screening of children in elementary and junior high schools would cost $US 0.36 per child and the benefit to cost ratio was nearly 8.0, and our ratio was approximately 3 based on the similar calculation method. In addition, data from questionnaire of The Study Group of Ultrasonographic Screening for CAKUT in Japan indicated that the screening cost per child would be ¥1,200 ($US15), and 3 potential dialysis patients would be found per 55,000 children. If dialysis in these 3 patients could be delayed for 3.7 years, screening would pay for itself[9]. These indicated that our screening would achieve better cost-benefit if we could decrease the cost, standardize the criterion, examined the outline, and improve adherence. Moreover, with the implementation and widespread of "Two-child policy" in China currently, we should consider its utility in the light of society with more children, because early screening can contribute greatly to

the child's ultimate quality of life.

However, there were several limitations need to be improved. We conducted our study in neonates with factors, such as preterm, low birth weight and so on, which was not a real population-based study. As almost half cases of mild-moderate RPD were lack of follow-up data, we could not predict the morbidity of CAKUT among all births. It was a pity that we did not find severe types of CAKUT, like PUV. In addition, the cost-effectiveness should be calculated in detail in future research.

Conclusion

Such a screening model for CAKUT based on three-level network among neonates in Shanghai, China was an integration of medical resources of CHCs, district MCH and tertiary children's hospitals. It was proved to be effective for the early detection, follow-up and intervention of CAKUT in early postnatal period. And it might be a replicable and reliable approach for CAKUT in other developing areas.

Acknowledgements

Thanks to all doctors in Department of Child Health of all the CHCs in Minhang District and Minhang MCH for their contribution.

Funding Source: This work was supported by Special Scientific Research Fund of the Ministry of Health, China (Grant number: 201002006), Shanghai Public Health Three-Year Action Plan (2015-2017) sponsored by Shanghai Municipal Government (Grant number: GWIV14.2), Chronic disease prevention and control project sponsored by Shanghai Hospital Developmental center (Grant number: SHDC12015301).

Financial Disclosure Statement for all authors: All authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of interest: None of the authors have had any financial interest in any products, devices or drugs used in the manuscript. There is no conflict of interest related to any commercial associations or financial relationships (consultancy, stock ownership, equity interest, patent licensing arrangements or payments for conducting or publicizing the study contained in the manuscript).

Contributors' Statement:

Hong Xu: Dr Xu conceptualized and designed the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Yinv Gong: Dr Gong carried out the work of screening and management, data collection, the initial analysis, drafted the initial manuscript, and approved the

final manuscript as submitted.

Ying Zhang: Dr Zhang carried out the work of screening and management, data collection, the initial analyse and approved the final manuscript as submitted.

Qian Shen, Liping Xiao: Drs Shen and Xiao coordinated and supervised data collection, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Yihui Zhai, Yunli Bi, Jian Shen, Hong Chen: Drs Zhai, Bi, Shen and Chen carried out the work of management, coordinated data collection and approved the final manuscript as submitted.

Yun Li: Dr Li carried out the work of screening and management, coordinated data collection and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical approval: The study was approved by the Research Ethical Committee of Children's Hospital of Fudan University.

Data sharing: No additional data are available.

What is Already Known on This Topic

Ultrasound screening for CAKUT in early postnatal period has been proposed and applied in several developed countries and regions.

What This Study Adds

The screening model based on three-level network is effective and feasible for early detection, follow-up and intervention of CAKUT among neonates in developing regions.

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Figure 1. The procedure of the three-level screening model for CAKUT in early postnatal period in Shanghai, China
CHCs: Community Health Centers; MinHang MCH: MinHang Maternal and Child Health Hospital; RPD: Renal pelvic dilation. Other abnormalities include renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney (MCDK), ectopical kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.

Figure 2. General data of the screening model

Figure 3. Remission of RPD
A Kaplan-Meier curve for RPD patients with normalization of ultrasound; B The remission time of different degree of RPD (median with interquartile range)

Figure 4. The ROC curve based on the APRPD index as an indicator of obstructive urology

Figure 5. The ROC curve based on the APRPD index as an indicator of the need for surgical intervention

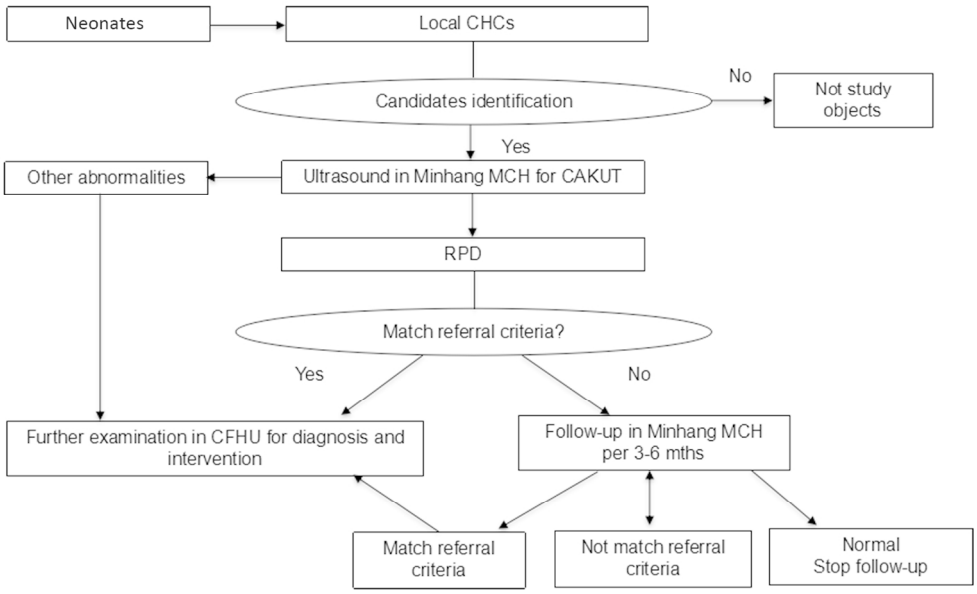

Figure 1. The procedure of the three-level screening model for CAKUT in early postnatal period in Shanghai, China

CHCs: Community Health Centers; MinHang MCH: MinHang Maternal and Child Health Hospital; RPD: Renal pelvic dilation. Other abnormalities include renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney (MCDK), ectopical kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.

122x75mm (300 x 300 DPI)

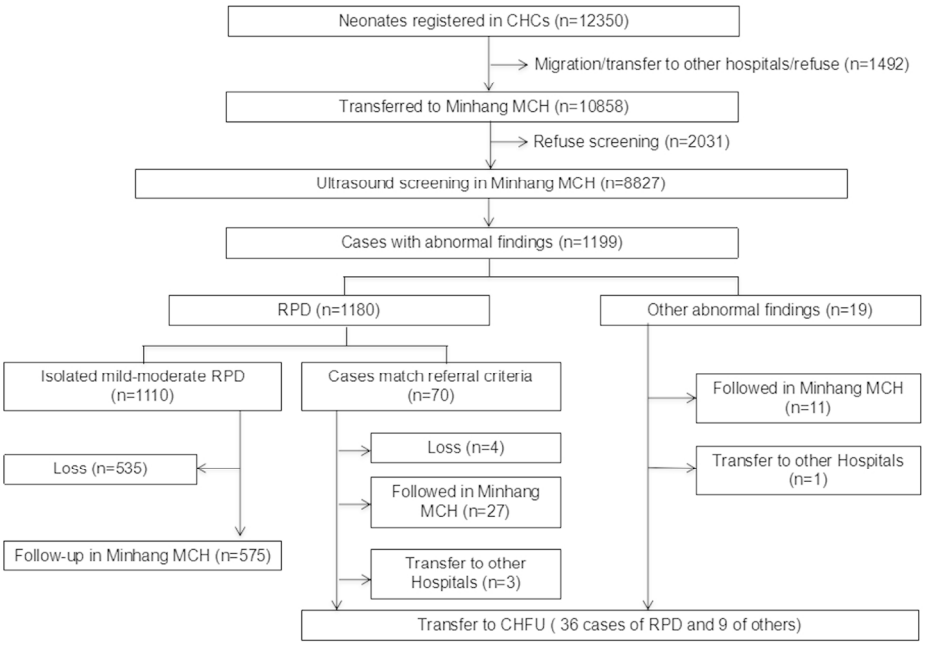

Figure 2. General data of the screening model

124x84mm (300 x 300 DPI)

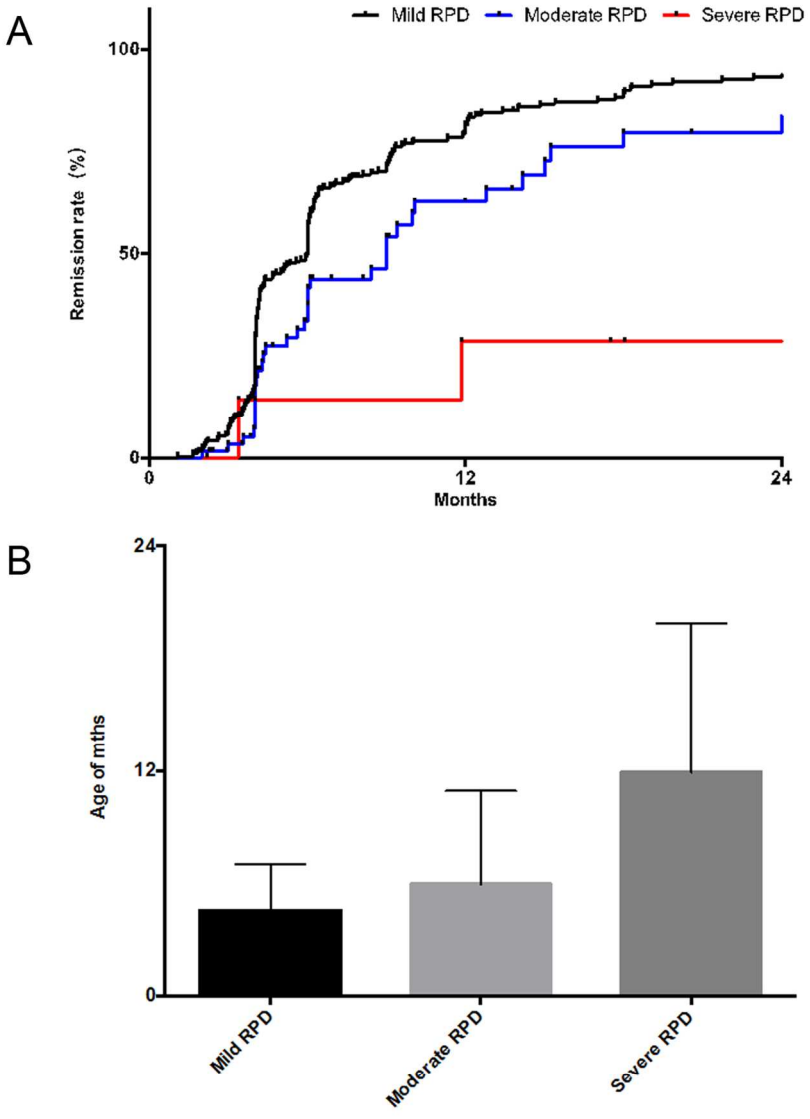

Figure 3. Remission of RPD
A Kaplan-Meier curve for RPD patients with normalization of ultrasound; B The remission time of different degree of RPD (median with interquartile range)

116x149mm (300 x 300 DPI)

