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Syphilis Incidence among Men Who Have Sex with Men in China: Results from a Meta-analysis

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Abstract

Background—Recent upsurge of syphilis infections among men who have sex with men (MSM) is one of the major challenges that facing China. However, the overall burden is still not clear. This study aims to summarize the incidence of syphilis among MSM in China by using meta-analysis.

Methods—We comprehensively searched PubMed-MEDLINE, China National Knowledge Infrastructure (CNKI) and Chinese Wanfang databases. Articles published between December 2009 and March 2015 that met the inclusion criteria were considerably involved in this meta-analysis. Two reviewers performed a quality assessment of the studies and extracted data for estimating the overall syphilis incidence. STATA 12.0 was used to summarize the overall incidence of syphilis.

Results—14 studies from 13 papers were included in this study. Follow-up duration of these studies ranged from 6 to 36 months, while drop-out rates ranged from 11.9% to 83.6%. The individual incidence rates of the included studies varied from 3.1/100 person-years (PYs) (95% CI, 0.8–5.3/100 PYs) to 38.5/100 PYs (95% CI, 28.9–48.1/ 100 PYs), with a pooled incidence of 9.6/100 PYs (95% CI, 7.0–12.2 /100 PYs). The subgroup meta-analysis revealed that incidence estimates were 38.5/100 PYs (95% CI, 28.9–48.1/100 PYs), 12.1/100 PYs (95%CI, 7.0–17.2/100 PYs), 11.2/100 PYs (95%CI, 0.7–23.1/100 PYs), 8.9/100 PYs (95%CI, 6.5–11.2/100 PYs), 5.7/100 PYs (95%CI, 3.4–8.0/100 PYs), and 3.1/100 PYs (95%CI, 0.8–5.3/100 PYs) in Northeast, North, Southwest, East, South and Northwest China, respectively.

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Conclusion—Syphilis incidence among Chinese MSM is high, and this may increase the spread of other sexual transmitted infections (STIs), including Human Immunodeficiency Virus (HIV). It is essential to integrate syphilis control programs with HIV control programs. This can be achieved by establishing public health response systems to monitor and control the epidemic of syphilis and HIV together in China.

Introduction

Syphilis remains a global problem with an estimated 12 million people infected each year, despite the existence of effective prevention measures, such as condoms, and effective and relatively inexpensive treatment options.[1] In China, syphilis accounted for 11.7 cases per 100,000 Chinese residents in 2009, which had increased by 2.1 times since 2005.[2] After free market reforms and the resulting social upheaval, China has experienced a re-emergence of syphilis since 1980.[3] Reducing the incidence and prevalence of syphilis related adverse outcomes will be a major public health challenge in the immediate future in low and middle income countries (LMICs), including China.[1]

A previous review reported that the syphilis prevalence in China among men who have sex with men (MSM) increased from 6.8% during 2003–2004 to 13.5% during 2007–2008 While Human Immunodeficiency Virus (HIV) prevalence rate increased from 1.3% during 2003–2004 to 4.7% during 2007–2008.[4] The review concluded that China was witnessing an increase in the proportion of MSM and they played a significant role in spreading syphilis.[9] However, it is important to examine whether the overall increase in the syphilis incidence in China is attributed to MSM. Admittedly the increasing number of female sex workers (FSWs) has been reported, which cannot be absolutely denied to be one of the major reasons for the high incidence of syphilis.[5] It is therefore quite necessary to determine the exact nature of the dynamics of incidence measures of syphilis.

Incidence measures are excellent tools for monitoring the epidemic of a disease.[6] However, the incidence measures of syphilis are still unclear, as findings from observational studies so far are largely inconsistent. The cases report and surveillance systems in China only provide the population prevalence of syphilis, while timely incidence data is insufficient.[7] To address this challenge, several cohort studies were conducted,[8,9] particular among MSM.[10,11] However, the limited sample size of individual studies and the geographic variations of these studies limited their ability to reveal the overall syphilis incidence burden in China. It is significant to synthesize the results from earlier studies and to provide most current syphilis incidence at the national level. Hence, meta-analysis, as a method that can be used to summarize the results of these separate studies is warranted. In addition, as earlier reviews did not specifically evaluate the role of different high-risk groups in explaining the disease dynamics it is necessary to gain insight into the regional variations and to estimate the incidence of syphilis at the national level. We therefore, systematically reviewed studies on syphilis published before March 2015. Addressing this public health issue was critical as the modifiable risk factors driving the epidemic of syphilis are amenable to proactive interventions, which will reduce the prevalence of other Sexually Transmitted Infections (STIs).

