THE PREVALENCE OF HEMOPHILIA IN MAINLAND CHINA: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract. The prevalence of hemophilia in mainland China was unclear; therefore, we can conducted a meta-analysis using existing data to evaluate the prevalence of hemophilia and its subtypes hemophilia A (HA), hemophilia B (HB), hemophilia C (HC) and Von Willebrand disease (VWD) in mainland China. We conducted a systematic literature review during August, 2011 using PubMed, EMBASE, and Cochrane Library in English and CBMDISK, CNKI, VIP and Wanfang Database in Chinese. We also carried out a search of general and specific hemophilia related websites. Reference lists of key reviews were hand-searched for further relevant research. Studies providing data of the prevalence of hemophilia or its subtypes were included. Meta-analysis was done using the generic inverse variance model. Twenty-two studies were included in the meta-analysis. The overall weighted prevalence of hemophilia was 3.6 per 100,000 and the prevalence among males was 5.5 per 100,000. The prevalence based on community studies was 2.9 per 100,000. The proportions of HA, HB, HC and VWD were 70.97%,16.13%,6.45% and 2.90%, respectively. The prevalences calculated in our study were higher than any previous studies in mainland China, but lower than the world-wide prevalences. The registration rate of hemophiliacs was extremely low. HA and HB were the major subtypes of hemophilia.

Keywords: hemophilia, prevalence, registration, systematic review, meta-analysis

INTRODUCTION

Hemophilia is a group of X-linked, recessive, hereditary clotting diseases (Ding *et al*, 2010). Hemophilia A (blood coagulation factor VIII deficiency, HA) and hemophilia B (blood coagulation factor IX deficiency, HB) are common subtypes of hemophilia. Hemophilia C (blood coagulation factor XI deficiency, HC) and Von Willibrand disease (Von Willibrand factor deficiency, VWD) are sometimes included in surveys of the prevalence of these diseases (Ding *et al*, 2010). Due to the low prevalence of hemophilia it is challenging to carry out epidemiological studies regarding hemophilia. There has been only one nationwide survey of hemophilia in mainland China (Chinese Col-

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laboration Group of Hemophilia, 1992). It was carried out by a Chinese hemophilia collaboration group in 24 provinces and cities and 37 districts in China between 1986 and 1989. The results published in 1992 showed a prevalence of hemophilia in mainland China of 2.73 per 100,000 with 80% being HA (Chinese Collaboration Group of Hemophilia, 1992). The aim of the current study was to estimate the prevalence of hemophilia in mainland China using existing data and compare it with the list of registered hemophilia patients.

MATERIALS AND METHODS

Search strategy

Searches were conducted in English and Chinese using PubMed, EMBASE, Cochrane library, CBM, CNKI, VIP and Wanfang database during August, 2011 using the terms "Hemophilia", "Epidemiology or prevalence" and "China or Chinese". We excluded studies carried out in Hong Kong, Macao and Taiwan because this data were not easily accessible. No retrieval limitations were set. Reference lists of key reviews and grey literature were hand-searched for further relevant studies. We also searched general and hemophilia related websites to capture all possible data.

Study inclusion criteria

For analysis and to reduce skewed data, selected studies had to fulfill the following criteria: 1. study objects needed to be Chinese patients with HA, HB, HC or VWD living in mainland China; 2. study content was comprised of reported data used to calculate the prevalence of hemophilia or the proportions of the subtypes; 3. study types needed to be observational studies with no controls to minimize the impact of patient selection criteria from the original study or disease surveillance studies.

Studies not matching the above inclusion criteria were excluded along with studies having the following criteria: 1) duplicate studies using the same literature, or having results already introduced in other literature from the same project; 2) Animal studies, *in vitro* studies and other basic medical studies; 3. lectures, reviews, commentaries and news.

The bibliographies, abstracts and full texts of the reviewed studies were examined in parallel by two researchers to determine whether to include the study. Disagreements were resolved by discussion or consulting experts.

Information extraction

Data were entered in duplicate by 2 researchers into Epidata 3.1. Data were entered. Extracted information included the study field (community or hospital), district, type of research, basic characteristics of study subjects, diagnostic methods used to detect hemophilia, the prevalence of hemophilia (numerator and denominator) and the proportions of subtypes of hemophilia.

Quality of the studies

The quality of the studies was assessed using criteria revised from Prins *et al* (2002). A score was given to each study based on the following criteria: external validity, internal validity, information, and other. The quality of the study was based on the score.

