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The prevalence of spinal muscular atrophy carrier in China

Evidences from epidemiological surveys

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Abstract

Introduction: Spinal muscular atrophy (SMA) was the second most fatal autosomal recessive hereditary disease in clinic. There had been no detailed study to characterize the prevalence of SMA carrier among people in China. So, we conducted a systematic review and meta-analysis to obtain a reliable estimation of the prevalence of SMA carrier to characterize its epidemiology for the first time.

Methods: We systematically searched for articles in kinds of important electronic databases, including PubMed, Embase, Wanfang Database and China National Knowledge Infrastructure (CNKI) to identify all relevant literatures about carrier rates of SMA in China. The prevalence was performed by forest plot choosing random effect models. The publication bias was evaluated by means of funnel plots and Egger test. The sensitivity analysis was carried out by the method of omitting any literature at a time. Combined with the results of subgroup analysis, the source of heterogeneity was also discussed absolutely.

Results: A total of 10 studies published between 2005 and 2016 were included in our analysis at last. The sample size ranged from 264 to 107,611 in included studies. The random effect models of meta-analysis showed that the overall carrier rate of SMA was 2.0% (95% confidence interval [CI], 1.7%–2.3%) in a heterogeneous set of studies ($I^2 = 64\%$). There was a gradual rise trend observed in the SMA carrier rate during the study period. The funnel plots and Egger test (Coef = 0.02, t = −0.45, $P = .667 > .05$) showed no obvious potential risk of publication bias.

Conclusion: The overall carrying rate of SMA was high as 2.0% and may be on a slow upward trend. So it was recommended that the countries should take active and effective measures to roll out routine prenatal screening and health genetic counseling for SMA as early as possible. What is more, further studies also need to be conducted to explore the etiology and epidemic factors of SMA to better control the risk of this common birth defect.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, DHPLC = denaturing high performance liquid chromatography, MLPA = multiplex ligation dependent probe amplification, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, SMA = spinal muscular atrophy, SMN = survival motor neuron.

Keywords: birth defects, meta-analysis, overall rate, prevalence, spinal muscular atrophy

1. Introduction

Spinal muscular dystrophy (SMA) was an autosomal recessive hereditary neuromuscular disease characterized by degenerative, symmetrical myasthenia and muscular atrophy with anterior spinal cord cell degeneration, which was the second most fatal autosomal recessive hereditary disease in clinical practice.[1] The expression of survival motor neuron (SMN) decreased by virtue of the homozygous deletion or tiny mutation of SMN1 gene, and the current study showed that SMN protein played an important role in the growth of neuronal axons, the formation of neuromuscular joints and the axial slurry transport of RNA.[2]

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CL and YG contributed equally to this paper.

All data generated or analyzed during this study are included in this published article (Additional file 1: PRISMA 2009 checklist.doc).

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The decrease of SMN protein expression leaded to the degeneration of alpha motor neurons in the anterior angle of spinal cord. SMA was exactly caused by the degeneration of anterior horn cells of the spinal cord, which leads to symmetric proximal muscle weakness and atrophy.[3] The SMN2 gene was highly homologous with the SMN1 gene that could encode some normal functional SMN protein to relieve the clinical symptoms of SMA disease.[4]

At present, the standard of clinical diagnosis of SMA was based on gene diagnosis. Of the about 96% SMA patients whose disorder was linked to chromosome 5q13, were characterized by a homozygous deletion of SMN1 exon 7, which resulted from unequal crossover or SMN1-to-SMN2 conversion events, and the other patients were most caused by point mutations in the SMN1 gene.[5] Therefore, by detecting the SMN1 gene whether existing homozygous deletion or happening point mutations affecting biological function, the population could be screened and diagnosed for SMA. Thus, through genetic counseling, prenatal diagnostic techniques were used to decrease the birth defect of SMA children in the population. The American College of Medical Genetics had recently recommended routine carrier screening for SMA disease. The American College of Obstetricians and Gynecologists also recommended all people thinking of becoming pregnant should be detected to see if they were a carrier. However, studies on the carrier rates of SMA present inconsistent results in China. The overall prevalence and geographic distribution of SMA was also very poorly described in the country even the world. There had also been no systematic pooled analysis of research articles published. Thus, we conducted a systematic review and meta-analysis to estimate the carrier rate of SMA for the first time. In this study, the significance was to incorporate the documentary evidence existed to grasp the epidemiological characteristic of SMA more accurately in China; the final aim was to strengthen the prevention and control of birth defects of SMA and further promote the screening and genetic counseling of the disease in prenatal diagnosis.