The objective of our current report study was to systematically estimate the syphilis incidence among MSM in China through meta-analysis. In order to accomplish the objective, a comprehensive meta analysis was conducted with a predefined protocol developed by the authors for search strategies, inclusion and exclusion criteria, data extraction, study quality rating criteria, summary of evidence and plan for analysis.

Methods

Criteria for Study Inclusion

To guarantee the quality of our study, the guidelines for meta-analyses of observational studies was followed by our study.[12] To be eligible, the studies included in our study must meet the following criteria: (1) they estimated incidence of syphilis infection (and reported the numbers of syphilis sero-convertors and total person-times followed up); (2) they had clear descriptions of study design, study location and sample size; (3) the targeting population was MSM in mainland China (excluding Hong Kong, Macao and Taiwan); (4) the language of these publications should only be English or Chinese. In case of multiple papers published from the same study, we only included the results with longest follow up period. In addition, the non-original studies that met the inclusion criteria were also excluded.

Search Strategy

Two authors performed the searching of articles published between December 2009 and March 2015 in PubMed, China National Knowledge Infrastructure (CNKI) and Wanfang (CNKI and Wanfang are Chinese database).

We used MeSH terms (see Panel-1). ‘MeSH’ stands for ‘Medical Subjects Headings’, which is the controlled vocabulary of thesaurus developed by the National Library of Medicine. It consists of sets of terms and aids in enabling the search process specific to the topic intended.

We further used the following review stages to review and extract the data:

Panel.1

Search Terms

1	“syphilis”,
2	“incidence”,
3	“recent infection”,
4	“acute infection”,
5	“seroconversion”,
6	“MSM”,
7	“gay”,
8	“sex between men”,
9	“China”.
10	Combination of the options of search terms 1 and 9 and 2 or 3 or 4 or 5 and 6 or 7 or 8 above

11	Combination of the options of search terms 1, 8 and 9 above
12	Limit 11 to "review articles"

Data collection and analysis

There were four stages of the review process as following

Stage 1. Identification of studies for inclusion—After independent screening and searching, the following information was extracted from the involved papers: study year, location, sample size, recruitment method, follow-up time, drop-out rate and reported syphilis incidence of each included study (Table 1).

Stage 2. Selection of relevant studies—Studies found by using the searching panel were independently assessed by using the agreed inclusion criteria. Disagreements between the first two reviewers were resolved by consulting the third author. The included studies were further categorized as those conducted in East China, North China, South China, Southwest China, Northeast China and Northwest China, based on Chinese geographic distribution system.

Stage 3. Quality assessment—A set of items were used to assess the methodological quality of the articles included in our study. Four features of included studies were assessed including: (1) study design: Cohort or Cross-section; (2) prospective study or retrospective study; (3) sample size ≥150 or not; (4) retention rate≥ 50% or not. Two authors independently evaluated the quality of included studies.

Stage 4. Data extraction and synthesis of results—Our initial search of the electronic database retrieved 52 studies (see Figure 1). As the first step, we included papers with titles and abstracts fulfilling the inclusion criteria. We finally included 13 papers based on consultation with experts and authors of earlier systematic reviews. We crosschecked with other databases and earlier reviews to identify additional papers. We then downloaded the full texts of the papers for review. We extracted the following information from the full texts: first author, year, country, study settings such as study design employed, respective inclusion criteria, job strain measurement and instruments for such measurement. Further, we assessed the quality of the studies by using the 'Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines as the reference.[13] The aim of these guidelines is to help authors report a wide array of systematic reviews to assess the benefits and harms of a health care intervention. PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.[14]

Diagnosis criteria of syphilis

To be consistent, the syphilis patients in the included study should be diagnosed as following: Firstly, Treponema Pallidum Particle Assay (TPPA) or Enzyme Linked Immunosorbent Assay (ELISA) was performed with the serum, and then the serum was performed with Rapid Plasma Regain (RPR) test or Toluidine Red Untreated Serum Test

(TRUST) when TPPA or ELISA test was positive according to the syphilis diagnosis criteria issued by National Health and Family Planning Commission of the People's Republic of China (WS 273–2007).