Statistical analysis

Classification of hemophilia subtypes varied by study. Most studies included HA and HB, and some included HC and VWD. The overall prevalence and proportions of subtypes were combined using the generic inverse variance model

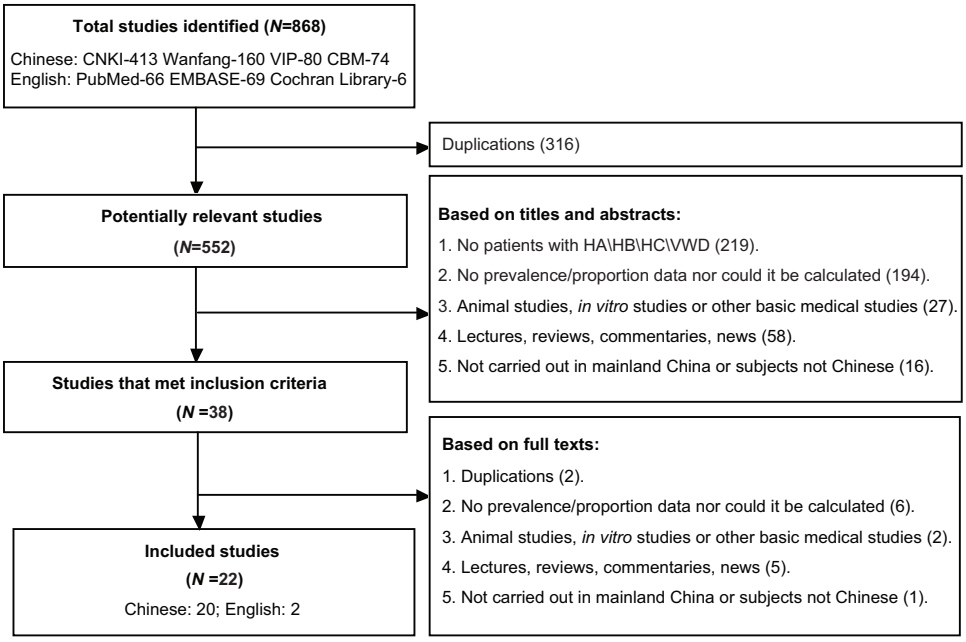

Fig 1–Flow diagram of studies chosen for this evaluation.

recommended by Sutton *et al* (2000) and Higgins *et al* (2003):

$$Y = \sum W_i Y_i \div \sum W_i$$

$$95\%CI\ of\ Y = Y \pm 1.96SQRT\ (1/\sum W_i)$$

where Y_i is the natural logarithm of the rate or proportion reported by the i_{th} study, $Y_i = \ln (d_i/q_i).d_i$ and q_i are the numerator and denominator, respectively, of the rate or proportion. W_i is the weight factor of the i_{th} study, $W_i = 1/Var_i = 1/(1/d_i + 1/q_i)$, Var_i is the variance of the i_{th} study. I^2 is the indicator of heterogeneity among the studies; is ranges from 0% to 100% and the larger it is, the greater the heterogeneity. A strength of this method is that it can endow different weights to the different studies based on their sample sizes. META-ANALYST was used to combine the prevalences and proportions. Subgroup analyses of the prevalences of hemophilia were carried out based on the study field, district, time of publication and subtype of hemophilia. Analysis and graphing were done using EXCEL2007, META-ANALYST or RevMan-5.

RESULTS

Basic information

In total, 868 articles were found in our study, of which 22 were used for the analysis: 20 were published in Chinese and 2 were published in English (Fig 1). The 22 studies were published during 1985-2010 and 16/22 were published during 1987-1992 (Fig 2). The reason for this clustering of studies is because a nationwide census of hemophilia was carried out between 1986 and 1989. General information regarding the 22 studies is shown in Table 1.

Quality of the studies

The mean quality assessment score of the included studies was 8.9/18 (2-13). The mean scores for external validity, internal validity and information were 2.3/6 (1-5), 3.7/6 (0-6) and 1.9/3 (0-3), respectively.

Table 1
Basic characteristic of included studies.