2. Methods

We conducted this meta-analysis and systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 checklists.[6] The systematic review and meta-analysis were conducted on the basis of an established protocol (PROSPERO 2019: CRD42019139218). No ethical approval was needed for this manuscript.

2.1. Search strategy

We searched for all available articles in four important electronic databases systematically, including PubMed, Embase, Wanfang Database and China National Knowledge Infrastructure (CNKI). Search strategy wasn't limited by the publication year. The search process was performed by two reviewers in parallel. The retrieval strategies for PubMed and Embase databases were: ((Spinal muscular atrophy[Title/Abstract]) AND carrier[Title/Abstract]) AND (China[Affiliation] OR Chinese[Affiliation]). Free text words were applied to Wanfang Database and CNKI, which belong to Chinese databases. Search terms included "Spinal muscular atrophy" and "carrier" limited in Abstract. We also retrieved the reference lists of included articles to identify potential studies as comprehensively as possible by Google scholar. The search time was updated in June 2018.

2.2. Inclusion and exclusion criteria

The studies were included in the analysis if they met the following criteria:

One diagnostic or screening technique was used at least; the study provided epidemiological indicators such as the number of carrier that the prevalence could be calculated; the research was mainly carried out in China; the results of published articles were written in English or Chinese; and the literature was a baseline data for cross-sectional surveys or a longitudinal study.

The studies were excluded based on the following criteria:

Exactly the same literature, or the subjects and data in the literature, had been published by other similar research institutes; academic lectures; reviews or interviews; sample size of literature survey was less than 200 cases; obviously irrelevant to SMA; study of non-cross-sectional surveys or sample population wasn't with good representative; quality evaluation of literature was confirmed bad.

2.3. Data extraction

Based on the above inclusion and exclusion criteria, literature screening and data extraction were independently completed and cross-checked by 2 researchers. When happening to the disagreement in the event, it would be handed over to a third researcher for adjudication. The specific methods were as follows: First, reading the topic and abstract for the initial sieve, and further screening the literature that may conform to the standard. Second, the Excel table was used to extract and record the research data, including: first author, publication time, province, sample number, design type, carrier, diagnostic criteria and other indicators. When the information for analysis was missing from the original studies, the corresponding author would be contacted by emails once a week. If the author didn't reply to us after sending the second email, the study was excluded from the related analysis. The outcome of interest was the carrier rate of SMA in different settings.

2.4. Quality assessment

The quality of each included study was assessed using the quality assessment criteria checklist with nine items adapted from an assessment tool for prevalence studies (supporting as Table 1), which was originally developed by Damian Hoy et al from Leboeuf-Yde and Lauritsen tool.[7] Each item was assessed as low or high risk of quality according to the criteria. For each item, if the article met the criteria, it was defined as low risk and one point was scored, otherwise it was defined as high risk and zero point was scored. The point for each item added up to a total score. Articles were defined as high quality with total score being at least seven points; total score of four to six points or zero to three points was defined as medium quality or low quality, respectively.

2.5. Statistical analysis

The meta-analysis was conducted for the pooled estimates. We carried out meta-analyses using RStudio Version 1.1.456 to achieve the progress. The random effect model and Q test based on the Chi-square test was adopted to evaluated the heterogeneity between the studies.[8] What is more, percentages of around 25% ($I^2=25$), 50% ($I^2=50$), and 75% ($I^2=75$) would mean low, medium, and high heterogeneity, respectively.[9] Sensitivity analysis was carried out by omitting each study at a time, and

Table 1

Risk of bias assessment tool.

Items
1. Representation
Was the study's target population a close representation of the national population?
2. Sampling
Was the sampling frame a true or close representation of the target population?
3. Random selection
Was some form of random selection used to select the sample OR was a census undertaken?
4. Non response bias
Was the likelihood of nonresponse bias minimal?
5. Data collection
Were data collected directly from the subjects (as opposed to a proxy)?
6. Case definition
Was an acceptable case definition used in the study?
7. Reliability and validity of study tool
Was the study instrument that measured the parameter of interest shown to have validity and reliability?
8. Data mode
Was the same mode of data collection used for all subjects?
9. Prevalence period
Was the length of the shortest prevalence period for the parameter of interest appropriate?

the results of meta-analysis combined effect test were shown and calculated by forest plot, including the 95% confidence interval (95% CI). At the same time, funnel plot and Egger test regression were used to evaluated the publication bias,[10] which was statistically significant when $P < .05$.