Statistical analysis

We obtained a pooled incidence by combining estimates from all the included studies. Data were initially entered and analyzed by using the Cochrane Collaboration's Review Manager software version 5 for Windows (Cochrane Collaboration, Oxford, England), and subsequently entered into a spreadsheet and re-analyzed by using the 'metan' command of STATA 12 version for Mac (STATA Corporation, College Station, Texas, USA). Outputs were crosschecked for internal consistency. In our study, incidence rate was defined as the ratios between the numbers of seroconverters and the total person-years contributed by all the participants during the follow-up period in each study. Pooled point estimate of incidence with corresponding 95% confidence intervals (CIs) of syphilis infection were calculated. Subgroup analyses based on geographic location were examined separately. Heterogeneity between studies was tested with the Q test ($p<0.10$ indicating a statistically significant heterogeneity) and the I^2 statistic (larger values showing the increasing heterogeneity, with25% as low, 50% as moderate and 75% as high heterogeneity between studies).[15] If the data were heterogeneous, random effect models were used for meta-analysis. Begger's test was used to detect the publication bias and the trim and fill method was used if significant publication bias existed.[16,17]

Results

Search Results

Overall, 52 articles (18 in English and 34 in Chinese) were found from the three data-bases. Among them, 19 articles were excluded after initial screening of the abstracts and an additional 20 articles were further removed after full text review. After exclusion, a total of 13 articles (6 in English[8,10,18–21] and 7 in Chinese[22–28]) were included in our final data analysis (Figure 1, PRISMA of the study). Among them, one article reported by Yang et al included two independent studies from two cities (Changzhou and Yangzhou) in one province,[8] and we treated this as two independent studies in this meta-analysis., thus, it came out of 14 independent studies.

Characteristic of Included Studies

Of the included studies, three were from north China (Beijing),[18,19,24](1–3) one from northwest China (Urumqi),[23] four from east China (Nanjing, Changzhou, Yangzhou and Suzhou) ,[8,21,26] two from southwest China (Chongqing and Mianyang) ,[22,27] one from northeast (Shenyang)[10] and two from south China (Yunnan and Nanning) [20,24] (Table 1). Among these studies, RDS method was used for initial recruitment in four studies while snowball-sampling method was used in ten studies. The dropout rates during the follow-up period were ranged between 11.9% and 83.6%. (Table1)

Methodological Qualities of Included Studies

Study quality varied in the included studies (Table1 and Table 2). All included studies were prospective cohort studies, and the follow-up duration reached six months or even longer. In the majority of the studies, there were concerns about the study sample's inaccurate representation of MSM population (external validity), which could be a potential problem. Four of the included studies[10,22] used respondent-driven sampling (RDS) to recruit participants, which may have better representativeness. Four studies had loss-to-follow-up rates greater than 50% [7, 24, 26] and one study did not report the dropout rate.[22] Of the 14 studies, six had total person time less than 150 PYs.[8,10,21,24,25,27]

Pooled incidence and Subgroup Meta-analysis

The syphilis incidence rate varied from 3.1/100PYs (95% CI, 0.8–5.3/100 PYs) to 38.5/100 PYs (95% CI, 28.9–48.1/100 PYs). Pooled data showed that the overall syphilis incidence among MSM between studies conducted between 2006 and 2012 in China was about 9.6/100 PYs (95% CI, 7.0–12.2/100 PYs (Figure 2). A substantial heterogeneity among the included studies was noted (Q test, $p<0.001$; $I^2 = 89.8$). There was statistically significant bias in publication (Begg's test, $p= 0.033$) (Figure 3). Trim and fill method was used to identify and adjust the asymmetry existing in the funnel plot, which was caused by publication bias. Findings processed by random effect models showed statistical significance ($Q=166.487$, $p<0.001$), an existence of publication bias which it couldn't affect the result.

We conducted the subgroup analysis by excluding Dong et al[28], as it included the pooled data of 8 cities with no specific incidence rate of each city given.[8,10,18–27] This subgroup meta-analyses revealed that incidence estimates were 8.9/100 PYs (95%CI, 6.5–11.2/100 PYs) for studies in East China, 12.1/100 PYs (95%CI, 7.0–17.2/100 PYs) for studies in North China, 5.7/100 PYs (95%CI, 3.4–8.0/100 PYs) for studies in South China, 11.2/100 PYs (95%CI, 0.7–23.1/100 PYs) for studies in Southwest China, 38.5/100 PYs (95% CI, 28.9–48.1/100 PYs) for studies in Northeast China, and 3.1/100 PYs (95%CI, 0.8–5.3/100 PYs) for studies in Northwest China(Figure 4).

Discussion

Our study pooled syphilis incidence among MSM between 2006 and 2012, and found a high syphilis incidence among Chinese MSM. Subgroup analysis further prompted that the syphilis incidence among Chinese MSM varied over different geographic regions. Our study added to the current literature by providing the pooled syphilis incidence of Chinese MSM, which is critical for the control of the resurgence STIs, including HIV.