Number	Study	District	Study field	Study type	Ages studied	Diagnostic methods	Diagnostic criterion	Numerator of prevalence	Denominator of prevalence
1	Liu, 1985	Eastern China	Community	Census	24.7/27.5 (2.5-44)	History-taking, physical examination,family study,clinical examination,screening test(PTT,APTT,PT,BT,PLT,CT),clinical diagnostic test (TGT,S-TGT,FVIII:C/FVIII:Ag,FIX:C/FIX:Ag), tourniquet test.	Unclear	8	350,000
2	Wang, 1985	Eastern China	Community	Census	20.89/19.5 (1.17-66)	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT), clinical diagnostic test (TGT,S-TGT,FVIII:C/FVIII:Ag).	Unclear	16	559,241
3	Yuan, 1987	Northeastern China	Community	Sampling survey	24.44/23 (15-40)	History-taking,family study,clinical examination,screening test (PT,CT,PCT), clinical diagnostic test (TGT,FVIII:C/FVIII:Ag).	Unclear	9	318,575
4	CCGH *et al*, 1987	Nationwide	Hospital	Case series	18/16 (1.5-61)	0	The diagnosis standard of hrombosis and hemostasis academic meeting in 1982	911	
5	CGHL *et al*, 1988	Northeastern China	Community	Census	(10-25)	0	Unclear	3	149,584
6	Chen and Lui, 1988	Eastern China	Hospital	Census	26.78/25.5 (3-65)	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,BT,PLT,CT), clinical diagnostic test (TGT,S-TGT,FVIII:C/FVIII:Ag,FIX:C/FIX:Ag),smear,tourniquet test.	Unclear	19	700,000
7	Hu *et al*, 1988	Eastern China	Community	Census	0	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,BT,PLT,CT,CRT), clinical diagnostic test (TGT,S-TGT,FVIII:C/FVIII:Ag,VWF:Ag).	Unclear	10	142,766
8	Wei *et al*, 1989a	Southern China	Community	Census	5.33/5.5 (2-9)	History-taking,family study,clinical examination,screening test (PTT,APTT,PT,CT), clinical diagnostic test (TGT,FVIII:C/FVIII:Ag,FIX:C/FIX:Ag).	Unclear	6	2,866,785
9	Sun *et al*, 1989	Central China	Community	Cross-sectional study	24 (0.33-55)	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,BT,CT,CRT), clinical diagnostic test (TGT,FVIII:C/FVIII:Ag).	The coagulation disorders diagnostic criteria of the First Chinese Hematology Society National Conference on thrombosis and hemostasis,1987	36	1,440,000
10	Zhang *et al*, 1989	Northwestern China	Community	Census	38.71/35 (9-78)	History-taking,family study,clinical examination,screening test (PTT,APTT,PT,BT,PLT,CT), clinical diagnostic test (TGT,S-TGT,FVIII:C/FVIII:Ag).	The coagulation disorders diagnostic criteria of the First Chinese Hematology Society National Conference on thrombosis and hemostasis,1987	7	150,777

Table 1 (Continued).

Number	Study	District	Study field	Study type	Ages studied	Diagnostic methods	Diagnostic criterion	Numerator of prevalence	Denominator of prevalence
11	Wei *et al*, 1989b	Nationwide	Unclear	Round-ups	(2-78)	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,BT,PLT),clinical diagnostic test) TGT,FVIII:C/FVIII:Ag)	The coagulation disorders diagnostic criteria of the First Chinese Hematology Society National Conference on thrombosis and hemostasis,1987	24	1,052,063
12	Anhui, 1991	Eastern China	Both	Sampling survey	22.08/22 (3-40)	History-taking,family study, clinical examination,screening test (PTT,APTT,PT,BT,PLT,CT), clinical diagnostic test (TGT,B-TGT,FVIII:C/FVIII:Ag,FIX:C/FIX:Ag), Gene diagnostic test)DOH)	The coagulation disorders diagnostic criteria of the First Chinese Hematology Society National Conference on thrombosis and hemostasis,1987	12	203,280
13	Lu *et al*, 1991	Central China	Community	Census	23.88/20.5 (3-65)	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,BT,PLT), clinical diagnostic test (TGT,B-TGT,FVIII:C/FVIII:Ag,FIX:C/FIX:Ag)	The diagnostic standard for hemophilia A and hemophilia B of Changzhou meeting,1982	8	189,591
14	Wang *et al*, 1991	Eastern China	Community	Cross-sectional study	14.2 (0.92-41)	History-taking,family study, clinical examination,screening test (BT,CT), clinical diagnostic test (TGT,FVIII:C/FVIII:Ag)	Unclear	18	510,487
15	Wei *et al*, 1991	Northeastern China	Community	Cross-sectional study	(2-37)	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,BT,CT), clinical diagnostic test (TGT,B-TGT,FVIII:C/FVIII:Ag,VWF:Ag)	The coagulation disorders diagnostic criteria of the First Chinese Hematology Society National Conference on thrombosis and hemostasis,1987	7	203,938
16	Zhao *et al*, 1991	Central China	Community	Cross-sectional study	(14-48)	Family study,clinical examination,screening test (PT), clinical diagnostic test (TGT)	Unclear	14	497,715
17	Yan *et al*, 1991	Southwestern China	Community	Cross-sectional study	0	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,CT,PCT), Clinical diagnostic test (TGT)	Unclear	5	238,150
18	CCGH *et al*, 1992	Nationwide	Both	Cross-sectional study	0	History-taking,clinical examination,screening test (PTT,APTT,PT,BT,PLT,CT), clinical diagnostic test (TGT,FVIII:C/FVIII:Ag,FIX:C/FIX:Ag,VWF:Ag), Ristow amphotericin cofactor measurement	The coagulation disorders diagnostic criteria of the First Chinese Hematology Society National Conference on thrombosis and hemostasis,1987	460	16,866,654
19	Jing *et al*, 1993	Southwestern China	Community	Census	19.58/21.5 (2.5-43)	History-taking,physical examination,family study,clinical examination,screening test (PTT,APTT,PT,BT,PLT,CT), clinical diagnostic test (TGT,S-TGT,FVIII:C/FVIII:Ag,FIX:C/FIX:Ag)	The coagulation disorders diagnostic criteria of the First Chinese Hematology Society National Conference on thrombosis and hemostasis,1987	18	808,762
20	Wei, 1996	Southern China	Hospital	Case series	0	0	Unclear	8	18,283
21	Zhang *et al*, 2003	Nationwide	Hospital	Case series	0	Clinical examination,Clinical diagnostic test (FVIII:C/FVIII:Ag,FIX:C/FIX:Ag,VWF:Ag)	Unclear	1190	-
22	Wang *et al*, 2010	Nationwide	Unclear	Screening	0	0	Unclear	1595	-