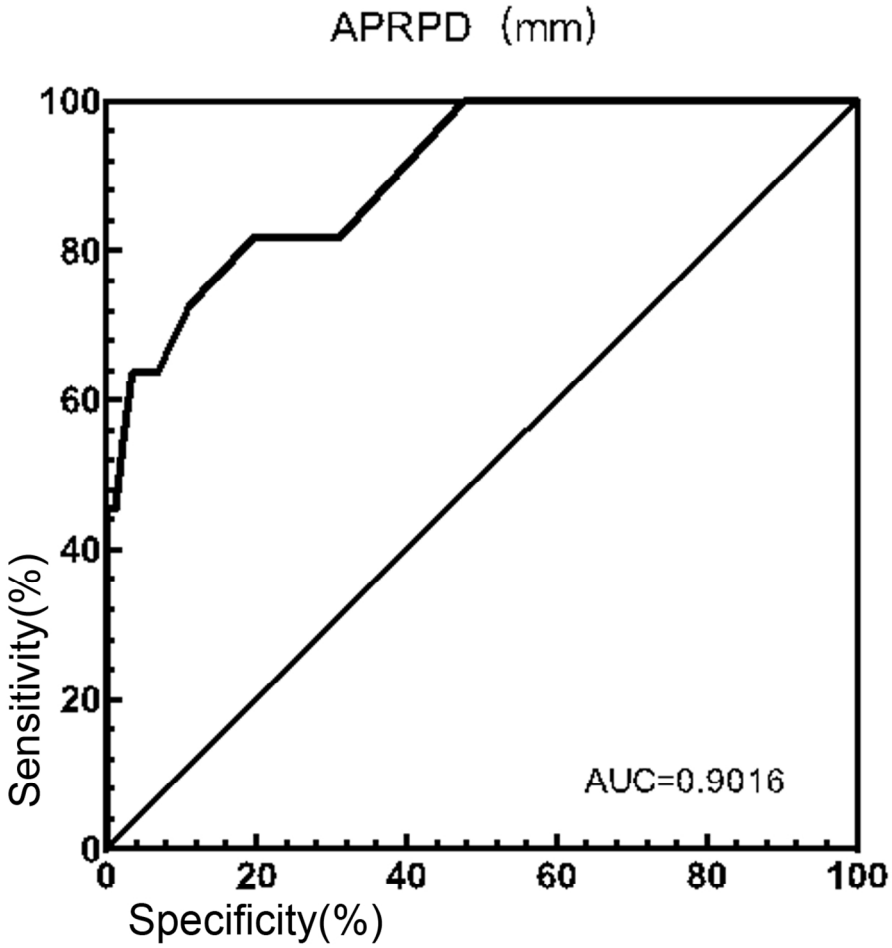

Figure 4. The ROC curve based on the APRPD index as an indicator of obstructive urology

117x117mm (300 x 300 DPI)

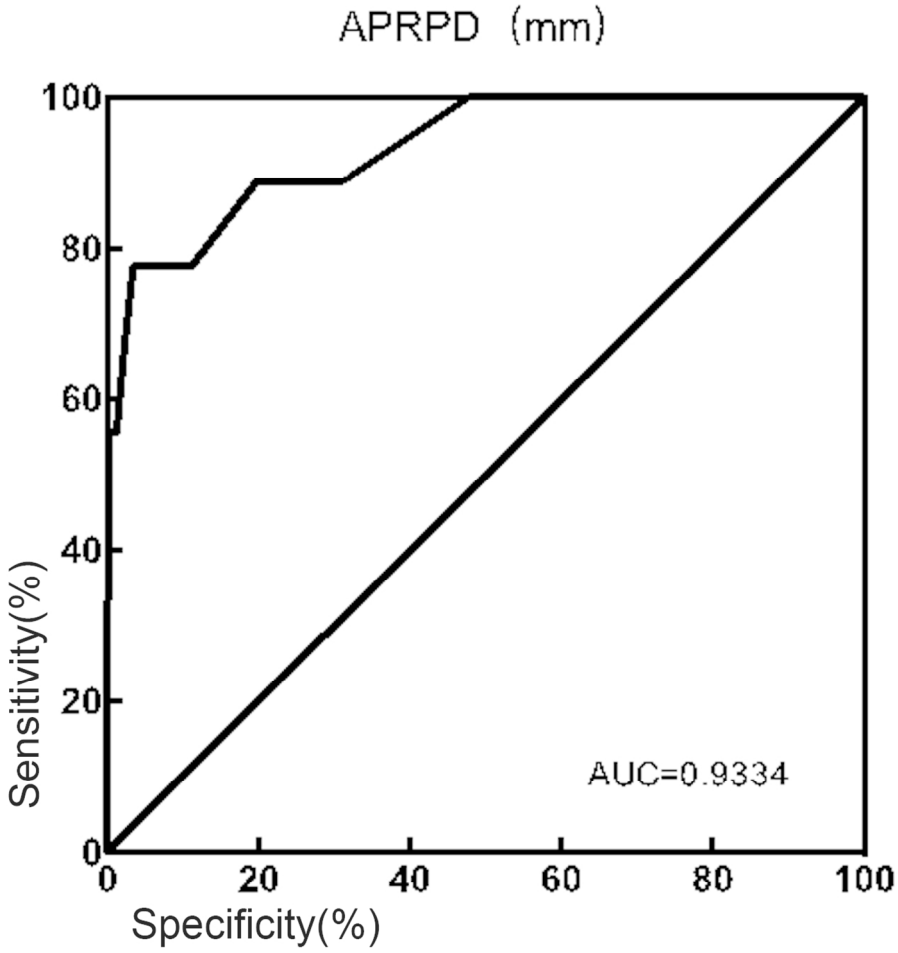

Figure 5. The ROC curve based on the APRPD index as an indicator of the need for surgical intervention

119x120mm (300 x 300 DPI)

Supplement Table 1 Details of RPD patients with specific diagnosis

Case	No.	Gender	APPD(mm)		CAKUT (Side)	Management	Surgery age (m)	Post operation condition
			Left	Right				
1	GXN	M	21	-	UPJO (L)	Pyeloplasty	1.5	RPD alleviated distinctly DRF 40.5%(6 mths after)
2	LZY	M	-	38	UPJO (R)	Pyeloplasty	1.5	RPD alleviated distinctly
3	WZC	M	8	60	UPJO(R)	External drainage+ Pyeloplasty	1.6	RPD alleviated distinctly
4	CJ	M	24	-	UPJO (L)	Pyeloplasty	8.0	RPD alleviated distinctly
5	GYX	M	-	21	UPJO (R)	Pyeloplasty	2.0	RPD alleviated distinctly DRF 46.6% (6 mths after)
6	ZCX	M	11	9	UPJO (L)	Follow-up	-	

7	ZXY	F	14	7	RD (Bi) Ureterectasia (L) Ureterocele (L)	Transurethral endoscopic unroofing of ureteroceles	2.0	RPD and Ureterectasia alleviated No UTI DRF normal
8	ZWS	M	8	-	RD with ipsilateral severe RPD and ectopic ureteral orifice (L)	Ureteral reimplantation	27.0	RPD and Ureterectasia alleviated DRF normal
9	JFR	M	12	-	RD(L) RD+ upper UPJO	LUPPN	36.0	RPD alleviated distinctly
10	ZSR	F	-	15	MU(R)	Ureteral reimplantation	27.0	Ureterectasia alleviated DRF<40%
11	JHB	M	8	-	MU(L)	Follow-up	-	

L: Left; R: Right; Bi: Bilateral; MU: Megaureter; RD: Renal duplication; DRF: differential renal function; LUPPN: laparoscopic upper pole partial nephrectomy.

BMJ Open

Early detection of congenital anomalies of the kidney and urinary tract in China: A community-based screening and referral network study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020634.R1
Article Type:	Research
Date Submitted by the Author:	08-Jan-2018
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Public health, Renal medicine, Urology
Keywords:	CAKUT, Ultrasound screening, Neonate, Three-level network

Title Page

Title: Early detection of congenital anomalies of the kidney and urinary tract in China: A community-based screening and referral network study

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World count: 2886

Keywords: CAKUT; Ultrasound screening; Neonate; Three-level network

Abstract

Objective: To establish an effective screening model of congenital anomalies of the kidney and urinary tracts (CAKUT) by ultrasound among neonates in Shanghai, China.

Methods: A three-level screening model for CAKUT in neonates based on child health care system was built in 2010 in Minhang District, Shanghai, China. The model was composed of the community health centers for identification of screening candidates, the district-level hospital, Minhang maternal and child health hospital for ultrasound screening of CAKUT and the tertiary hospital, Children's Hospital of Fudan University for diagnosis and intervention. The positive results of ultrasound screening were divided into renal pelvic dilatation (RPD) and other abnormal findings of renal and urinary system. And the cut-off points for the likelihood of the presence of obstructive uropathy and the need for surgery was determined by ROC curve. Demographic and clinical data were collected from all hospitals in the model.

Results: A total of 8827 infants were screened from 2010-2015, the absolute and relative rates of different degrees of RPD classified by anterior-posterior pelvic diameter (APRPD) were: mild (5-9.9mm) - 984(11.1%), moderate (10-14.9mm) - 176(2.0%), severe (≥15mm) - 20(0.2%). Of the 639 cases with RPD followed up, 11 cases were diagnosed as obstructive uropathies. Of them, 9 cases underwent surgery at a median age of 2-month-old. Meanwhile, 85.4% of mild RPD, 62.5% of moderate and 30.0% of severe resolved spontaneously

(mostly within 12 months of age). Other renal and urinary morphological abnormalities were diagnosed in 15 (0.2%). The APRPD cut-off point for significant obstructive uropathy and need for surgery was 9.7mm and 13.5mm, respectively.

Conclusions: The three-level screening model is an effective and feasible strategy for early detection and intervention of CAKUT in early postnatal period. The strategy could be useful in China and other developing areas where medical resources are limited.

Article Summary

Strengths and limitations of this study

1. The first regional community-based screening program of CAKUT in neonates in China.
2. A large and nearly population-based study, nested within an organized screening and referral program that emphasized hierarchical management of RPD for early detection and intervention of obstructive uropathy in early postnatal period.
3. The study highlights the importance of integrating medical resources and engaging local community and district hospital partners prior to undertaking more screening efforts for undetected congenital anomalies in neonates and infants in developing areas.
4. Our efforts to characterize the outcome of RPD are limited by the loss of nearly half mild-moderated RPD cases, which prohibits us from drawing objective inferences.

The Main Body of the Manuscript

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are common anomalies detected prenatally, which account for approximately 20%-30% of all prenatal anomalies and occur in 3-6 per 1000 live births.[1] CAKUT is considered as the leading cause of chronic kidney disease (CKD) in children[2] and even leads to end stage of renal disease (ESRD) at adult.[3]

Majority of children with CAKUT are diagnosed prenatally in most developed countries,[4 5] largely due to the widespread use of fetal ultrasonography. Recently, postnatal ultrasound screening was reported to be a useful method in the early detection and intervention of CAKUT,[6-9] as it could not only confirm abnormalities detected in fetus, but also detect the undiscovered abnormalities during prenatal period,[5 10] which may minimize renal damage and in turn improves the quality of life.

It was reported that the occurrence of CAKUT were associated with small gestational age, maternal gestational diabetes, oligohydramnios, maternal age and so on.[11-13] Melo BF et al[14] also identified prematurity, low birth-weight, oligohydramnios, and CAKUT with renal involvement were independent risk factors for early mortality in CAKUT patients.

Health-checks of infants are obligatory according to *"The rules of systematic health check-up of 0 to 6 years-old children in Shanghai (on trial)"*, newborns would be visited at about 2 weeks of age by specialized nurses from local

community health centers (CHCs) and be informed to build health records and perform their first health-check at about 1 month of age in local CHC, then systematic health checks would be performed regularly till to 6 year-old. CHCs and secondary hospitals (mostly maternal and child healthcare hospitals, MCH) play vital roles in this public child healthcare network. CHCs were considered as the basic networks of public health surveillance and medical service, such as basic health-check and health education. However, their limited medical training leads to a lack of recognition of CAKUT and CKD. Secondary hospitals are committed to guarantee the health of local children with complete equipment, However, they are short of management experience for specific pediatric diseases, like CAKUT. Hence, it is imperative to propose a useful strategy to improve the situations and make rational use of medical resources.

In the current study, we established a novel three-level screening model, which was composed of CHCs for identification of screening candidates, the district Maternal and Child Healthcare Hospital (MCH) for ultrasound screening of CAKUT and the tertiary hospital, Children's Hospital of Fudan University (CHFU) for specific diagnosis and intervention. In addition, the CHFU provided training for CHCs and the district MCH. And then we practiced our postnatal urinary ultrasound screening and management for CAKUT based on the model in Shanghai, China.