Our study got recent overall syphilis incidence among MSM from a totally new perspective. It came from original studies from various provinces or municipalities while defusing likely bias as much as possible. In national level, most of the other studies had only reported syphilis prevalence including systematical reviews.[35,36] We demonstrated that overall syphilis incidence was as high as about 9.6/100 PYs in MSM of China. The high incidence of syphilis may lead to high prevalence of syphilis over a period of time in MSM. This has been evidenced by other studies conducted in China. For example, a systematical review

reported that median syphilis prevalence from 2000 to 2005 among MSM was 14.56%.[35] Another pooled analysis of Chinese MSM showed that the syphilis prevalence among MSM was as high as 13.5% during 2007 and 2008, and it increased over time.[4] Since MSM shared the most prevalence of syphilis infection among FSWs (1.4% per year), MSM (4.5% per year) and drug users (1.0% per year), [35] those were regarded as high risk behavior groups of HIV infection in last several years. Outcomes from all relevant studies urge the researchers and policy maker to emphasize syphilis prevention in China. Despite implementation of different intervention strategies over last decade, the coverage of syphilis screening, treatment and partner services still need to be improved, in order to reduce the prevalence and incidence of syphilis.

The high incidence also suggests that large proportion of Chinese MSM may be engaged in condomless anal intercourse (CAI) or condomless vaginal intercourse (CVI). The high incidence of syphilis and the high risk behaviors of MSM may further increase the chance of HIV and other STI transmissions in MSM, as syphilis infection is a well known risk factor for HIV acquisition.[29] The high incidence may also be due to co-existence of several of high risk behaviors (CAI, CVI, et al.),[30,31] and other STIs.[4,32] It may be also due to large size of the sexual network of MSM.[33] Some social factors also contribute to epidemic of syphilis in MSM: same-sex marriage is unavailable and unprotected by present law; stigma toward MSM from mainstream population still exists, population mobility impels the youth to face unfamiliar circumstance and to cope with stress. To control these situations, policy making should take these factors into integral consideration.

Despite being completely curable, syphilis continues to affect disproportionate proportion of persons globally, often causing acute illness and infertility, and as a meaningful driver of the epidemic of HIV and other STIs.[34] Thus, it is a key issue to monitor and evaluate the incidence of syphilis periodically and implement appropriate interventions. The current Chinese national monitoring system based on the series cross-sectional studies, has failed to report the increased incidence of syphilis.[7] Our study offers an urgent priority to oversee the syphilis epidemic among MSM in China.

Our study indicated that MSM in Northeast China have higher syphilis incidence. Studies conducted in Beijing and Chongqing also reported high incidence. This finding concurs with the HIV prevalence in MSM of these two cities where there is higher HIV prevalence than the average.[4] Since syphilis and HIV share almost the same transmission routes and risk behaviors, strategies to control the epidemic of these two infections should be combined together. Health education for the youth on both HIV and syphilis should be available. Clinical and public health doctors should be on the alert of their patients' both syphilis and HIV infection. Any possibility of infection would be identified by laboratory testing. We cannot rule out the likely result due to the small sample size and available data of only few person-years. Besides geographic regions, other factors such as methods of recruitment, occupations or regular active sites may also contribute to the incidence of syphilis. However, similar to other meta-analysis studies, our study suffered from the problems of publication and selection bias from the original studies (for example, 83.6% participants were lost to follow-up in the study conducted in Yangzhou). Despite using the weighted analysis in our

study, the bias induced by these issues may still exist, which, therefore, might mislead our results.

We concluded that the syphilis incidence in Chinese MSM was high, and high incidence may increase the chance of HIV and other STIs transmission. It is crucial to integrate syphilis control programs with HIV control programs. This can be addressed by establishing public health response systems to monitor and control the epidemic of syphilis as well as HIV in key populations in China, especially MSM.