The subgroup analysis was conducted based on predefined variables such as diagnostic methods to explore possible sources of heterogeneity among different studies, and the geographic regions was divided according to the authoritative province level in China. The graph of risk of quality assessment was conducted with Review Manager Version 5.2. The time-year point diagram of SMA carrier in Chinese different regions was drawn through ggplot2 functions in R language.

3. Results

3.1. General information about included studies

The 185-research literature were founded based on the efficient search strategy established. Through Endnote X7 program and initial browsing to find and remove duplicate literature, reading the full text of the remaining literature and eventually 10 studies were included that met the inclusion criteria (as Fig. 1). The inclusion studies were published from

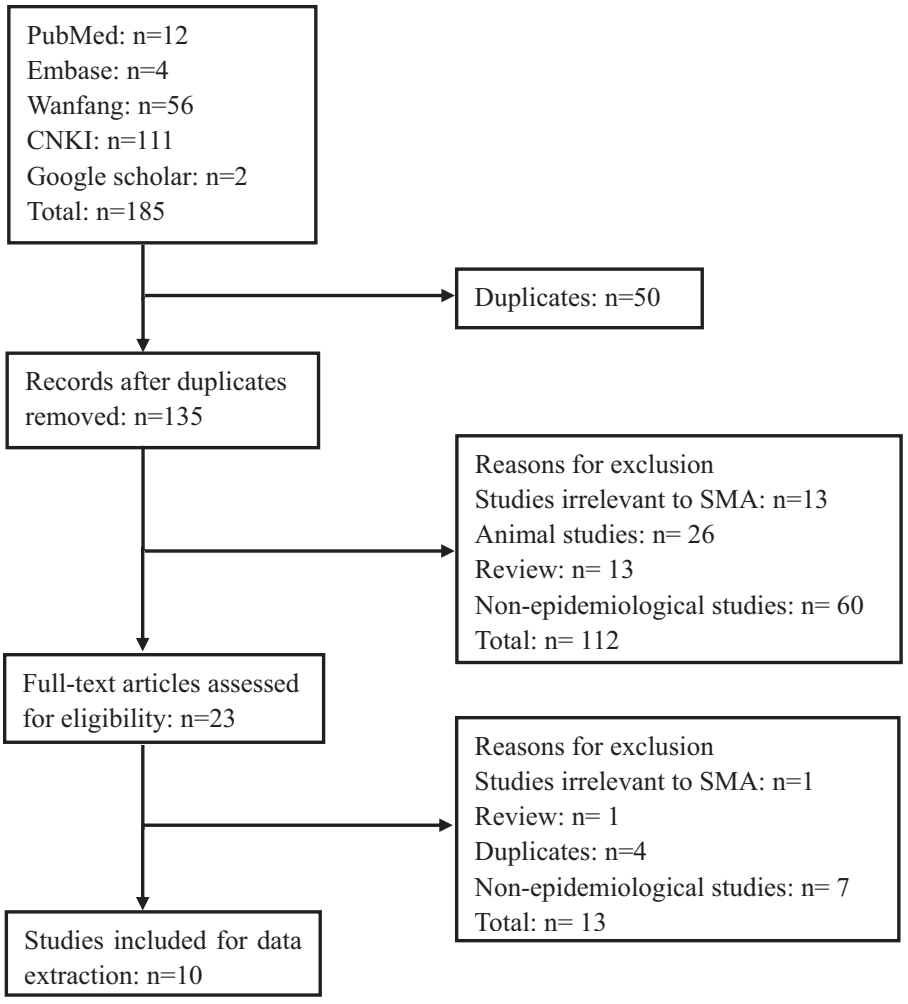

Figure 1. Flow chart of included/excluded studies.

Table 2

The basic features of the studies included.