Study objects and methods

The screening model

Minhang District, with a population of 2.5 million and around 30 thousand births per year, was selected to build the novel screening model. The model was based on child healthcare system and summarized in Fig.1. It consisted of the CHCs for identification of screening candidates, the district hospital, Minhang MCH for ultrasound screening of CAKUT and the tertiary hospital, Children's Hospital of Fudan University for specific diagnosis and intervention, also named as three-level network.

To propose a screening strategy suitable for the developing country with large population, we carried out our ultrasound screening for CAKUT in neonates with such criteria in priority (Table 1).

Table 1 Criteria for priority screening

Criteria
Low birth weight (birth weight less than 2500 grams)
Macrosomia (birth weight more than 4000 grams)
Premature delivery (gestational weeks less than 37 weeks)
Oligohydramnios
Malposition/ Cephalopelvic disproportion
Pregnancy at advanced age (more than 35 years old)
Gestational diabetes mellitus
Gestational hypertension syndrome/proteinuria
Intracranial hemorrhage or infection
Neonatal hyperbilirubinemia

The study Objects

All newborns were registered in the local CHCs in Minhang District at about 28 days of age, while those met the criteria (Table 1) would be informed of a referral to Minhang MCH and ultrasound screening of CAKUT at once. Here the ultrasound test was allowed for a delay to 3 months old to ensure that the

vast majority of neonates examined.

The study was approved by the Research Ethical Committee of Children's Hospital of Fudan University, and informed consents were obtained from all parents or guardians before all procedures in this study.

Test methods and classification

Ultrasound test was carried out by ultrasonographers in Minhang MCH, they received one-week training including practice and specialized lecture courses every year by professional ultrasonographers in CHFU. All study objects were screened by GE-730 (USA, General Electric) scanner with a 5-7 MHz convex type transducer. The recordings consisted of six bilateral renal images,[8] including one longitudinal and two transverse images obtained in the supine position. The anterior-posterior pelvic diameter (APRPD) was measured on transverse images of the kidneys to evaluate the severity of renal pelvic dilatation (RPD). The urinary bladder was also observed in the supine position. Images were recorded when abnormalities were identified.

The following indexes were measured and obtained via ultrasonography: (1) Number, size and location of kidneys; (2) RPD and caliectasis; (3) Echogenicity; (4) Other positive findings indicating cysts or tumors. Shape and wall thickening of the urinary bladder, as well as ureterectasis (inner diameter of ureter ≥5 mm) were also recorded.

RPD was defined as APRPD ≥5 mm and was further classified into three degrees: mild (5 to 9.9 mm), moderate (10 to 14.9 mm) and severe (larger

than 15 mm). [15]

Management and follow-up

When abnormalities were detected, the guardians of the affected infants were informed. Depending on the severity, we explained the situation and recommended a protocol including follow-up and further examination.

1) For cases with unilateral APRPD ≥15 mm, bilateral APRPD ≥10 mm whether or not caliectasis, ureterectasis or parenchyma thinning, or unilateral APRPD 5-14.9 mm or bilateral APRPD 10-14.9 mm with caliectasis and/or ureterectasis, or other abnormal findings of kidneys, ureters and bladder, the guardians would be recommended to transfer the infants to CHFU immediately for further examinations to obtain specific diagnosis and suitable intervention. While further examinations performed in CHFU include repeated ultrasound, urinalysis, diuretic-loaded diethylene-triamine-pentaacetic acid renography (DTPA), magnetic resonance urography (MRU), and micturating cystourethrography (MCU) or dimercaptosuccinic acid renal scintigraphy (DMSA) if necessary.

2) For cases with isolated unilateral APRPD 5-14.9 mm or bilateral APRPD 5-9.9 mm, follow-ups of ultrasound were performed in MinHang, MCH every 3-6 months combined with regular health checks, and guardians would be told to check urine test immediately if an unknown fever occurs.

3) During regular follow-up, RPD deteriorated in conditions which were listed as 1), or persistent unilateral APRPD 10-14.9mm until 1 year old, or

febrile/recurrent urinary tract infection developed, would be transferred for further examinations mentioned above.

Screening of CAKUT and follow-ups of RPD in Minhang MCH was conducted by the department of Child Care, while management of severe cases in CHFU was performed by the department of nephrology and urology, together.

Data collection and statistical analysis

All demographic and clinical data were collected from Minhang MCH and CHFU in the model. Enumeration data were presented as median (P_{25}, P_{75}) and rate. In the population studied, the rate of abnormal findings was calculated. The proportion of patients diagnosed and treated surgically was determined for individual groups of RPD.

In cases with RPD, the subsequent diagnostic and therapeutic measures were analyzed. The receiver operating characteristic (ROC) curve was plotted to enable us to define an appropriate APRPD cut-off point to select children requiring further surveillance and detect patients who require surgical treatment. Statistical analysis was performed with Prism 6 software.

Results

The overall condition

Between Sept.2010 and Sept.2015, 12350 consecutive newborns met the criteria, which accounted for about 8% of all births during the study period. Of these, 10858 neonates actually transferred to Minhang MCH on schedule and

urinary ultrasound screening was performed in 8827 infants [(Male: Female=1.3:1), the mean screening rate was 81.3% (8827/10858), which was increased over years and reached 96% in 2015 (Fig. 2). The median age at screening was 40 (33,60) days. Infants with factors such as premature delivery and/or low birth weight accounted for 61.4%, and then followed by macrosomia (23.7%).

RPD was found in 1180 (13.4%) with an approximate male to female ratio of 2.2:1. Classified by APRPD, the incidence rates of RPD in individual groups were as follows: mild (5-9.9 mm), 984 (11.1%); moderate (10-14.9 mm), 176 (2.0%); severe (larger than 15 mm), 20 (0.2%).

The follow-up data of RPD

Among cases with RPD, 70 cases were in accordance with the referral criterion for further examinations. 36 of them followed according to the previous procedure to CHFU, another 30 patients were still under observation mainly in Minhang MCH, so the total case-management rate of severe patients reached 94.3% based on the three-level network. 575 cases with isolated mild-moderate RPD were followed up in Minhang MCH, approximately 51.8% in general.

Combining all followed-up data of RPD, 11 of the 36 patients transferred to CFHU and obtained specific diagnosis, 6 cases of ureteropelvic junction obstruction (UPJO), 3 cases of renal duplication with ipsilateral RPD, and 2

cases of megaureter. Surgery was performed in 9 cases at a median age of 2 month-old (Supplement 1). As to other RPD cases (Table 2, Fig 3A), 85.4% of mild, 62.5% of moderate and 30.0% of severe resolved spontaneously, mainly within 12 months of age (Fig 3B). And persistent pelvic dilatation continued significantly longer in moderate and severe cases than in mild ones (P=0.0134).

Table 2 The outcome of RPD followed up

	Mild	Moderate	Severe	Total
No. followed-up (% No. RPD)	507 (51.5)	113 (64.2)	20 (100.0)	640 (54.2)
No. of diagnosed (% No. followed-up)	2 (0.6)	3 (2.7)	6 (30.0)	11 (1.7)
Diagnosis	MU (1) RD (1)	UPJO (1) RD (2)	UPJO (5) MU (1)	UPJO (6) RD (3) MU (2)
No. resolution (% No. followed-up)	433 (85.4)	70 (62.5)	6 (30.0)	509 (79.5)

MU: Megaureter; RD: Renal duplication

Of all RPD followed up, 85.4% were mild RPD, 62.5% of moderate RPD and 30.0% of severe RPD resolved spontaneously, while others were either still under follow up or only followed for a period.

Other abnormal findings of renal and urinary system

Nineteen cases were detected with other findings, and 15(0.2%) were diagnosed as CAKUT, 7 cases with unilateral renal aplasia (URA), two with renal duplication, two with renal dysplasia (one was bilateral), one with multicystic renal dysplasia (MCDK), one with renal ectopia, one with ureterectasia (diagnosed as ureterovesical junction obstruction, UVJO), one with renal cyst. One case with URA combined with ipsilateral VUR staging V,

developed renal damage and underwent operation at 11-month-old, preventing further kidney deterioration. The case with bilateral renal dysplasia developed to ESRD at 6 years old under monitor. The rest four cases were normal by repeated ultrasound in CHFU within one month, two presented with unclear boundaries of renal cortex and medulla, one with ureterocele and the last one with ureterectasia.

Data of the ROC curve

The ROC curve for postnatal ultrasound screening was plotted, and the area under the curve (AUC = 0.901, 95% CI：0.813~0.990) was calculated (Fig. 4). Based on the ROC, the ideal APRPD cut-off point for the detection of significant obstructive uropathy appears to be 9.7 mm and more, the sensitivity was 81.8% (95%CI: 48.2%~97.7%), the specificity was 80.3% (95%CI: 77.0%~83.3%), +LR and –LR were 4.13 and 0.23.

When to indicate the need for surgery intervention, the area under the curve was AUC = 0.9334 (95% CI: 0.850~1.017) (Fig. 5), and ideal APRPD cut-off point appears to be 13.5 mm and more, the sensitivity was 77.8% (95%CI: 40.0%~97.2%), the specificity was 96.5% (95%CI: 94.8%~97.8%), +LR and –LR were 22.3 and 0.2, respectively.

Discussion

Our rationale of CAKUT screening was to perform the screening before the occurrence of renal damage and as many neonates as possible could be screened. In Japan, health checks at 1 month-age were very popular because public health plans cover the fee. Junko Yoshida et al[8] proposed that mass screening for CAKUT at 1-month-old health check was timely and technically appropriate, and more than 90% of infants born at their hospital received renal ultrasound screening as part of their routine health checks during the study period. What's more, Masami Tsuchiya et al[9] also advocated an established ultrasonographic screening system for CAKUT in Japan. Similarly in Italy, Vito Antonio Caiulo et al[6] conducted their ultrasound screening at the age of 2 months, combined with routine health check. According to *The management of high-risk infants (low-birth-weight) in Shanghai (on trial)*, routine health checks after birth are performed in CHCs at the age of 1 month, which are supervised by the district MCH. Furthermore, the district MCH should monitor all newborns' data, especially those with factors of preterm, low birth weight and so on. In the present study, we conducted our screening combined with public Child Healthcare system in Shanghai, urinary ultrasound screening was part of routine health checks during the study period. More than 80% candidate neonates were examined in their first 3 months of life, what was remarkable that the screening rate increased gradually and reached to 96% in 2015, indicating the raising awareness regarding the importance of early detection of CAKUT in CHCs, MCH and guardians. Moreover, the district hospital, Minhang

MCH was actually the central hub of the screening model, screening candidates identified from CHCs, conducting follow-up of cases with mild-moderate RPD and transferring cases with severe findings to tertiary hospital. At the same time, it played a significant role in medical and social education, which reflected from the increasing screening rates over years. Otherwise, CHFU was not only used for diagnosing and treating cases with CAKUT, but also used for designing, training and quality supervision. Such a screening model was an example of integration of the original child healthcare delivery system and tertiary children's hospital, practicing hierarchical management model and making medical resource more rationally. When regarding to follow-up, almost all severe cases, who met the referral criteria, were transferred or followed up under the cooperation of CHFU and Minhang MCH. It was currently the first community-based screening program of CAKUT in China.

Junko Yoshida et al[8] indicated that a pelvic dilatation of ≥ 5 mm was sufficient to find all dilated systems. However, evaluation was made certainly easier by increasing the specificity of setting the criterion for abnormal RPD of APRPD ≥ 10 mm according to the recent multidisciplinary consensus of urinary tract dilation (UTD) classification system, which proposed that renal pelvis was considered to be normal when the APRPD <10 mm postnatally.[16] With APRPD greater than 5mm as the criterion of RPD in our study, 1180 infants (13.4%) were classified as having RPD. While several studies used an

APRPD ≥ 10 mm as the threshold, the frequency ranged from 1.1%-2.8%,[6 17 18] and some other studies chose SFU stage 2 or higher to judge, like Masami Tsuchiya et al[9] screened 5700 1-month-old infants, yielding 114 RPD cases (2.0%). What's more, all these studies showed similar diagnostic rate of 12%-13% in cases with RPD, which mainly consists of UPJO (20%-70%), VUR (30%-60%) and other obstructive uropathies (20%-30%). In our study, the incidence rate of RPD was decreased to 2.2% if the criterion of APRPD changed to ≥ 10 mm consequently, similar to the previous findings. However, we had only 9 cases (4.6%) diagnosed specifically. Compared with the study by Masami Tsuchiya et al,[9] they reported that 8 (53.3%) out of 15 cases were operated on severe uropathies, while that of our study was 88.9%. The relatively low diagnosed rate might attribute to our strict indications for further examination and low parents' compliance. In addition, we totally detected 0.2% cases with other types of CAKUT, which was similar to others.[7 9] So as to the follow-up data of mild-moderate RPD,[18] we found that cases with APRPD 5-9.9mm, 85% of cases had undergone a spontaneous normalization as demonstrated on renal US within 12-month-old, even in APRPD≥10mm, about 60% got resolution.