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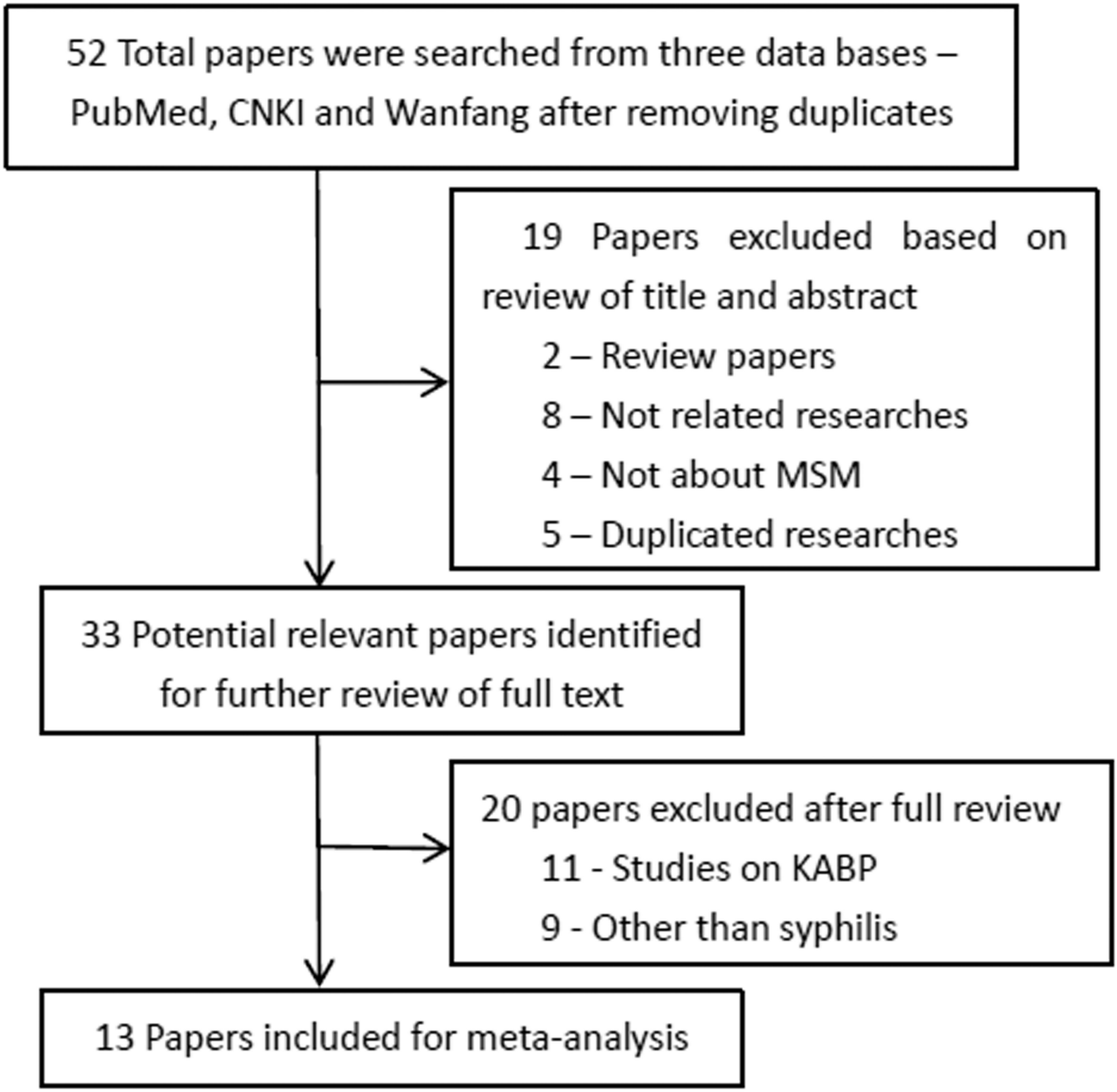

Fig.1.
Identification, review, and selection of studies included in the meta-analysis.