CCGH, Chinese Collaboration Group of Hemophillia; CGHL, Collaboration Group of Hemophilia of Liaoyuan.

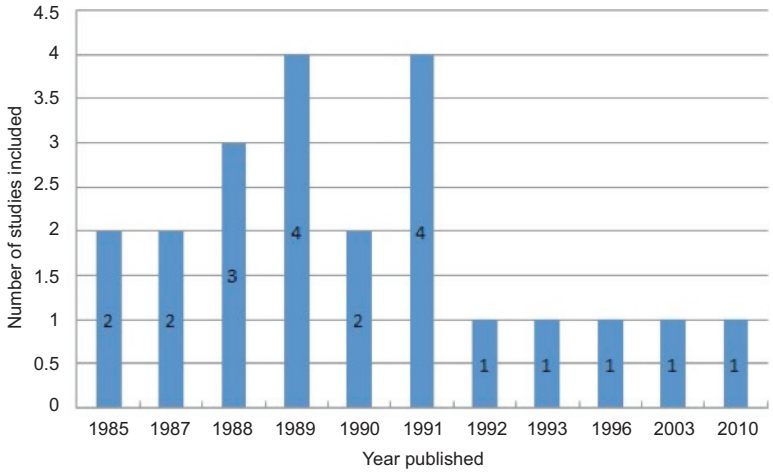

Fig 2–Distribution of included studies by publication year.

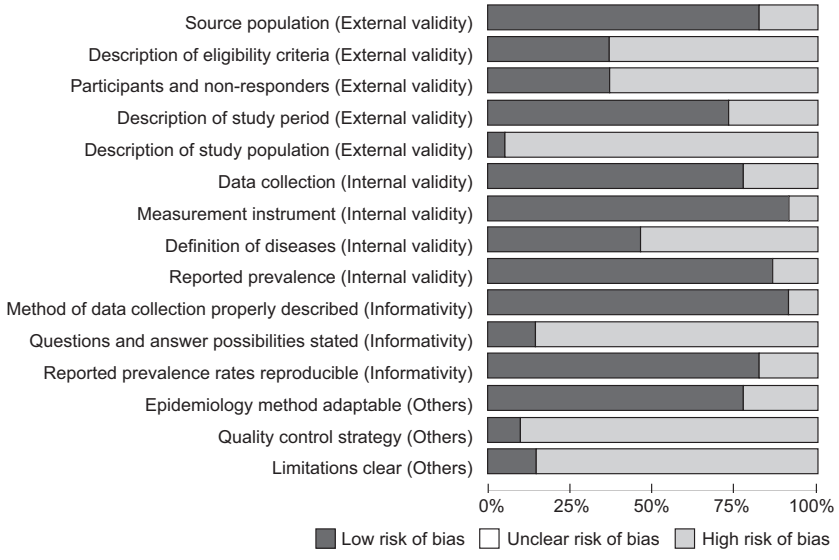

Fig 3–Quality of included studies.