Based on the ROC curve, we calculated that the ideal APRPD cut-off point for the detection of significant obstructive uropathy and indication for surgical intervention was 9.7mm and 13.5mm, which is in contradiction to such analyses in some studies.[7 19] In the case of a screening test, the most

important parameter is its sensitivity. In fact, we diagnosed two cases with CAKUT in an APRPD of 5-9.9mm, one was diagnosed with renal duplication with mild ipsilateral RPD and ectopic ureteral orifice, the other was detected with remarkable ureterectasia on following ultrasounds. Therefore, we proposed APRPD ≥10mm as criterion of RPD who required follow-up and further examinations, as well as APRPD 5-9.9mm with ureterectasia or other abnormal findings. While for cases with isolated APRPD ≥5-9.9mm, education of UTI was even more important in case of pathological abnormalities, such as VUR.

In a study from Sheih et al,[20] they estimated that renal ultrasound screening of children in elementary and junior high schools would cost $US 0.36 per child and the benefit to cost ratio was nearly 8.0, and our ratio was approximately 3 based on the similar calculation method. In addition, data from questionnaire of The Study Group of Ultrasonographic Screening for CAKUT in Japan indicated that the screening cost per child would be ¥1,200 ($US15), and 3 potential dialysis patients would be found per 55,000 children. If dialysis in these 3 patients could be delayed for 3.7 years, screening would pay for itself[9]. These indicated that our screening would achieve better cost-benefit if we could decrease the cost, standardize the criterion, examined the outline, and improve adherence.

However, there were several limitations need to be improved. We conducted our study in neonates with factors, such as preterm, low birth weight and so on,

which was not a real population-based study. We would promote ultrasound screening for CAKUT in all neonates in the further study. As almost half cases of mild-moderate RPD were lack of follow-up data, we could not predict the exact morbidity of CAKUT among all births. In addition, the cost-effectiveness should be calculated in detail in future research.

Conclusion

Such a screening model for CAKUT based on three-level network among neonates in Shanghai, China was an integration of medical resources of CHCs, district MCH and tertiary children's hospitals. It proved to be effective for the early detection, follow-up and intervention of CAKUT in early postnatal period. This replicable and reliable approach would be applicable to CAKUT screening program in other developing areas.

Acknowledgements

Thanks to all doctors in Department of Child Health of all the CHCs in Minhang District and Minhang MCH for their contribution.

Funding Source: This work was supported by Special Scientific Research Fund of the Ministry of Health, China (Grant number: 201002006), Shanghai Public Health Three-Year Action Plan (2015-2017) sponsored by Shanghai Municipal Government (Grant number: GWIV14.2), Chronic disease

prevention and control project sponsored by Shanghai Hospital Developmental center (Grant number: SHDC12015301).

Financial Disclosure Statement for all authors: All authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of interest: None of the authors have had any financial interest in any products, devices or drugs used in the manuscript. There is no conflict of interest related to any commercial associations or financial relationships (consultancy, stock ownership, equity interest, patent licensing arrangements or payments for conducting or publicizing the study contained in the manuscript).

Contributors' Statement:

Hong Xu: Dr Xu conceptualized and designed the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Yinv Gong: Dr Gong carried out the work of screening and management, data collection, the initial analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Ying Zhang: Dr Zhang carried out the work of screening and management, data collection, the initial analyse and approved the final manuscript as submitted.

Qian Shen, Liping Xiao: Drs Shen and Xiao coordinated and supervised data collection, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Yihui Zhai, Yunli Bi, Jian Shen, Hong Chen: Drs Zhai, Bi, Shen and Chen carried out the work of management, coordinated data collection and approved the final manuscript as submitted.

Yun Li: Dr Li carried out the work of screening and management, coordinated data collection and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Ethical approval: The study was approved by the Research Ethical Committee of Children's Hospital of Fudan University.

Data sharing: No additional data are available.

What is Already Known on This Topic

Ultrasound screening for CAKUT in early postnatal period has been proposed and applied in several developed countries and regions.

What This Study Adds

The screening model based on three-level network is effective and feasible for

early detection, follow-up and intervention of CAKUT among neonates in developing regions.

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Figure 1. The procedure of the three-level screening model for CAKUT in early postnatal period in Shanghai, China

CHCs: Community Health Centers; MinHang MCH: MinHang Maternal and Child Health Hospital; RPD: Renal pelvic dilation. Other abnormalities were other renal and urinary malformations, including renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney (MCDK), ectopical kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.

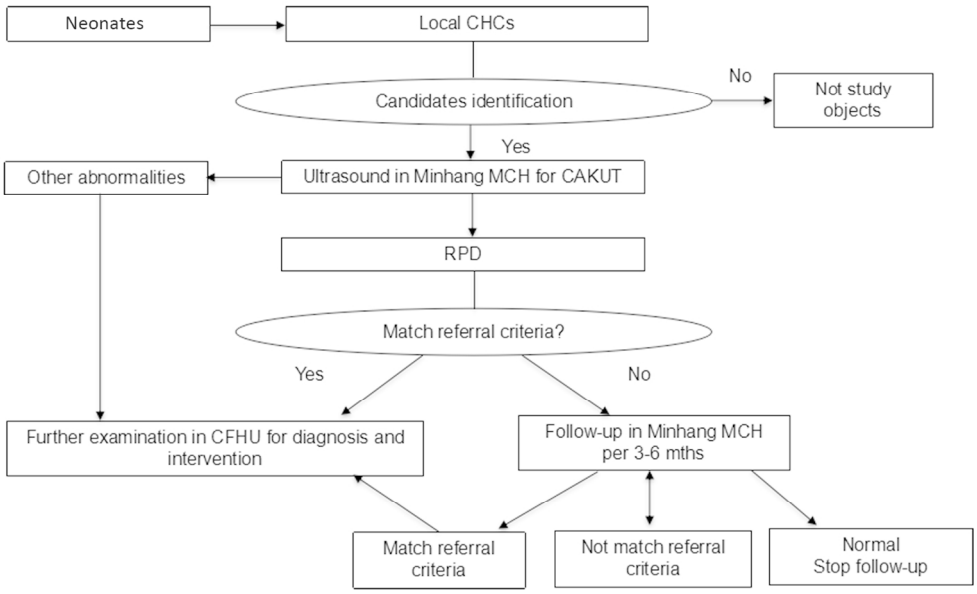
Figure 2. General data of the screening model

Other abnormalities were other renal and urinary malformations, including renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney (MCDK), ectopical kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.

Figure 3. Resolution of RPD
A Kaplan-Meier curve for RPD patients with normalization of ultrasound; B The resolution time of different degree of RPD (median with interquartile range)

Figure 4. The ROC curve based on the APRPD index as an indicator of obstructive uropathy

Figure 5. The ROC curve based on the APRPD index as an indicator of the need for surgical intervention



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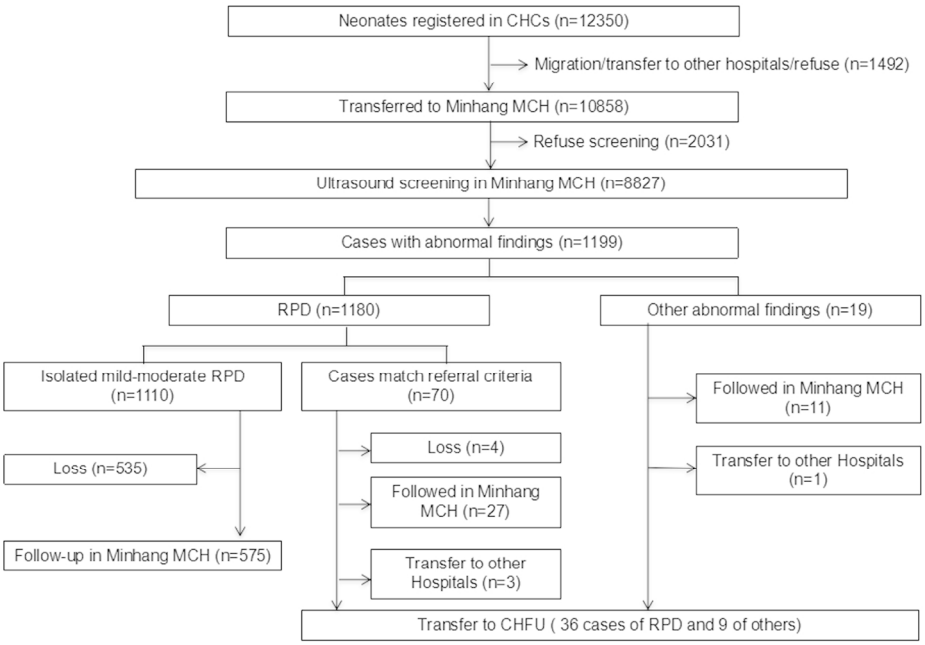

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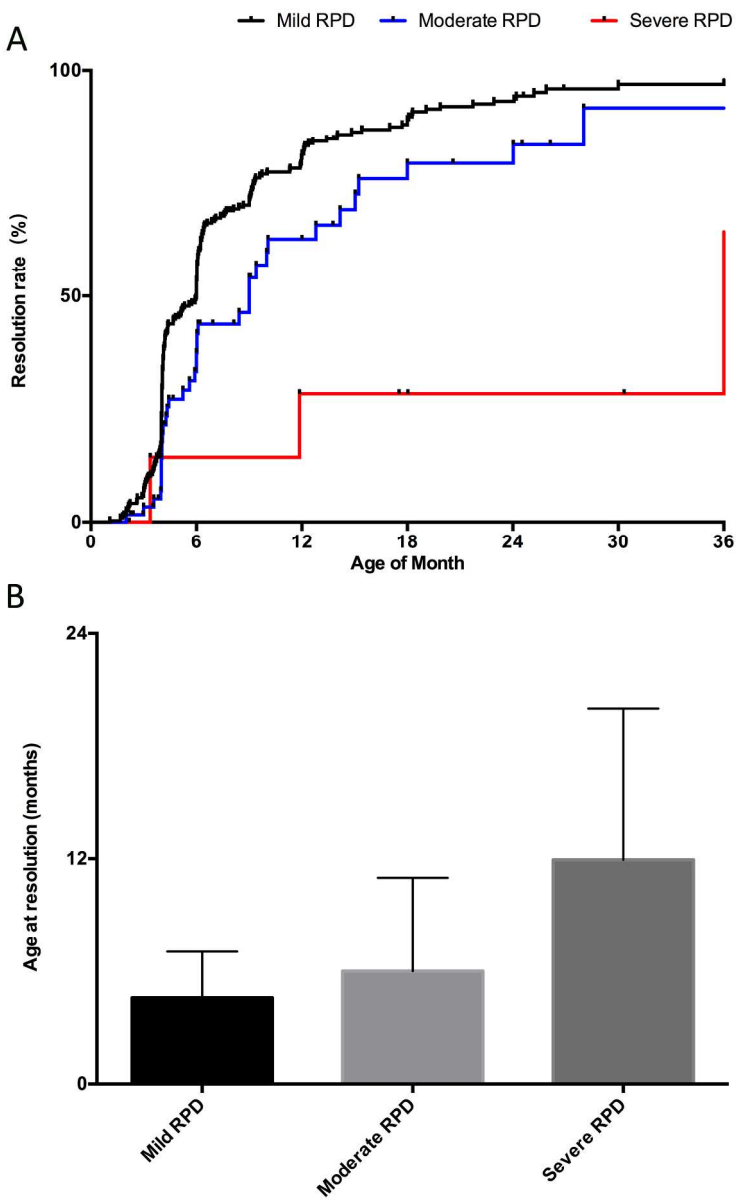