Study	Year	Location	Regions	Subjects	Sample	Carrier	Diagnostic methods
Jing He[*]	2014	Fujian	East China	Normal	421	13	MLPA
Bo Gong[†]	2013	Shanghai	East China	Pregnant women	1200	21	Multiplex PCR-DHPLC
Wanjin Chen[‡]	2005	Fujian	East China	Normal	264	5	Real-time Fluorescent PCR
Qunguang Zeng[§]	2014	Sichuan	Southwest China	Pregnant women	427	9	DHPLC
Gong B[‖]	2013	Shanghai	East China	Pregnant women	4719	90	Multiplex PCR-DHPLC
Chan V[¶]	2005	Hong Kong	South China	Normal	569	9	Real-time Fluorescent PCR
Jianqiang Tan[€]	2016	Guangxi	South China	Pregnant women	5000	61	Multiplex PCR-DHPLC
Shengyuan Zhu[£]	2010	Guangdong	South China	Neonate cord blood	1712	41	DHPLC
Xiaoxin Qu[¥]	2013	Shanghai	East China	Pregnant women	1741	45	Real-time Fluorescent PCR
Yining Su[©]	2011	Taiwan	Taiwan China	Pregnant women	107611	2262	Multiplex PCR-DHPLC

DHPLC = denaturing high performance liquid chromatography, MLPA = multiplex ligation dependent probe amplification.

[*]Jing He, Xiangping Yao, Qijie Zhang, Ning Wang, Wanjin Chen. Screening of Spinal Muscular Atrophy Carriers in Fujian district by the Multiple Linkage Dependent Probe Amplification technology. Paper presented at: The 17th National Conference on Neurology of Chinese Medical Doctor Associationin 2014; Xiamen city, Fujian, China.

[†]Bo Gong. Screening of carrying rate of spinal muscular atrophy mutation in Shanghai district, 2013.

[‡]Chen W, Wu Z, Wang N, Lin M, Mu-rong S. Quantitative studies on SMN1 gene and carrier testing of spinal muscular atrophy. *Zhonghua yi xue yi chuan xue za zhi= Zhonghua yixue yichuanxue zazhi= Chinese journal of medical genetics.* 2005;22(6):559-602.

[§]Zeng G, Zheng H, Cheng J, et al. Analysis and carrier screening for copy numbers of SMN and NAIP genes in children with spinal muscular atrophy. *Zhonghua yi xue yi chuan xue za zhi= Zhonghua yixue yichuanxue zazhi= Chinese journal of medical genetics.* 2014;31(2):152–155.

[‖]Gong B, Zhang L, Hou Y, et al. Carrier screening for spinal muscular atrophy in 4719 pregnant women in Shanghai region. *Zhonghua yi xue yi chuan xue za zhi= Zhonghua yixue yichuanxue zazhi= Chinese journal of medical genetics.* 2013;30(6):670-672.

[¶]Chan V, Yip B, Yam I, et al. Carrier incidence for spinal muscular atrophy in southern Chinese. *J Neurol.* 2004;251(9):1089-1093.

[€]Jianqiang Tan. the Zhejiang Medical Genetics Annual Conference in 2016, the 1st National Academic Conference of Genetics Doctor Association of the Chinese Medical Doctor Association, the 15th National Academic Conference of Medical Genetics of the Chinese Medical Doctor Association; Hangzhou city, Zhejiang, China.

[£]Sheng-Yuan Z, Xiong F, Chen YJ, et al. Molecular characterization of SMN copy number derived from carrier screening and from core families with SMA in a Chinese population. *European journal of human genetics: EJHG.* 2010;18(9):978-984.

[¥]Qu X, Xiao B, Ji X, Jiang W, Yang Z, Tao J. A pilot study on spinal muscular atrophy carrier screening in Shanghai region using real-time PCR. *Zhonghua yi xue yi chuan xue za zhi= Zhonghua yixue yichuanxue zazhi= Chinese journal of medical genetics.* 2013;30(1):1-4.

[©]Su YN, Hung CC, Lin SY, et al. Carrier screening for spinal muscular atrophy (SMA) in 107,611 pregnant women during the period 2005–2009: a prospective population-based cohort study. *PLoS One.* 2011;6(2):e17067.

2005 to 2016, with sample sizes ranging from 264 to 107611 cases. Two of these studies were outside mainland China, belonging to Hong Kong and Taiwan region of China. All the studies covered 7 provinces, municipalities or autonomous regions in China, and the corresponding geographical regions to which they belong were also listed (as Table 2). The time-year point diagram of rate in Chinese different regions was shown as Figure 2.