Thus, the quality of the included studies was not good. This could be related to when the studies were published. The main factors affecting quality were description of study population, statement of questions and answer possibilities, quality control and limitations clarity (Fig 3).

Prevalence of hemophilia

Total prevalence. Nineteen studies were used to estimate the prevalence of hemophilia in mainland China (Liu, 1985; Wang, 1985; Chen and Liu, 1988; Hu *et al*, 1988; Sun *et al*, 1989; Lu *et al*, 1991; Wang *et al*, 1991; Zhao *et al*, 1991; Chinese Collaboration Group of Hemophilia, 1992; Jing *et al*, 1993; Wei, 1996; Yuan *et al*, 1987; The Collaboration Group of Hemophilia of Liaoyuan *et al*, 1988; Wei *et al*, 1989a; Zhang *et al*, 1989; Wei *et al*, 1989b; The Investigation Group of Hemophilia of Anhui, 1991; Wei *et al*, 1991; Yan *et al*, 1991). Eight of these included the census results reported in 1992 (Yuan *et al*, 1987; The Collaboration Group of Hemophilia of Liaoyuan *et al*, 1988; Wei *et al*, 1989a; Zhang *et al*, 1989; Wei *et al*, 1989b; The Investigation Group of Hemophilia of Anhui, 1991; Wei *et al*, 1991; Yan *et al*, 1991). The remaining 11 studies gave a weighted prevalence of hemophilia in mainland China of 3.6 per 100,000 (95%CI: 2.7-4.9 per 100,0000). Sensitivity analysis was done by combining all the studies except the national

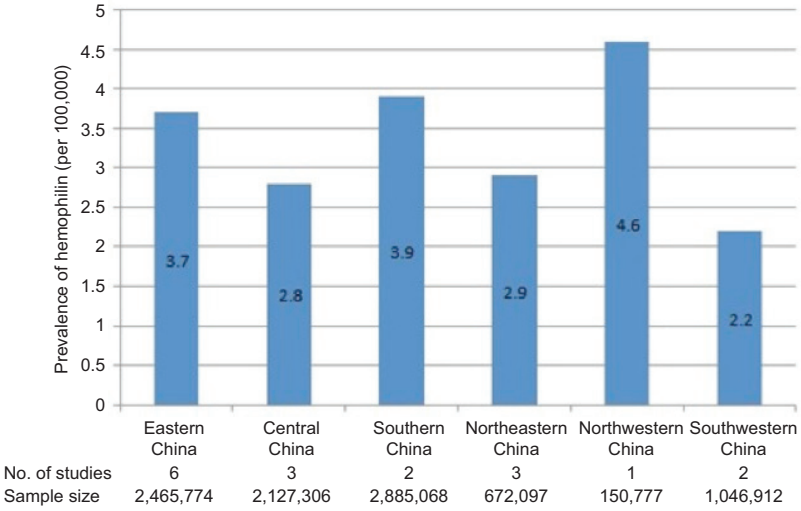

Fig 4–District–distributions of included studies.

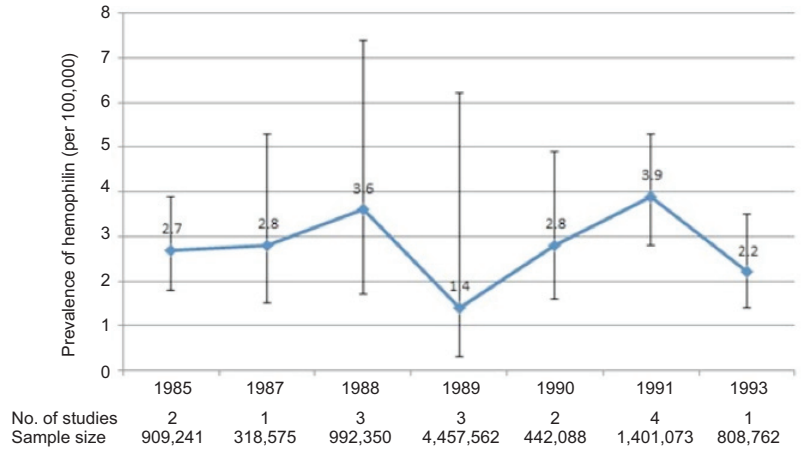

Fig 5–Time trends of hemophilia prevalence.

census which gave a pooled prevalence of hemophilia of 3.1 per 100,000 (Table 2).