Figure 3. Resolution of RPD
A Kaplan-Meier curve for RPD patients with normalization of ultrasound; B The resolution time of different degree of RPD (median with interquartile range)

175x270mm (300 x 300 DPI)

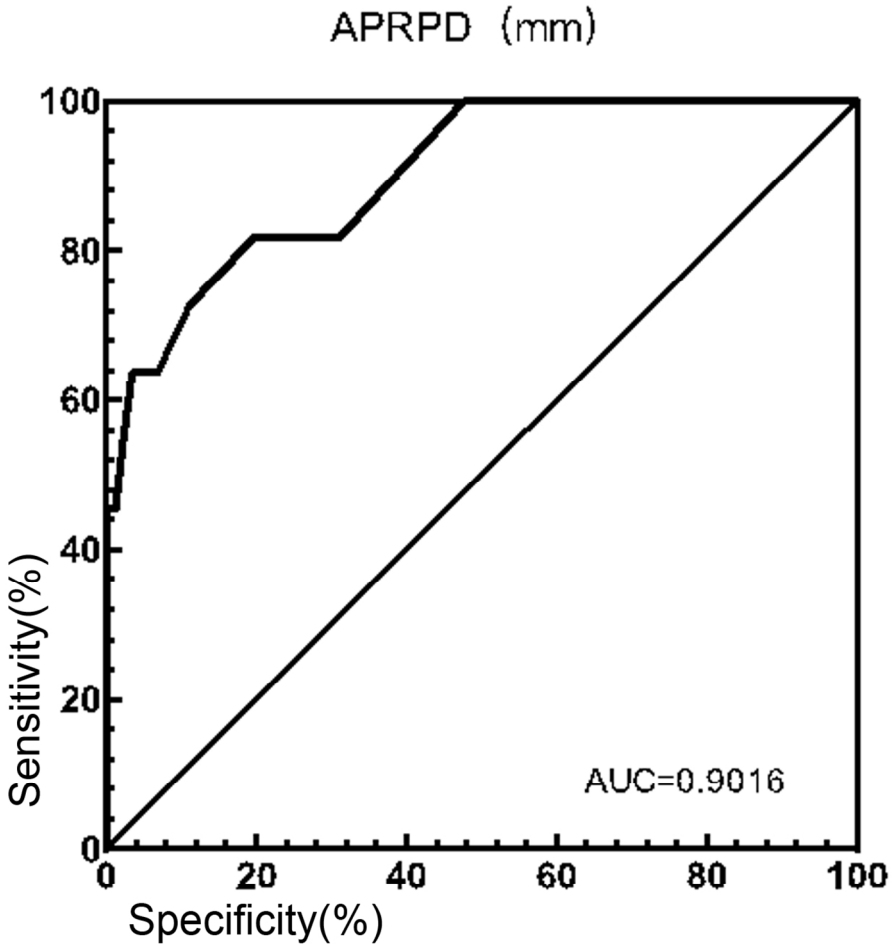

Figure 4. The ROC curve based on the APRPD index as an indicator of obstructive urology

117x117mm (300 x 300 DPI)

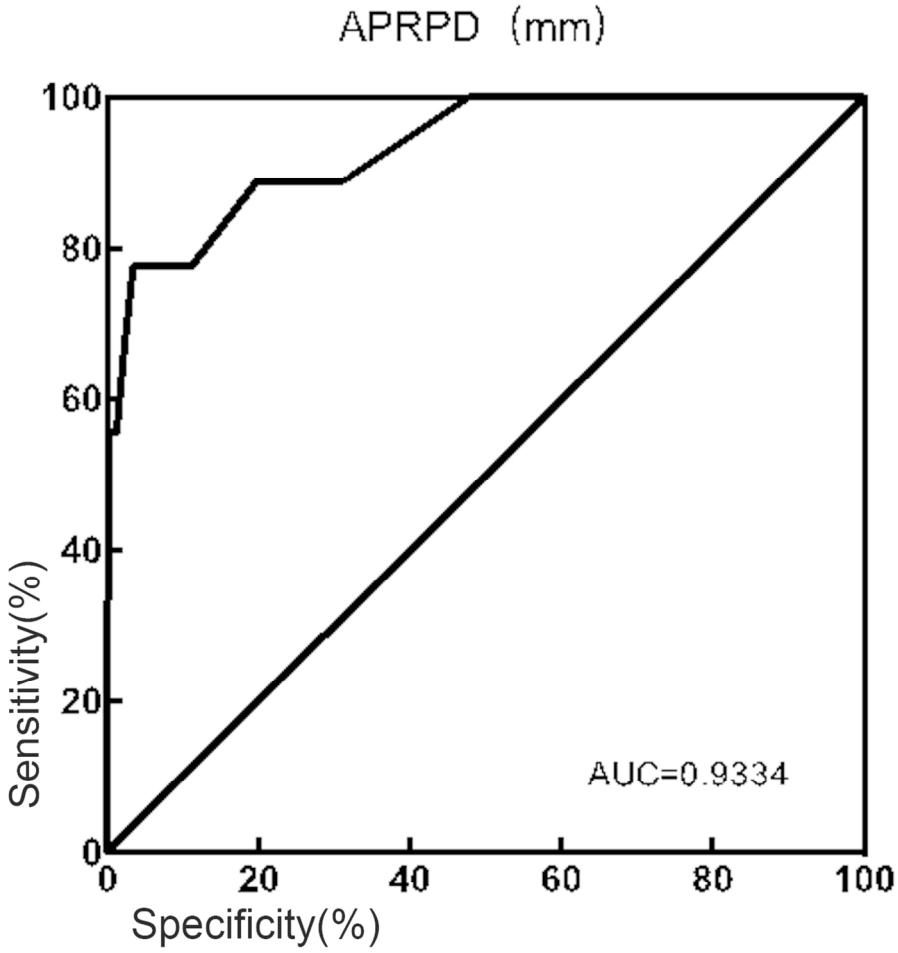

Figure 5. The ROC curve based on the APRPD index as an indicator of the need for surgical intervention

119x120mm (300 x 300 DPI)

Supplement Table 1 Details of RPD patients with specific diagnosis

Case	No.	Gender	APPD(mm)		CAKUT (Side)	Management	Surgery age (m)	Post operation condition
			Left	Right				
1	GXN	M	21	-	UPJO (L)	Pyeloplasty	1.5	RPD alleviated distinctly DRF 40.5%(6 mths after)
2	LZY	M	-	38	UPJO (R)	Pyeloplasty	1.5	RPD alleviated distinctly
3	WZC	M	8	60	UPJO(R)	External drainage+ Pyeloplasty	1.6	RPD alleviated distinctly
4	CJ	M	24	-	UPJO (L)	Pyeloplasty	8.0	RPD alleviated distinctly
5	GYX	M	-	21	UPJO (R)	Pyeloplasty	2.0	RPD alleviated distinctly DRF 46.6% (6 mths after)
6	ZCX	M	11	9	UPJO (L)	Follow-up	-	

7	ZXY	F	14	7	RD (Bi) Ureterectasia (L) Ureterocele (L)	Transurethral endoscopic unroofing of ureteroceles	2.0	RPD and Ureterectasia alleviated No UTI DRF normal
8	ZWS	M	8	-	RD with ipsilateral severe RPD and ectopic ureteral orifice (L)	Ureteral reimplantation	27.0	RPD and Ureterectasia alleviated DRF normal
9	JFR	M	12	-	RD(L) RD+ upper UPJO	LUPPN	36.0	RPD alleviated distinctly
10	ZSR	F	-	15	MU(R)	Ureteral reimplantation	27.0	Ureterectasia alleviated DRF<40%
11	JHB	M	8	-	MU(L)	Follow-up	-	

L: Left; R: Right; Bi: Bilateral; MU: Megaureter; RD: Renal duplication; DRF: differential renal function; LUPPN: laparoscopic upper pole partial nephrectomy.

BMJ Open

Early detection of congenital anomalies of the kidney and urinary tract: Cross-sectional results of a community-based screening and referral study in China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-020634.R2
Article Type:	Research
Date Submitted by the Author:	18-Mar-2018
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Public health, Renal medicine, Urology
Keywords:	Congenital anomalies of the kidney and urinary tract (CAKUT), Ultrasound screening, Neonate, Three-level network

Title Page

Title: Early detection of congenital anomalies of the kidney and urinary tract: Cross-sectional results of a community-based screening and referral study in China

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World count: 3101

Keywords: Congenital anomalies of the kidney and urinary tract (CAKUT); Ultrasound screening; Neonate; Three-level network

Abstract

Objective To establish an effective screening model of congenital anomalies of the kidney and urinary tract (CAKUT) using ultrasound among neonates in Shanghai, China.

Design Cross-sectional study

Setting A three-level screening model for CAKUT in neonates based on the child health care system was established since 2010 in Minhang District, Shanghai, China.

Participants During 2010–2015, neonates with criteria such as preterm, low birth weight, and so on were eligible to participate in the study. Cases with renal pelvis dilatation (RPD) and other abnormal renal findings were managed based on presumed strategies.

Main Outcome Measures The proportion of RPD and other renal and urinary tract anomalies; number of diagnosed CAKUT under integrated management, especially obstructive uropathy. The anterior–posterior pelvic diameter (APRPD) cut-off points for likelihood of obstructive uropathy and need for surgery.

Results A total 8827 infants were consecutively screened. Absolute and relative rates of different degrees of RPD classified by APRPD were: mild (5–9.9 mm), 984 (11.1%); moderate (10–14.9 mm), 176 (2.0%); severe (≥15 mm), 20 (0.2%). Of 639 followed cases with RPD, 11 were diagnosed as obstructive uropathies. Of these, 9 patients underwent surgery, at median age 2 months.

A total 85.4% of mild, 62.5% of moderate. and 30.0% of severe RPD cases resolved spontaneously. Other renal and urinary morphological abnormalities were diagnosed in 15 (0.2%) patients. The APRPD cut-off points for significant obstructive uropathy and need for surgery were 9.7 mm and 13.5 mm, respectively.

Conclusions This three-level screening model is an effective and feasible strategy for early detection and intervention of CAKUT in the early postnatal period, especially for patients with high-grade RPD and other renal and urinary malformations. This strategy could be useful in China and other developing areas with limited medical resources.

Article Summary

Strengths and limitations of this study

1. This is the first regional community-based screening program of CAKUT among neonates in China.
2. A large, nearly population-based study, nested within an organized screening and referral program that emphasized hierarchical management of RPD, for early detection and intervention of obstructive uropathy in the early postnatal period.
3. Integration of medical resources promoted management of CAKUT in district-level hospitals.
4. Our efforts to characterize the outcome of RPD were limited by the loss of nearly half of the cases with mild to moderate RPD, which prohibited us from drawing objective inferences.

Main Body of the Manuscript

Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT) are common anomalies detected prenatally, accounting for approximately 20%–30% of all prenatal anomalies and occurring in 3–6 per 1000 live births.[1] CAKUT is considered the leading cause of chronic kidney disease (CKD) in children[2] and can lead to end-stage renal disease (ESRD) in adults.[3]

Most children with CAKUT are diagnosed prenatally in developed countries,[4-5] largely because of the widespread use of fetal ultrasonography. Recently, postnatal ultrasound screening has been reported to be a useful method in the early detection and intervention of CAKUT,[6-9] as this technique can not only confirm abnormalities detected in the fetus but it can also detect undiscovered abnormalities during the prenatal period,[5,10] which may minimize renal damage and thereby improve quality of life.

It has been reported that the occurrence of CAKUT is associated with small gestational age, maternal gestational diabetes, oligohydramnios, maternal age, and so on.[11-13] Melo et al.[14] also identified prematurity, low birth weight, oligohydramnios, and CAKUT with renal involvement as independent risk factors for early mortality in patients with CAKUT.