3.2. Risk of quality assessment

The risk assessment tool showed that all studies had better quality scores and fluctuated at 5–8 points. Figure 3 summarized and

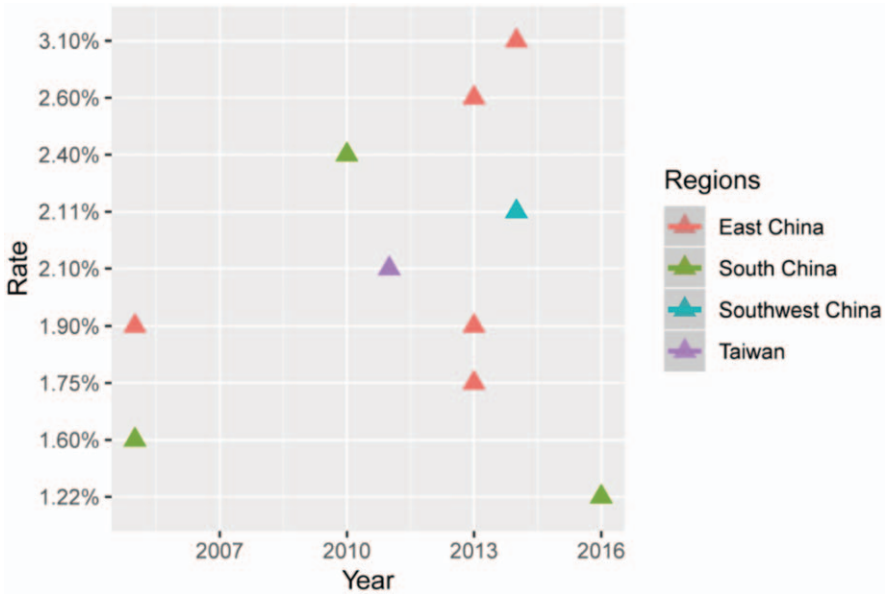

Figure 2. Time-year point diagram of SMA carrier in Chinese different regions; drawn through ggplot2 functions in R language.

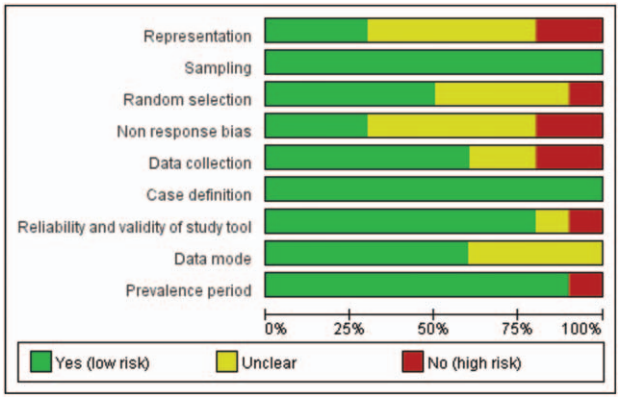

Figure 3. Risk of quality assessment for all included studies.

showed the percentage of the included studies for each item of the assessment tool.

3.3. Overall prevalence and publication bias

In this meta-analysis, as Figure 4, the overall prevalence of SMA carrier was 2.0% (95% CI: 1.7%–2.3%). Considering $I^2=64\%$ ($P<.01$), existing medium degree of heterogeneity, the results of random-effect model was adopted in our study. As shown in the Figure 5, the funnel plot demonstrated that the scatter points of 10 studies included showed a symmetric distribution nearly, suggesting that there was no obvious publication bias existing, and Egger test (Coef=0.02, t=−0.45, $P=.667>.05$) also showed no obvious potential risk of publication bias (as Fig. 6). The result of forest plot suggested that there was moderate heterogeneity and the source of heterogeneity need to be further explored.

3.4. Subgroup and sensitivity analysis

Subgroup analysis was based on the most likely source factors of heterogeneity. These studies were divided into different subgroups by diagnostic methods. The results of subgroup analysis were summarized in Figure 7. The pooled prevalence of studies diagnosed by DHPLC method was 23 per 1000 people (2.3%, 95% CI: 1.8%–3.1%, $I^2=0\%$), which was almost same with the studies in the group of Real-time Fluorescent PCR method (2.3%, 95% CI: 1.8%–3.0%, $I^2=5\%$). The pooled prevalence of the group named Multiplex PCR-DHPLC was 17 per 1000 people (1.7%, 95% CI: 1.4%–2.2%, $I^2=84\%$), lower than the other methods'. There was need to explore the possible sources of heterogeneity by the right way. Sensitivity analysis was carried out by omitting each study at a time, and the results showed that the heterogeneity would be 0 after omitting the study of Jianqiang Tan 2016 (as Table 3), suggesting that the literature was the most important reason for the heterogeneity of this meta-analysis. At this point, the pooled effect value recalculated was 2.1% (95% CI: 2.0%–2.2%, $I^2=0$). The literature's effect on the original results was not enough significant, which also reflected that the meta-analysis and original results were stable and the literature was no need to be eliminated.