Prevalence of hemophilia in the community and in hospitals

Subgroup analysis was done by study location. The weighted prevalence of hemophilia in the community was 2.9 per 100,000 (95%CI: 2.5-3.3 per 100,000) in 10 related studies. Two hospital-based study found the prevalence of hemophilia was 43.8 per 100,000 in pediatric patients or 2.7 per 100,000 population (Table 2).

Prevalence of hemophilia in males

Seventeen studies reported the prevalence of hemophilia in males (Liu, 1985; Wang, 1985; Chen and Liu, 1988; Hu *et al*, 1988; Sun *et al*, 1989; Lu *et al*, 1991; Zhao *et al*, 1991; Chinese Collaboration Group of Hemophilia *et al*, 1992; Jing *et al*, 1993; Yuan *et al*, 1987; The Collaboration Group of Hemophilia of Liaoyuan *et al*, 1988; Wei *et al*, 1989a; Zhang *et al*, 1989; Wei *et al*, 1989b; The Investigation Group of Hemophilia of Anhui *et al*, 1991; Wei *et al*, 1991; Yan *et al*, 1991). Of these, 8 included the nation-wide census (Yuan *et al*, 1987; The Collaboration Group of Hemophilia of Liaoyuan *et al*, 1988; Wei *et al*, 1989a; Zhang *et al*, 1989; Wei *et al*, 1989b; The Investigation Group of Hemophilia of Anhui *et al*, 1991; Wei *et al*, 1991; Yan *et al*, 1991). The weighted prevalence of hemophilia in males was 5.5 per 100,000 (95%CI: 4.6-6.5 per 100,000) based on the

Table 2
Prevalence of hemophilia.

Items	No. of studies	Hemophilias A,B,C and Von Willibrand disease		Hemophilias A and B Only	
		Prevalence (95%CI) (per 100,000)	Results of sensitivity analysis	Prevalence (95%CI) (per 100,000)	Results of sensitivity analysis
Total prevalence	11	3.6 (2.7-4.9)	3.1 (2.4-4.0)	2.7 (2.3-3.0)	2.8 (2.4-3.0)
Study field					
Community	10	2.9 (2.5-3.3)	-	2.7 (2.3-3.0)	-
Hospital	1	43.8	-	2.7	-
Male	9	5.5 (4.6-6.5)	5.2 (4.2-6.5)	5.0 (4.4-5.7)	5.0 (3.6-6.8)

CI, Confidence interval.

Table 3
Prevalence of different subtypes of hemophilia.

Subtypes of hemophilia	Total population as denominator		Male population as denominator	
	No. of studies	Prevalence (95%CI) (per 100 000)	No. of studies	Prevalence (95%CI) (per 100,000)
A	10	2.2 (1.9-2.6)	9	4.2 (3.5-5.0)
B	10	0.5 (0.4-0.7)	9	1.0 (0.7-1.5)
C	4	0.3 (0.1-1.4)	4	0.6 (0.1-2.8)
VWD	1	0.09	1	0.17

CI, Confidence interval; VWD, Von Willibrand's disease.

remaining 9 studies. Sensitivity analysis was done and the pooled prevalence of hemophilia among males was 5.2 per 100,000 (Table 2).

Prevalence of hemophilia by districts

Excluding the reports of the nationwide census, subgroup analysis was done by district for the remaining 17 studies (Fig 4). The pooled prevalences of hemophilia in eastern China, central China, southern China, northeastern China, northwestern China and southeastern China were: 3.7 per 100,000 (95%CI: 2.6-5.1 per 100,000), 2.8 per 100,000 (95%CI: 2.1-3.6 per 100,000), 3.9 per 100,000 (95%CI: 0-9.3 per 100,000), 2.9 per 100,000 (95%CI: 1.8-4.5 per 100,000), 4.6 per 100,000 and 2.2 per 100,000 (95%CI: 1.5-3.3 per 100,000), respectively.

Chronological prevalence of hemophilia

Subgroup analysis was done by year of study publication (Fig 5). The prevalence of hemophilia remained about the same between 1985 and 1993. A study published in 1996 was not included in Fig 5; it studied children in the hospital and the prevalence of hemophilia was 43.8 per 100,000.