Health checks of infants are obligatory according to the “rules of systematic health check-ups for children 0–6 years old in Shanghai (on trial)”, Newborns are visited at about 2 weeks of age by specialized nurses from local

community health centers (CHCs) and parents are informed to build health records. The first infant health check is performed at about 1 month of age in a local CHC, then systematic health checks are regularly conducted up to age 6 years. CHCs and secondary hospitals (mostly Maternal and Child Healthcare (MCH) hospitals) play vital roles in this public child healthcare network. CHCs are considered the basic network of public health surveillance and medical services, such as basic health checks and health education. However, limited medical training among staff at CHCs leads to a lack of recognition of CAKUT and CKD. Secondary hospitals are committed to guaranteeing the health of local children as they have more adequate equipment. However, staff at secondary hospitals lack experience in managing specific pediatric diseases, like CAKUT. Hence, it is imperative to propose a useful strategy to improve this situation and make rational use of medical resources.

In the current study, we established a novel three-level screening model, composed of CHCs for identification of screening candidates, the district Maternal and Child Healthcare (MCH) hospital for ultrasound screening of CAKUT, and the tertiary hospital, Children's Hospital of Fudan University (CHFU), for specific diagnosis and intervention. In addition, CHFU provided training for staff of the CHCs and district MCH hospital. We conducted postnatal urinary ultrasound screening and management of CAKUT based on this model in Shanghai, China.

Study participants and methods

Screening model and study design

Minhang District in Shanghai, with a population of 2.5 million and around 30 thousand births per year, was selected to establish this novel screening model. The model was based on the child healthcare system and is summarized in Fig.1. The model comprised the CHCs for identification of screening participants; the district hospital, Minhang MCH hospital, for urinary tract ultrasound screening of CAKUT and follow-up; and the tertiary hospital, CHFU, for specific diagnosis and intervention; we referred to this structure as a three-level network.

To propose a screening strategy suitable for developing countries with a large population, we carried out a cross-sectional ultrasound screening for CAKUT based on the three level network in neonates, with certain criteria for priority screening, listed in Table 1.

Table 1 Criteria for priority screening

Criteria
Low birth weight (birth weight less than 2500 grams)
Macrosomia (birth weight more than 4000 grams)
Premature delivery (gestational weeks less than 37 weeks)
Oligohydramnios
Malposition/ Cephalopelvic disproportion
Pregnancy at advanced age (more than 35 years old)
Gestational diabetes mellitus
Gestational hypertension syndrome/proteinuria
Intracranial hemorrhage or infection
Neonatal hyperbilirubinemia

Study participants

All neonates who met the criteria (Table 1) were theoretically eligible to

participate in the study, conducted from September 2010 to September 2015. Participants were identified in local CHCs when they were first registered, at about 1 month old. Identified neonates were then transferred to Minhang MCH hospital for urinary ultrasound screening. Allowance was made for conducting ultrasound screening at up to 3 months of age, to ensure that the vast majority of neonates were examined.

The study was approved by the Research Ethical Committee of Children's Hospital of Fudan University. Informed consent was obtained from all parents or guardians before all procedures in this study.

Test methods and classification

Ultrasound tests were carried out by ultrasonographers at Minhang MCH hospital. Each year, these staff receive one-week training, including practice and specialized lecture courses, taught by professional ultrasonographers at CHFU. All study participants were screened using a GE Voluson 730 scanner (GE Healthcare, Little Chalfont, UK) with a 5–7 MHz convex-type transducer. Recordings consisted of six bilateral renal images,[8] including one longitudinal and two transverse images obtained in the supine position. The anterior–posterior pelvic diameter (APRPD) was measured on transverse images of the kidneys, to evaluate the severity of renal pelvis dilatation (RPD). The urinary bladder was also observed in the supine position. Images were recorded when abnormalities were identified.

The following indexes were measured and obtained via ultrasonography: (1)

number, size, and location of kidneys; (2) RPD and caliectasis; (3) echogenicity; (4) other positive findings indicating cysts or tumors. The shape and wall thickening of the urinary bladder, as well as ureterectasis (inner diameter of the ureter ≥5 mm) were also recorded.

RPD was defined as APRPD ≥5 mm and was further classified into three degrees: mild (5–9.9 mm), moderate (10–14.9 mm), and severe (≥15 mm).[15]

Management and follow-up

When abnormalities were detected, the guardians of the affected infants were informed. Depending on the severity, we explained the situation and recommended a protocol including follow-up and further examination.

1) For cases with isolated unilateral APRPD ≥15 mm, bilateral APRPD ≥10 mm with or without caliectasis, ureterectasis or parenchymal thinning, unilateral APRPD 5–14.9 mm or bilateral APRPD 10–14.9 mm with caliectasis and/or ureterectasis, or other abnormal findings of the kidneys, ureters, and bladder, guardians were recommended to transfer the infants to CHFU immediately for further examination, to obtain a specific diagnosis and suitable intervention. Additional examinations performed at CHFU included repeated ultrasound, urinalysis, diuretic-loaded diethylenetriamine pentaacetic acid (DTPA) renography, magnetic resonance urography (MRU), and micturating cystourethrography (MCU) or dimercaptosuccinic acid (DMSA) renal scintigraphy, if necessary.

2) For cases with isolated unilateral APRPD 5–14.9 mm or bilateral APRPD

5–9.9 mm, ultrasound follow-up was performed at MinHang MCH hospital every 3–6 months combined with regular health checks, and guardians were told to take infants for urine testing immediately if unknown fever occurred.

3) During regular follow-up, if RPD deteriorated in cases with conditions listed in 1) above, cases with persistent unilateral APRPD 10–14.9 mm up to 1 year old, or in whom febrile/recurrent urinary tract infection developed, the case would be transferred for further examination, as mentioned above.

Screening of CAKUT and follow-up of cases with RPD at Minhang MCH hospital was conducted by the department of Child Care, whereas severe cases in CHFU were managed jointly by the department of nephrology and urology, and partially by Minhang MCH hospital to ensure more cases under follow-up.

Data collection and statistical analysis

All demographic and clinical data in the model were collected from Minhang MCH and CHFU hospitals. Enumeration data were presented as median (P_{25}, P_{75}) and rate. The proportion of RPD and other renal and urinary tract abnormal findings was calculated in the study population, and the number of patients diagnosed and treated surgically was determined for individual groups of cases with RPD.

In cases with RPD, the subsequent diagnostic and therapeutic measures were analyzed. The receiver operating characteristic (ROC) curve was plotted to enable us to define an appropriate APRPD cut-off point to select for children

requiring further surveillance, and to detect patients who require surgical treatment. Statistical analysis was performed using Prism 6 software (GraphPad Software, La Jolla, CA, USA).

Patient involvement

No patients were involved in setting the research or the outcome measures, nor were they involved in developing the recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. We will disseminate the results of the study through academic communication and Medical Popular Science Education.

Results

Overall condition

Between September 2010 and September 2015, a total 12,350 consecutive newborns met the criteria, accounting for about 8% of all births during the study period. Of these, 10,858 neonates were transferred to Minhang MCH hospital on schedule, and urinary ultrasound screening was performed in 8827 infants (sex ratio=1.3:1). The mean screening rate was 81.3% (8827/10858), which increased each year and reached 96% in 2015 (Fig. 2). The median age at screening was 40 (33.60) days. Infants with presumed risk factors, such as premature delivery and/or low birth weight, accounted for 61.4% of participants, followed by those with macrosomia (23.7%).

RPD was found in 1180 (13.4%) infants, with an approximate sex ratio of 2.2:1. Classified by APRPD, the incidence rates of RPD in individual groups were as follows: mild (5–9.9 mm), 984 (11.1%) cases; moderate (10–14.9 mm), 176 (2.0%) cases; and severe (≥15 mm), 20 (0.2%) cases.

Follow-up data of RPD

Among cases with RPD, 70 met any referral criterion for further examination. Of these, 36 were followed at CHFU, according to the previous procedure, and another 30 patients remained under observation, mainly at Minhang MCH hospital. Therefore, the total case-management rate of severe patients reached 94.3%, based on the three-level network. A total 575 cases (approximately 51.8%) with isolated mild to moderate RPD were followed up at Minhang MCH hospital.

Combining all followed-up data of RPD cases, 11 of the 36 patients transferred to CHFU obtained a specific diagnosis, as follows: 6 cases of ureteropelvic junction obstruction (UPJO), 3 cases of renal duplication with ipsilateral RPD, and 2 cases of megaureter. Surgery was performed in 9 cases at median age 2 months (Supplement 1). As for other RPD cases (Table 2, Fig. 3A), 85.4% of mild, 62.5% of moderate, and 30.0% of severe cases resolved spontaneously, mainly within 12 months of age (Fig. 3B). Persistent pelvic dilatation continued significantly longer in moderate and severe cases than in mild ones (P=0.0134).

Table 2 Outcome of RPD case follow up

	Mild	Moderate	Severe	Total
No. followed-up (% No. RPD)	507 (51.5)	113 (64.2)	20 (100.0)	640 (54.2)
No. of diagnosed (% No. followed-up)	2 (0.6)	3 (2.7)	6 (30.0)	11 (1.7)
Diagnosis	MU (1) RD (1)	UPJO (1) RD (2)	UPJO (5) MU (1)	UPJO (6) RD (3) MU (2)
No. resolution (% No. followed-up)	433 (85.4)	70 (62.5)	6 (30.0)	509 (79.5)

MU, megaureter; RD, renal duplication.

Of all RPD cases followed up, 85.4% with mild, 62.5% with moderate, and 30.0% with severe RPD resolved spontaneously; the remaining cases were either still in follow-up or were only followed for a period.

Other abnormal findings of the renal and urinary system

Other abnormal findings were detected in 19 cases, as follows: 15 (0.2%) were diagnosed with CAKUT, 7 with unilateral renal aplasia (URA), two with renal duplication, two with renal dysplasia (one was bilateral), one with multicystic renal dysplasia (MCDK), one with renal ectopia, one with ureterectasia (diagnosed as ureterovesical junction obstruction), and one with renal cyst. One patient with URA, combined with ipsilateral vesicoureteral reflux (VUR) stage V, developed renal damage and underwent surgery at 11 months old, thereby preventing further kidney deterioration. The patient with bilateral renal dysplasia developed ESRD at 6 years old and was monitored. The remaining four cases were normal by repeated ultrasound at CHFU within 1 month; two had unclear boundaries of the renal cortex and medulla, one had a ureterocele, and the last patient had ureterectasia.

Data of the ROC curve

The ROC curve for postnatal ultrasound screening was plotted, and the area under the curve calculated (area under curve (AUC) = 0.901, 95% confidence interval (CI): 0.813–0.990) (Fig. 4).

Based on the ROC, the ideal APRPD cut-off point for the detection of significant obstructive uropathy appears to be 9.7 mm or more, with sensitivity 81.8% (95% CI: 48.2%–97.7%), specificity 80.3% (95% CI: 77.0%–83.3%), positive likelihood ratio (+LR) 4.13, and negative likelihood ratio (–LR) 0.23.

When the need for surgical intervention was indicated, the AUC was 0.9334 (95% CI: 0.850–1.017) (Fig. 5). The ideal APRPD cut-off point appears to be 13.5 mm or more, with sensitivity 77.8% (95% CI: 40.0%–97.2%), specificity 96.5% (95% CI: 94.8%–97.8%), +LR 22.3, and –LR 0.2.