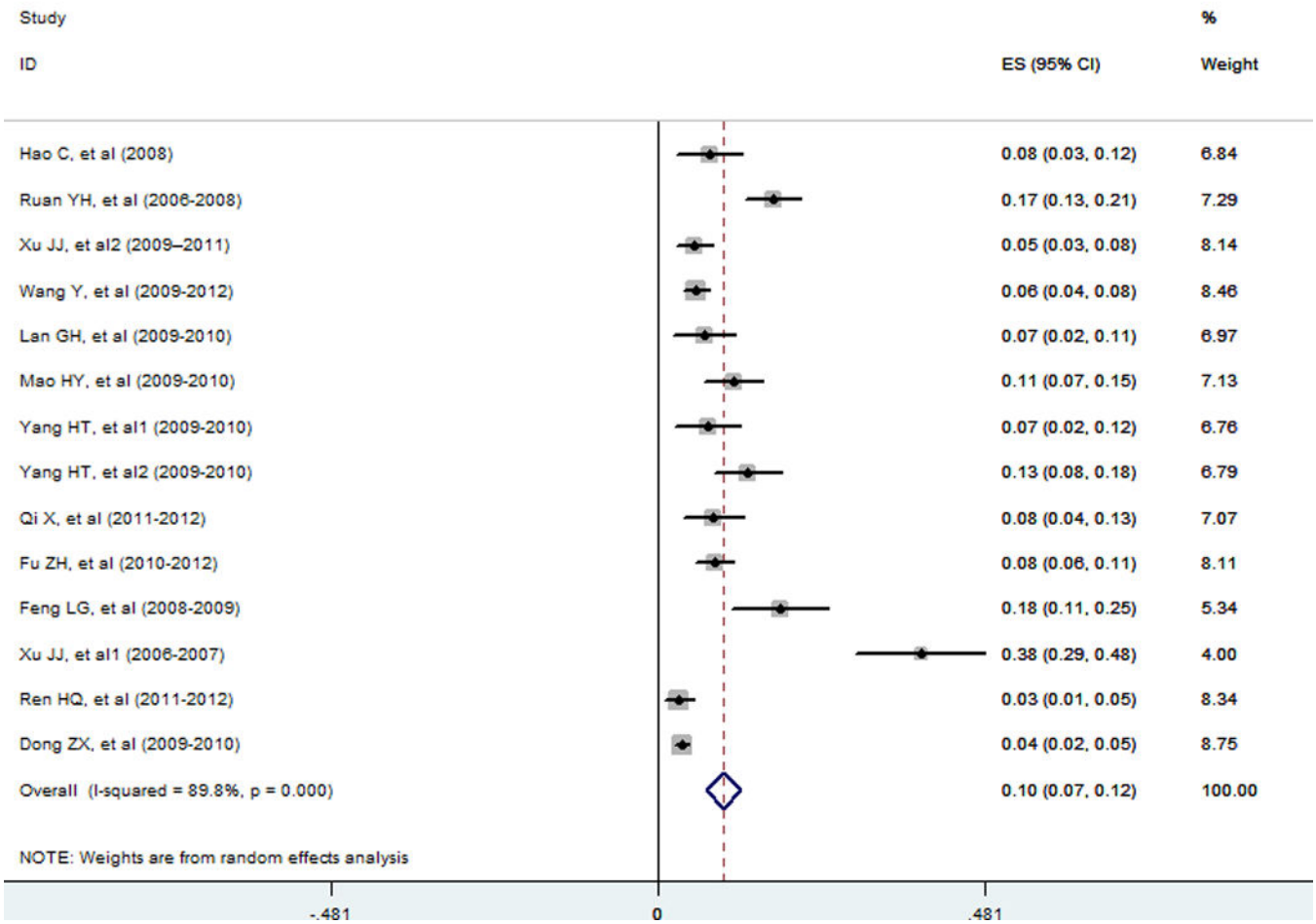

Fig.2.

Forest plots of overall incidence of syphilis in Chinese MSM from included studies. CI, confidence intervals; I-squared, inconsistency index.