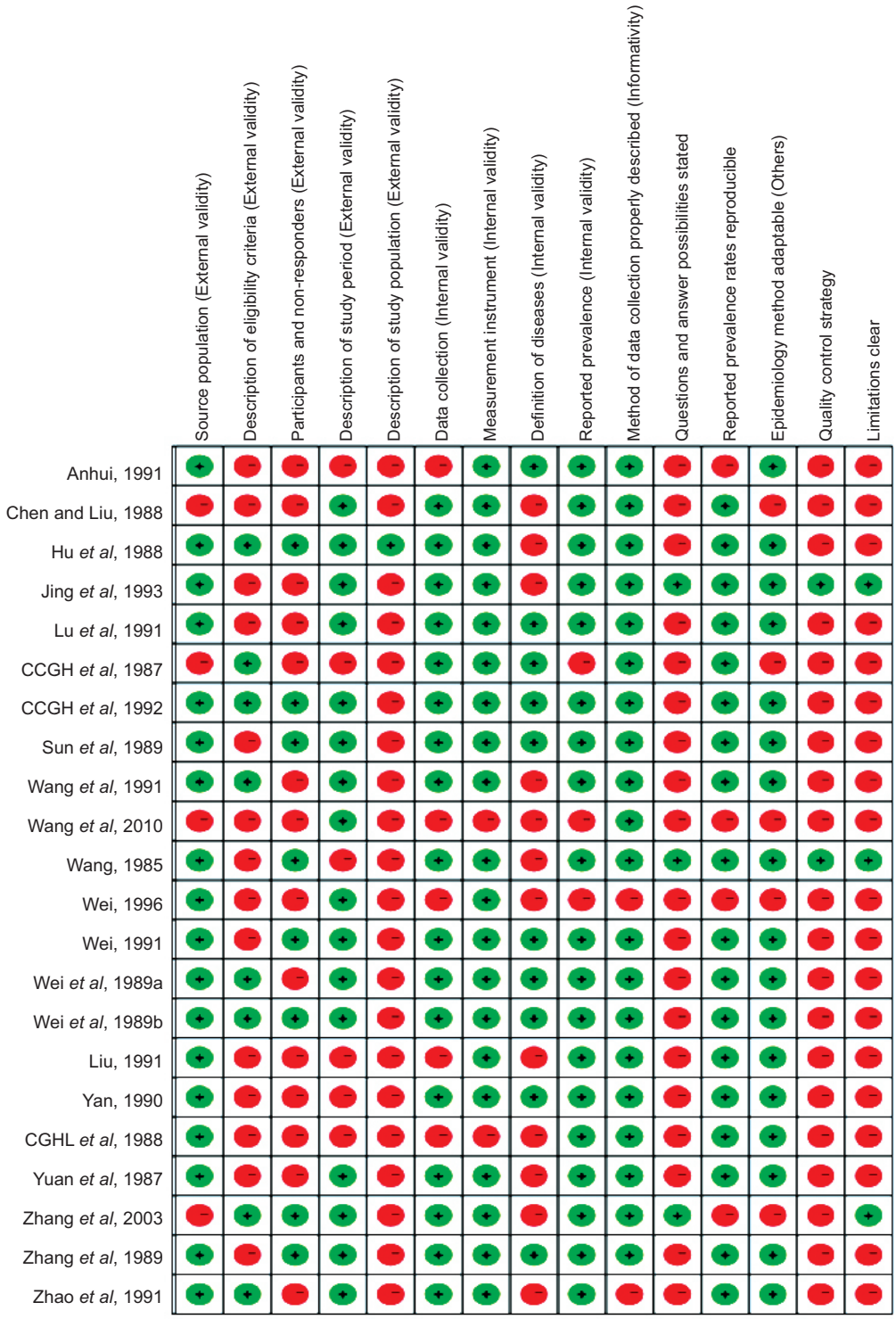

Fig 6–Quality of included studies. CCGH, Chinese Collaboration Group of Hemophillia; CGHL, Collaboration Group of Hemophilia of Liaoyuan.

Prevalence of different subtypes of hemophilia

The results of the studies that reported the prevalence of HA, HB, HC and VWD were combined (Table 3). The pooled prevalences of HA, HB, HC and VWD were 2.2, 0.5, 0.3 and 0.09 per 100,000 respectively. The prevalences of HA, HB, HC and VWD in males were 4.2, 1.0, 0.6 and 0.17 per 100,000, respectively.