Discussion

Our rationale for CAKUT screening was to perform screening before the occurrence of renal damage and in as many neonates as possible. In Japan, health checks at 1 month old are very popular because public health plans cover the fee. Yoshida et al.[8] proposed that mass screening for CAKUT at the 1-month-old health check was timely and technically appropriate; more than 90% of infants born at their hospital received renal ultrasound screening as part of their routine health checks during the study period. Tsuchiya et al.[9] also advocated an established ultrasonographic screening system for CAKUT in Japan. Similarly, Caiulo et al.[6] conducted ultrasound screening in Italy at age

2 months, combined with routine health checks. According to “management of high-risk infants (low-birth-weight) in Shanghai” (on trial), routine health checks after birth are performed in CHCs at age 1 month, which are supervised by the district MCH hospital. Furthermore, the district MCH hospital monitors data of all newborns’, especially those with presumed risk factors of preterm, low birth weight and so on. In the present study, we conducted our screening in combination with the public Child Healthcare system in Shanghai, with urinary ultrasound screening as part of routine health checks during the study period. More than 80% of candidate neonates were examined in their first 3 months of life. It was remarkable that the screening rate increased gradually and reached 96% in 2015, indicating increased awareness about the importance of early detection of CAKUT in CHCs, MCH hospitals, and among guardians. Moreover, the district hospital, Minhang MCH hospital, was actually the central hub of the screening model, with screening candidates identified in CHCs and the MCH hospital conducting follow-up of cases with mild to moderate RPD and transferring severe cases to the tertiary hospital. At the same time, Minhang MCH hospital played a significant role in medical and social education, which was reflected in the increasing screening rates seen over the study period. CHFU was not only responsible for diagnosing and treating cases with CAKUT but also used for designing, training, and quality supervision. Such a screening model is an example of integration with an existing child healthcare delivery system and a tertiary children’s hospital, forming a working hierarchical

management model and making more rational use of medical resources. Regarding follow-up, nearly all severe cases met the criteria for referral and were transferred or followed up with in cooperation with CHFU and Minhang MCH hospitals. Ours is the first community-based screening program of CAKUT in China.

Yoshida et al.[8] indicated that RPD of ≥5 mm was sufficient to find all dilated systems. However, evaluation would be made easier by increasing the specificity, setting the criterion for abnormal RPD at APRPD ≥10 mm, according to the recent multidisciplinary consensus regarding a urinary tract dilation (UTD) classification system, which proposes that the renal pelvis is considered normal with APRPD <10 mm postnatally.[16] With APRPD ≥5 mm as the criterion for RPD used in our study, 1180 infants (13.4%) were classified as having RPD. Several studies have used APRPD ≥10 mm as the threshold, with frequency ranging from 1.1%–2.8%;[6 17 18] other studies have chosen Society for Fetal Urology (SFU) grade 2 or higher, such as Tsuchiya et al.[9] who screened 5700 infants aged 1 month, yielding 114 RPD cases (2.0%). What's more, all these studies showed similar diagnostic rates (12%–13%) in cases with RPD, mainly consisting of UPJO (20%–70%), VUR (30%–60%), and other obstructive uropathies (20%–30%). In our study, the incidence of RPD decreased to 2.2% if the criterion was changed to APRPD ≥10 mm, similar to previous findings. However, we had only 9 cases (4.6%) with specific diagnoses. Compared with the study by Tsuchiya et al,[9] which reported that 8

(53.3%) of 15 cases required surgery for severe uropathies, that proportion in our study was 88.9%. The relatively low diagnosis rate might be attributed to our strict indications for further examination and low parental compliance. In addition, we detected a total 0.2% of cases with other types of CAKUT, similar to other studies.[7,9] As to follow-up data of patients with mild to moderate RPD,[18] we found that those with APRPD 5–9.9 mm (85% of cases) had undergone spontaneous normalization, as demonstrated by renal ultrasound before age 12 months. Even in patients with APRPD ≥10 mm, about 60% achieved resolution.

Based on the ROC curve, we calculated that the ideal APRPD cut-off points for detection of significant obstructive uropathy and indication for surgical intervention were 9.7 mm and 13.5 mm, respectively, which contradict the analyses in some studies.[7 19] In the case of a screening test, the most important parameter is its sensitivity. In fact, we diagnosed two patients with CAKUT who had APRPD 5–9.9 mm; one was diagnosed with renal duplication with mild ipsilateral RPD and ectopic ureteral orifice, and the other had remarkable ureterectasia detected on follow-up ultrasounds. Therefore, we propose APRPD ≥10 mm as the criterion for determining those patients with RPD who require follow-up and further examination, as well as APRPD 5–9.9 mm to detect those with ureterectasia or other abnormal findings. For isolated cases with APRPD ≥5–9.9 mm, education about urinary tract infection is even more important in cases of pathological abnormalities, such as VUR.

Sheih et al.[20] estimated that renal ultrasound screening of children in elementary and junior high schools would cost USD 0.36 per child, with a benefit to cost ratio of nearly 8.0; our ratio was approximately 3, based on a similar calculation method. In addition, data from questionnaires of the Study Group of Ultrasonographic Screening for CAKUT in Japan indicate that the screening cost per child would be JPY 1,200 (USD 15), and three potential dialysis patients would be identified per 55,000 children. If dialysis in these three patients could be delayed for 3.7 years, screening would pay for itself[9]. These findings indicate that our screening would achieve better cost-benefit if we could decrease the cost, standardize the criteria, examine the outline, and improve adherence.

There were several limitations in this study that must be addressed. We conducted our study among neonates with presumed risk factors, such as preterm, low birth weight, and so on; therefore, this was not an actual population-based study. We aim to promote ultrasound screening for CAKUT in all neonates in a future study. As nearly half of patients with mild to moderate RPD lacked follow-up data, we could not predict the exact morbidity of CAKUT among all births. In addition, cost-effectiveness should be calculated in detail in future research.

Conclusion

A screening model for CAKUT among neonates based on the present

three-level network in Shanghai, China integrates the medical resources of CHCs, district MCH hospital, and tertiary children's hospitals. This model proved to be effective for the early detection, follow-up, and intervention of CAKUT, particularly for cases with high-grade RPD and other renal and urinary anomalies in the early postnatal period. This replicable and reliable approach is applicable to CAKUT screening programs in other developing areas.

Acknowledgments

Thanks go to all doctors in the Department of Child Health of all the CHCs in Minhang District and Minhang MCH hospital for their contribution.

Funding: This work was supported by the Special Scientific Research Fund of the Ministry of Health, China [grant number: 201002006], the Shanghai Public Health Three-Year Action Plan (2015–2017) sponsored by the Shanghai Municipal Government [grant number: GWIV14.2], and the Chronic Disease Prevention and Control Project sponsored by the Shanghai Hospital Developmental Center [grant number: SHDC12015301].

Financial Disclosure Statement for all authors: All authors have indicated that they have no financial relationships relevant to this article to disclose.

Competing interests: None of the authors have any financial interest in any

products, devices or drugs used in the manuscript. There is no conflict of interest related to any commercial associations or financial relationships (consultancy, stock ownership, equity interest, patent licensing arrangements or payments for conducting or publicizing the study contained in the manuscript).

Contributors' Statement:

Hong Xu: Dr. Xu conceptualized and designed the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Yinv Gong: Dr. Gong carried out the work of screening and management, data collection, the initial analysis, drafted the initial manuscript, and approved the final manuscript as submitted.

Ying Zhang: Dr. Zhang carried out the work of screening and management, data collection, and the initial analysis, and approved the final manuscript as submitted.

Qian Shen, Liping Xiao: Drs. Shen and Xiao coordinated and supervised data collection, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

Yihui Zhai, Yunli Bi, Jian Shen, Hong Chen: Drs. Zhai, Bi, Shen, and Chen carried out the work of management, coordinated data collection, and approved the final manuscript as submitted.

Yun Li: Dr. Li carried out the work of screening and management, coordinated

data collection, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and have agreed to be accountable for all aspects of the work.

Ethical approval: The study was approved by the Research Ethical Committee of Children's Hospital of Fudan University.

Data sharing: No additional data are available.

What is Already Known on This Topic

Ultrasound screening for CAKUT in the early postnatal period has been proposed and applied in several developed countries and regions.

What This Study Adds

The screening model based on a three-level network is effective and feasible for early detection, follow-up, and intervention of CAKUT among neonates in developing regions.

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Figure legend

Figure 1. Procedure of the three-level screening model for congenital anomalies of the kidney and urinary tract (CAKUT) in the early postnatal period in Shanghai, China

Other abnormalities: other renal and urinary malformations, including renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney, ectopic kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.

CHCs, Community Health Centers; Minhang MCH, Minhang Maternal and Child Health hospital; RPD, renal pelvic dilation; CHFU, Children's Hospital of Fudan University.

Figure 2. General data of the screening model

Other abnormal findings: other renal and urinary malformations, including renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney, ectopic kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.

CHCs, Community Health Centers; Minhang MCH, Minhang Maternal and Child Health hospital; RPD, renal pelvic dilation; CHFU, Children's Hospital of Fudan University.

Figure 3. Resolution of renal pelvic dilation (RPD)

A) Kaplan–Meier curve for RPD patients with normalization of ultrasound findings. B) Resolution time of different degrees of RPD (median with interquartile range).

Figure 4. ROC curve based on the anterior–posterior pelvic diameter (APRPD) index as an indicator of obstructive uropathy.

Figure 5. ROC curve based on the anterior–posterior pelvic diameter (APRPD)

index as an indicator of the need for surgical intervention.

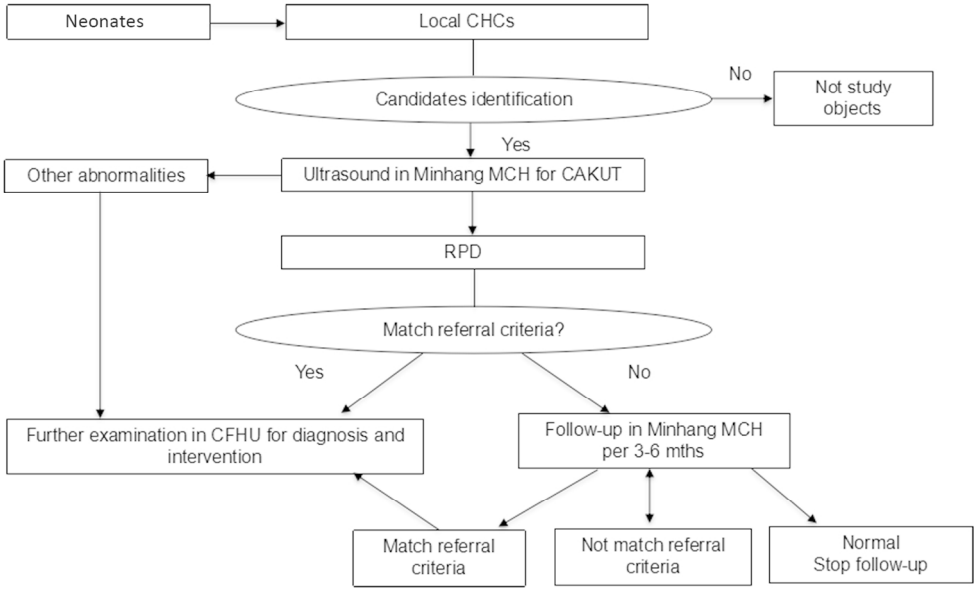

Figure 1. The procedure of the three-level screening model for CAKUT in early postnatal period in Shanghai, China

CHCs: Community Health Centers; MinHang MCH: MinHang Maternal and Child Health Hospital; RPD: Renal pelvic dilation. Other abnormalities include renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney (MCDK), ectopical kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.

122x75mm (300 x 300 DPI)

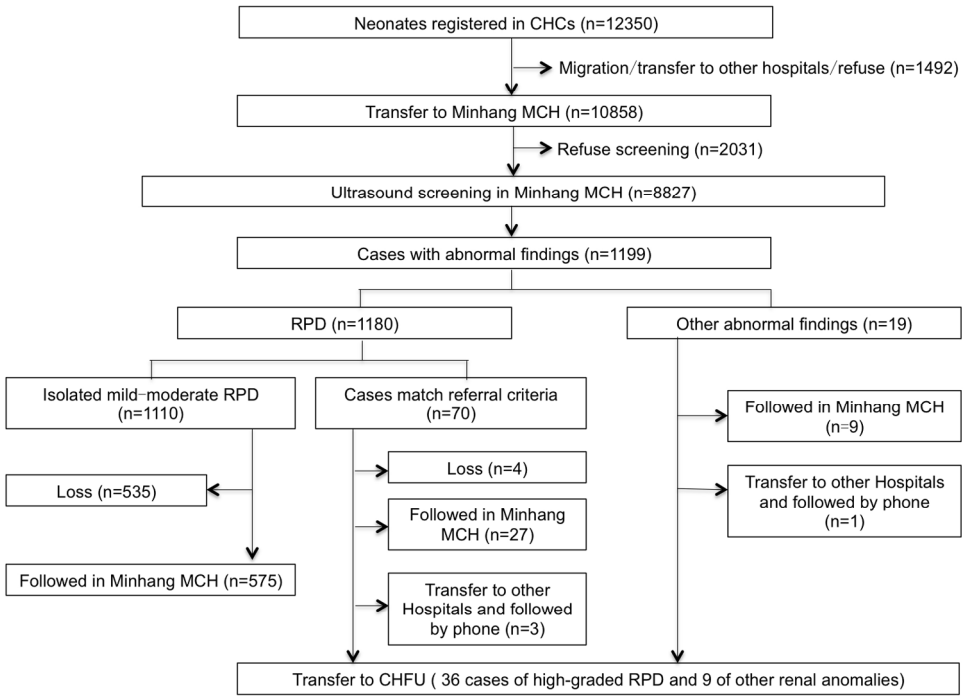

Figure 2. General data of the screening model ‼ ┼ Other abnormal findings: other renal and urinary malformations, including renal agenesis, renal hypoplasia/dysplasia, multicystic dysplastic kidney, ectopic kidney, polycystic kidney, horseshoe kidney, double renal pelvis, megaureter and so on, except renal parenchyma calcification or renal calculus.‼ ┼ CHCs, Community Health Centers; Minhang MCH, Minhang Maternal and Child Health hospital; RPD, renal pelvic dilation; CHFU, Children's Hospital of Fudan University.