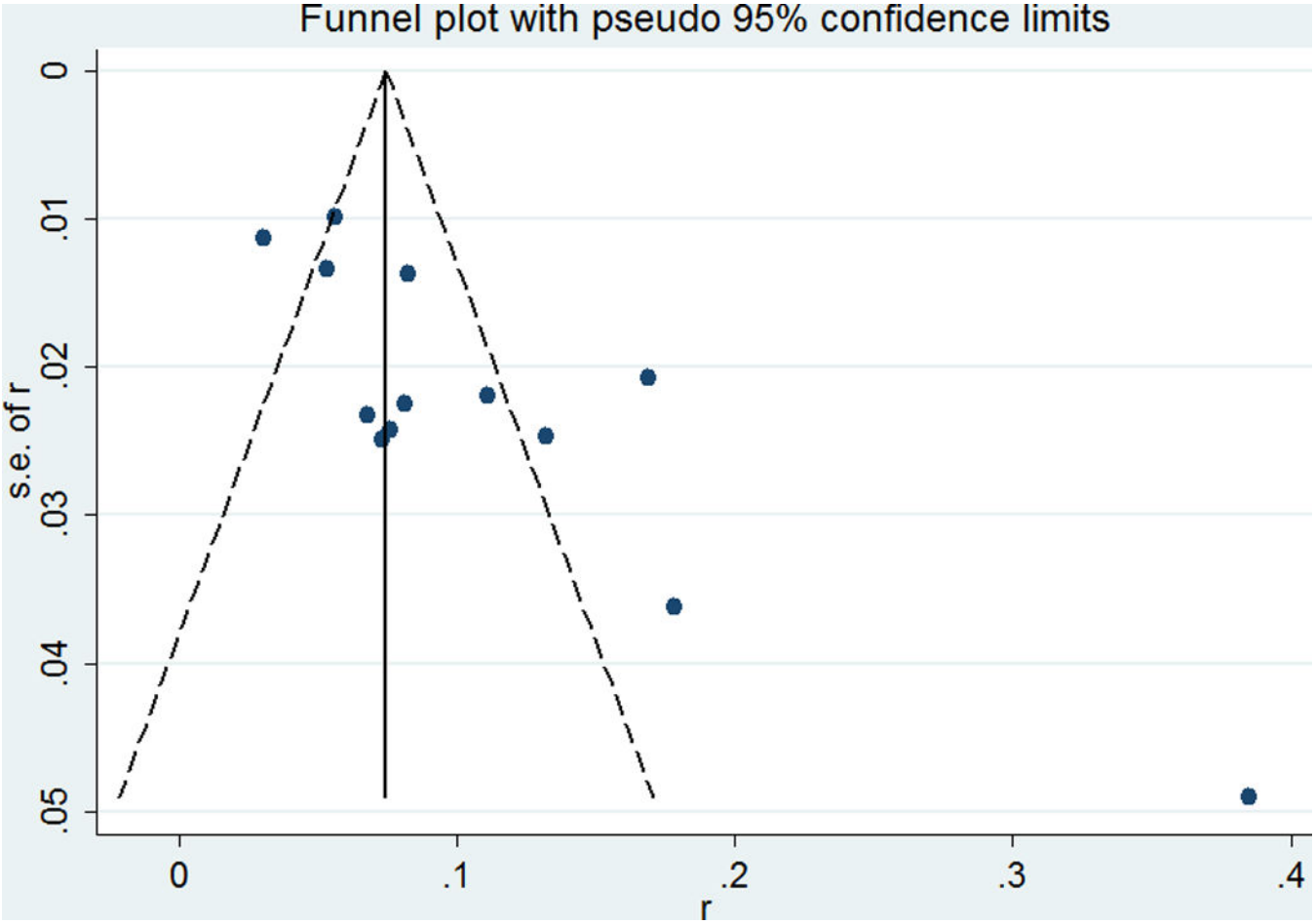

Fig.3.
Funnel plot of publication bias of syphilis in Chinese MSM from included studies.