4. Discussion

Meta-analysis, as an analytical method in system evaluation, was a systematic and objective comprehensive summary of multiple independent research results using appropriate statistical methods on the basic of strict design.[11] Through increasing the sample quantity to improve the statistical efficiency and effect estimation, the inconsistency in the research results could be solved.[12] Under the actual situation at present, due to the complexity of implementation and data management later of large-scale epidemiology, there also being many circulation links and uncontrollable factors, the design of each study wasn't all comprehensive in terms of gender, age, regional cultural background, economic conditions and risk factors.[12] Furthermore, there were differences in laboratory conditions and personnel levels of various research institutions. To some extent, all together, these would affect the results of individual studies as well as the final meta-analysis conclusions.

In our study, through the comprehensive and efficient system search and literature screening, a total of 10 studies were included, all which were from high-quality epidemiological survey data. The total sample amount exceeded 120,000. For the

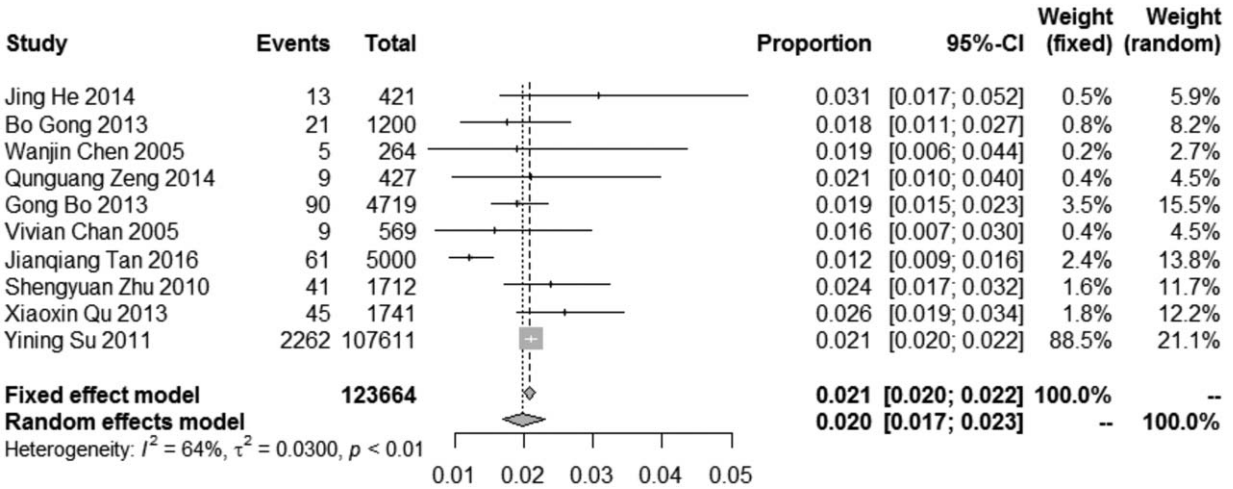

Figure 4. Forest plot of overall prevalence of SMA carrier among people in China with corresponding 95% confidence intervals (95% CI).