235x171mm (300 x 300 DPI)

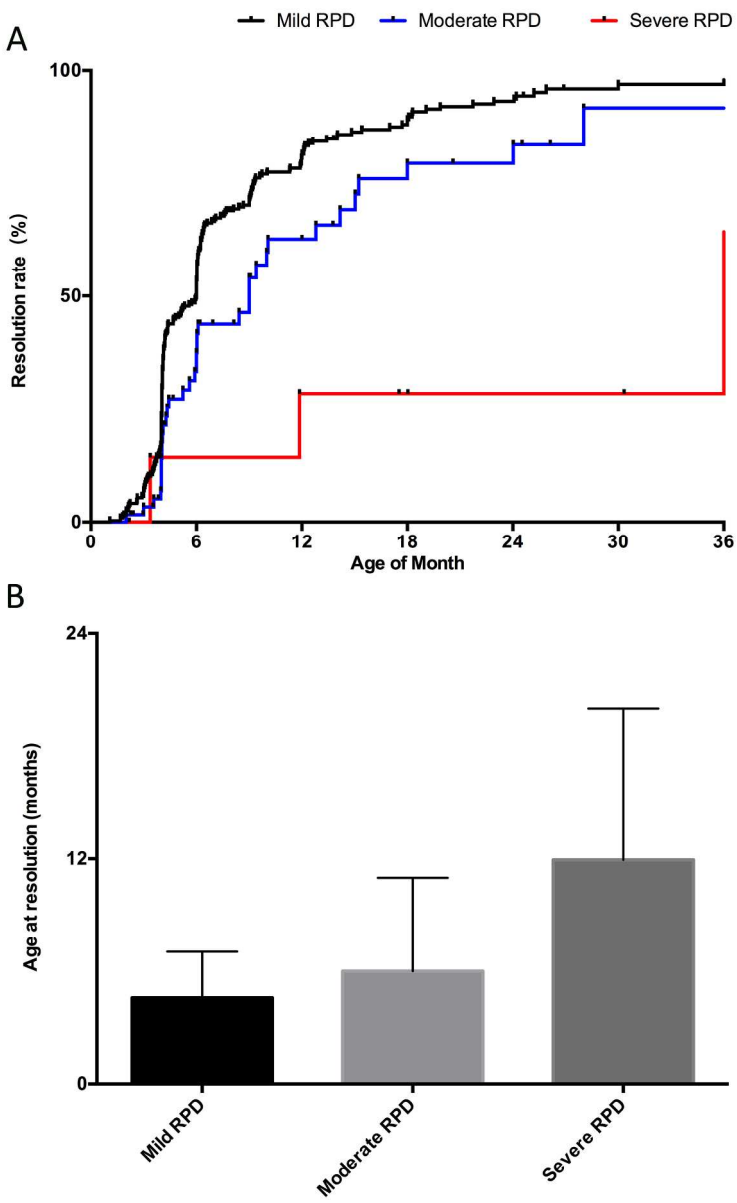

Figure 3. Resolution of RPD
A Kaplan-Meier curve for RPD patients with normalization of ultrasound; B The resolution time of different degree of RPD (median with interquartile range)

175x270mm (300 x 300 DPI)

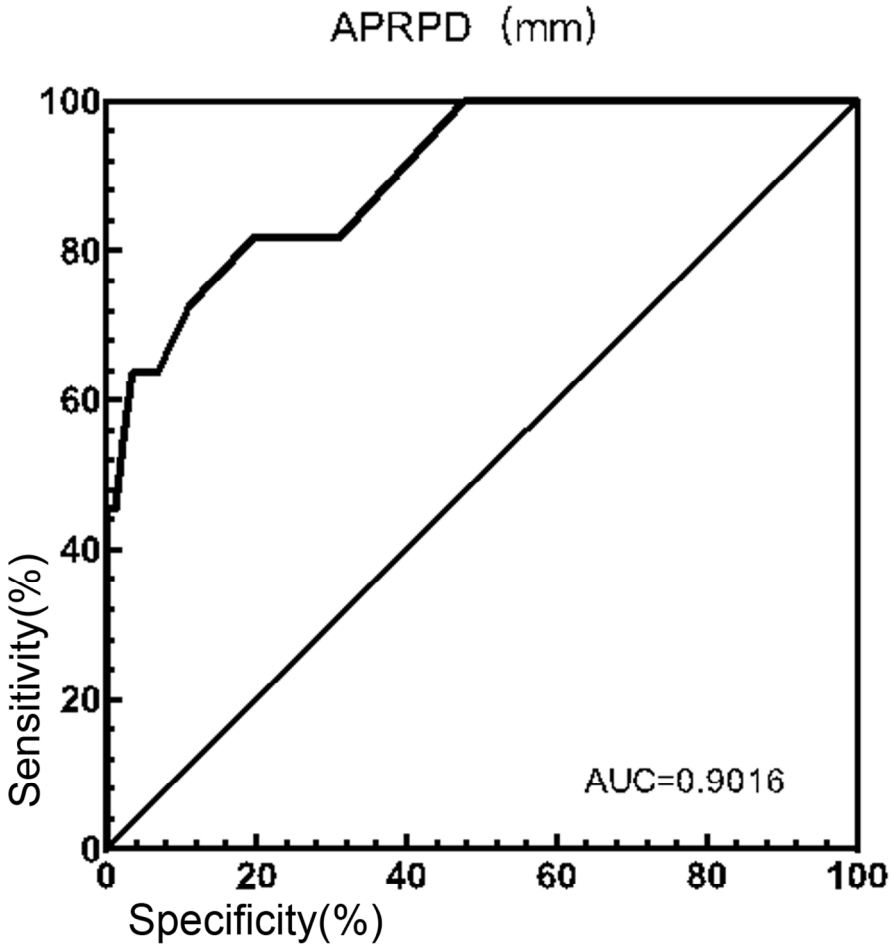

Figure 4. The ROC curve based on the APRPD index as an indicator of obstructive urology

117x117mm (300 x 300 DPI)

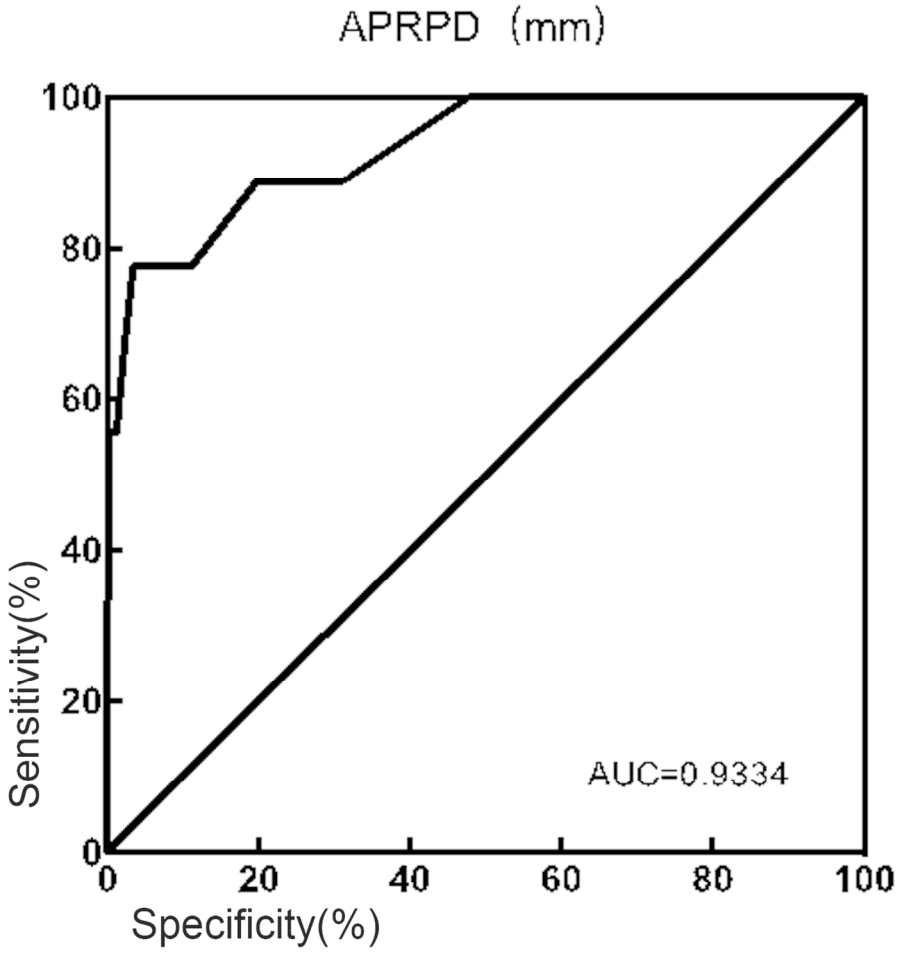

Figure 5. The ROC curve based on the APRPD index as an indicator of the need for surgical intervention

119x120mm (300 x 300 DPI)

Supplement Table 1 Details of RPD patients with specific diagnosis

Case	No.	Gender	APPD(mm)		CAKUT (Side)	Management	Surgery age (m)	Post operation condition
			Left	Right				
1	GXN	M	21	-	UPJO (L)	Pyeloplasty	1.5	RPD alleviated distinctly DRF 40.5%(6 mths after)
2	LZY	M	-	38	UPJO (R)	Pyeloplasty	1.5	RPD alleviated distinctly
3	WZC	M	8	60	UPJO(R)	External drainage+ Pyeloplasty	1.6	RPD alleviated distinctly
4	CJ	M	24	-	UPJO (L)	Pyeloplasty	8.0	RPD alleviated distinctly
5	GYX	M	-	21	UPJO (R)	Pyeloplasty	2.0	RPD alleviated distinctly DRF 46.6% (6 mths after)
6	ZCX	M	11	9	UPJO (L)	Follow-up	-	

7	ZXY	F	14	7	RD (Bi) Ureterectasia (L) Ureterocele (L)	Transurethral endoscopic unroofing of ureteroceles	2.0	RPD and Ureterectasia alleviated No UTI DRF normal
8	ZWS	M	8	-	RD with ipsilateral severe RPD and ectopic ureteral orifice (L)	Ureteral reimplantation	27.0	RPD and Ureterectasia alleviated DRF normal
9	JFR	M	12	-	RD(L) RD+ upper UPJO	LUPPN	36.0	RPD alleviated distinctly
10	ZSR	F	-	15	MU(R)	Ureteral reimplantation	27.0	Ureterectasia alleviated DRF<40%
11	JHB	M	8	-	MU(L)	Follow-up	-	

L: Left; R: Right; Bi: Bilateral; MU: Megaureter; RD: Renal duplication; DRF: differential renal function; LUPPN: laparoscopic upper pole partial nephrectomy.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	10

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	Fig. 2
		(c) Consider use of a flow diagram	Fig. 2
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	11-13
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	11-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-14
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	14-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.