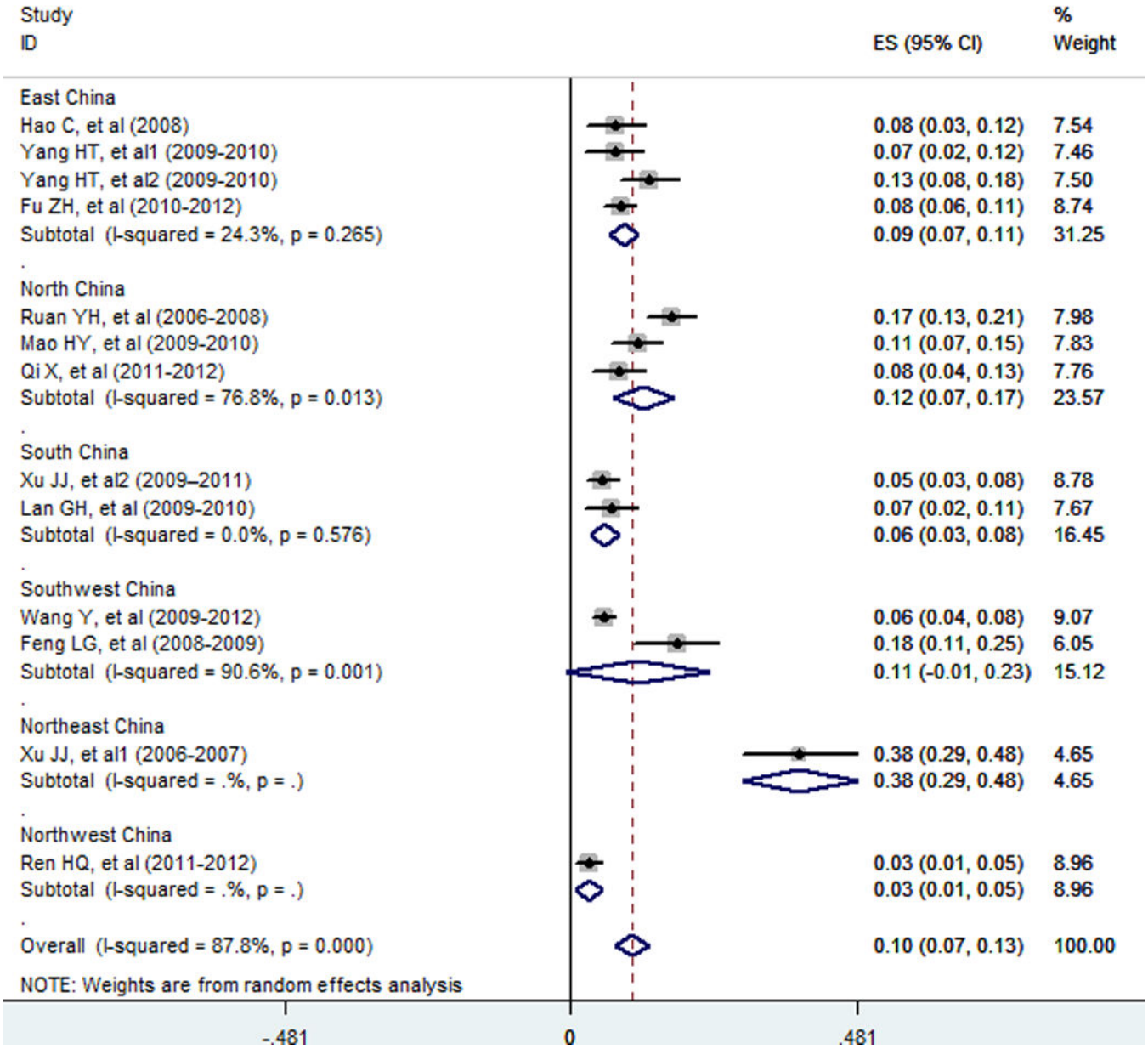

Fig.4.

Forest plots of subgroup incidence of syphilis in Chinese MSM from included studies Subgroups classification was based on the study location.

Table 1

Summarized information of the studies included in meta-analysis.

Study name	Study year	Study location	Recruitment method(s)	Sample size(person-years)	Reported syphilis incidence(100 PYs)	Follow-up (months)	Drop-out (%)
Hao C, et al.[12]	2008	Nanjing	RDS	118.73	7.58	6	28.16
Ruan YH, et al.[13]	2006–2008	Beijing	IBR,RDS	325.8	16.9	12	13.8
Xu JJ, et al.[14]	2009–2011	Yunnan	SNR	279.1	5.3	18	29.9
Wang Y, et al.[15]	2009–2012	Mianyang	RDS/SBR	535.5	5.6	36	NR
Ren HQ, et al.[16]	2011–2012	Urumqi	SBR	229	3.06	12	24.76
Lan GH, et al.[17]	2009–2010	Nanning	SBR	117.5	6.8	12	60.53
Mao HY, et al.[18]	2009–2010	Beijing	IBR,RDS	204.27	11.11	8	45.4
Yang HT, et al[8]	2009–2010	Yangzhou	SNR,SBR	109.1	7.3	12	83.6
Yang HT, et al.[8]	2009–2010	Changzhou	SNR,SBR	188.7	13.2	12	64
Qi X, et al.[19]	2011–2012	Beijing	SBR	147.55	8.13	6	11.9
Fu ZH, et al.[20]	2010–2012	Suzhou	SBR,SNR	399.9	8.25	30	47.2
Feng LG, et al.[21]	2008–2009	Chongqing	SBR	112	17.8	6	56.15
Xu JJ, et al.[9]	2006–2007	Shenyang	SNR	98.7	38.5	12	44
Dong ZX, et al.[22]	2009–2010	8 Cities	SBR	1106.67	3.5	12	17.84

Abbreviations: NR: not reported; RDS: Respondent-driven sampling; SBR: Snow-ball recruitment; SNR: social network recruitment; IBR: internet based recruitment

Table2

Quality assessment of study design.

Study name	Cohort	Prospective	Sample size (person-years) ≥150	Follow-up retention ≥50%	Follow-up duration ≥6 months
Hao C, et al.[12]	√	√	×	√	√
Ruan YH, et al.[13]	√	√	√	√	√
Xu JJ, et al.[14]	√	√	√	√	√
Wang Y, et al.[15]	√	√	√	N/A	√
Ren HQ, et al.[16]	√	√	√	√	√
Lan GH, et al.[17]	√	√	×	×	√
Mao HY, et al.[18]	√	√	√	√	√
Yang HT, et al[8]	√	√	×	×	√
Yang HT, et al[8]	√	√	√	×	√
Qi X, et al.[19]	√	√	√	√	√
Fu ZH, et al.[20]	√	√	√	√	√
Feng LG, et al.[21]	√	√	×	×	√
Xu JJ, et al[9]	√	√	×	√	√
Dong ZX, et al.[22]	√	√	√	√	√