Proportions of different subtypes of hemophilia

Only HA and HB included. Data from 9 studies included only subtypes HA and HB, giving a total sample of 1701 (Liu, 1985; Wang, 1985; Chen and Liu, 1988; Lu *et al*, 1991; Wang *et al*, 1991; Jing *et al*, 1993; Zhang *et al*, 1989; The Investigation Group of Hemophilia of Anhui *et al*, 1991; Wang *et al*, 1991). The pooled proportions of HA and HB were 80.9% (95%CI: 68.7-89.2) and 19.1% (95%CI: 10.8-31.3), respectively.

HA, HB, HC and VWD included. Data from 3 studies included all 4 subtypes (HA, HB, HC and VWD), giving a total sample of 2561 (Chinese Collaboration Group of Hemophilia, 1992; Zhang *et al*, 2003; Chinese Collaboration Group of hemophilia, 1997). The pooled proportions of HA, HB, HC and VWD were 76.5% (95%CI: 72.7-79.9), 13.3% (95%CI: 12-14.7), 1.8% (95%CI: 1.2-2.8) and 4.3% (95%CI: 3-6.1), respectively; 4.1% of hemophiliacs were not classified.

DISCUSSION

The prevalences of hemophilia in the USA, England, Switzerland, France, Finland and Japan in 2003 were: 10 per 100,000, 6.9 per 100,000, 6.6 per 100,000, 6.3 per 100,000, 5.0 per 100,000 and 2.3-2.6 per 100,000, respectively (Higgins *et al*, 2003). The overall weighted prevalence of hemophilia in our study was 3.6 per 100,000 and was 2.9 per 100,000 in the community. Our results are lower than in western countries and higher than in Japan. There are no regional or ethnic differences in hemophilia prevalence and the prevalence of hemophilia has been recognized to be between 10 per 100,000 and 15 per 100,000 (Yang, 2008). The results of our study indicate the prevalence of hemophilia in East Asia may be lower than in Europe and America. Another possibility is that many hemophiliacs remain undetected or unreported in mainland China. There may be 2 reasons for this: 1). health care professionals in China are not familiar with hemophilia and its clinical manifestations; 2). the laboratory investigations required to diagnose hemophilia may not be adequate.

The results of the nationwide census carried out by the Chinese collaboration Group of Hemophilia in 24 provinces and cities and 37 districts of China between 1986 and 1989 found a prevalence of hemophilia of 2.73 per 100,000, with HA comprising 80% (Chinese Collaboration Group of Hemophilia, 1992). The combined prevalence in our study was higher than that of nationwide census, but the prevalence in the community in our study was close to their census. The reason for the higher prevalence in our study could be that it included hospital based studies. Future prevalence studies need to include hospital-based data to avoid underestimation of the prevalence. In our study, HA and HB were the main subtypes of hemophilia found comprising 70%-80% and 10%-20% of the total, respectively. The proportions of HC and VWD combined comprised less than 10% of the total. These proportions are similar to other studies (Ding *et al*, 2010).

We excluded the results of studies in-

cluded in the nation-wide census from our meta-anaysis. The results of these studies when combined gave a pooled prevalence of 2.2 per 100,000 (95%CI: 0.9-4.7 per 100,000). The excluded studies were mainly from eastern and central China. If these were included, the prevalence of hemophilia in the community in eastern and Central China would be higher than the national average. The district distribution of hemophilia prevalence confirms this (Fig 4). The chronological prevalence of hemophilia did not change much over time.

During the sixth nationwide population census in 2010-2011, the total population of mainland China was 1,370,536,875. Using the prevalence of hemophilia in mainland China found in our study, the number of hemophiliacs in mainland China is estimated to be 49,339. The National Information Management Center for Hemophilia covers 31 medical units in different provinces and municipalities and is the only official registration institution for hemophilia authorized by the Chinese Ministry of Health. On July 4, 2012, the total number of registered hemophiliacs was 10,652. The registration rate for hemophilia in mainland China is low. To improve management, it is necessary to improve the registration of hemophiliacs. One way to improve registration is to include more hospitals, then more hemophiliacs would be detected in time to avoid becoming disabled.

Due to its low prevalence, it is difficult to collect epidemiological data regarding hemophilia. There has been only nationwide census of hemophilia in mainland China and similar surveys are scarce. Knowledge of the prevalence of hemophilia in mainland China is limited. Under this circumstance, a systematic review and meta-analysis is a feasible and credible way to evaluate the prevalence of hemophilia. The quality of this study was affected by several limitations: most of the included studies were conducted before 1993 and were of inadequate quality, but those have the best data available. When we studied the prevalence using only high quality studies, the results were similar (Fig 6).

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