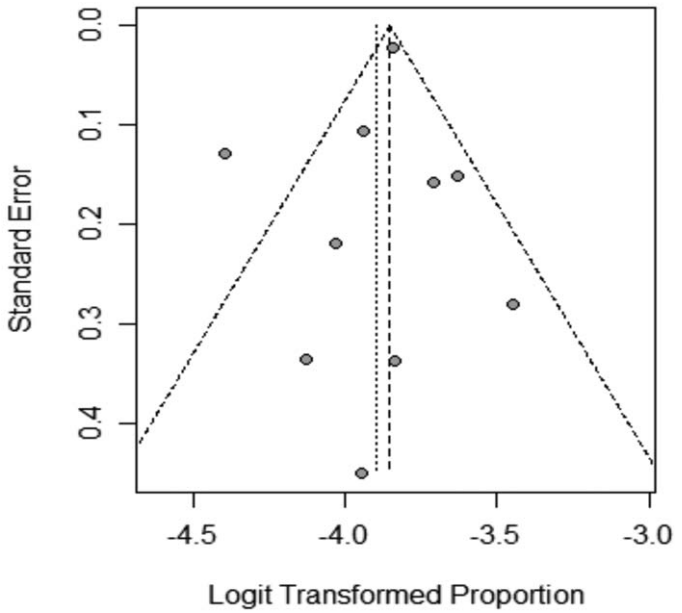

Figure 5. Funnel plot of the studies included in the meta-analysis.

first time, meta-analysis was used to report the prevalence of SMA carrier in China as the pooled rate of 2.0% (95% CI: 1.7%–2.3%), which was closer to the results of foreign surveys 1/40–1/60.[13–15] From the view of literatures source included, the latest literature research was 2016 year, with timeliness. From the view of space, the literatures were centered on South China and east China districts, of which were exactly located on developed economic areas, reflecting that the epidemiology study of SMA was only in the preliminary stage in China. It was an urgent need to invest more financial resources and workforce to cover less developed areas in aim to obtain more comprehensive epidemiological data of SMA disease. In addition, taking into account that the use of different diagnostic method on the same population may lead to difference in prevalence, but the diagnostic technology and criteria weren't yet uniform in China. Therefore, the relevant departments need to work together to make unified norms of epidemiological research of SMA, which also should be performed by the professionals. This would be a useful revelation for the prevention and control cause of the whole birth defects.

According to our study, in this meta-analysis, forest plot showed a moderate degree of heterogeneity in the studies included. So, we adopted the random effect model to merge the results, funnel plot and Egger test suggesting no significant publication bias. As for the heterogeneity, we adopted the subgroup analysis and omitting each study at a time to explore and solve the problem successfully. The reliability of system evaluation and meta-analysis was guaranteed. The final pooled results showed that the carrying rate of SMA population was up to 2.0%. Based on this, we recommended that all women who were ready to have children take the SMA-screening detection before pregnancy or in the early pregnancy period.[16] If a woman was a carrier, her husband would be detected, and if the couples were both carrier, they had to be offered the genetic counseling to guide fertility.[17]

However, there were some limitations in the analysis of our study. First, although the carrying rate of SMA was high, the actual incidence wasn't really high right now. So, the SMA-screening detection wasn't routinely carried out in China, the number of literatures meeting the inclusion criteria was limited and didn't cover all provinces in the country. Second, the basic information of the survey subjects wasn't recorded comprehensively, resulting that the possible influencing factors of SMA prevalence couldn't be explored from the epidemiological perspective. Finally, also on account of no sufficient literatures, it wasn't possible to further construct the predictive model with equation according to the time-year trend by the RStudio program.

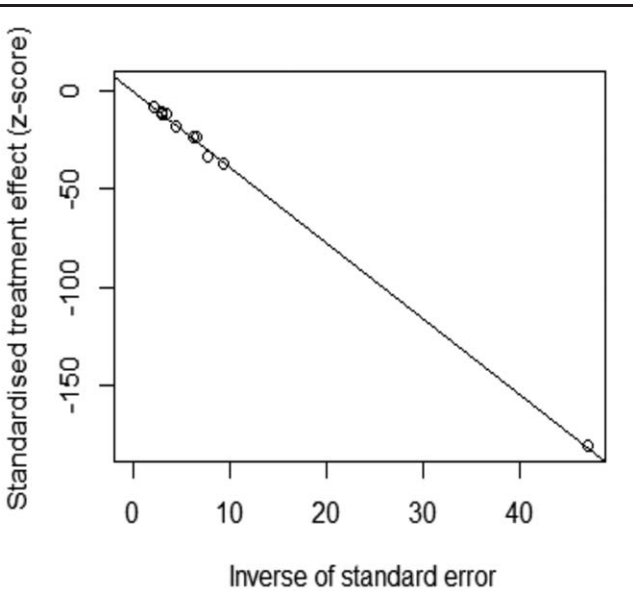

Figure 6. Egger's test of the studies included in the meta-analysis. (Coef = 0.02, t = -0.45, $P = .667 > .05$).

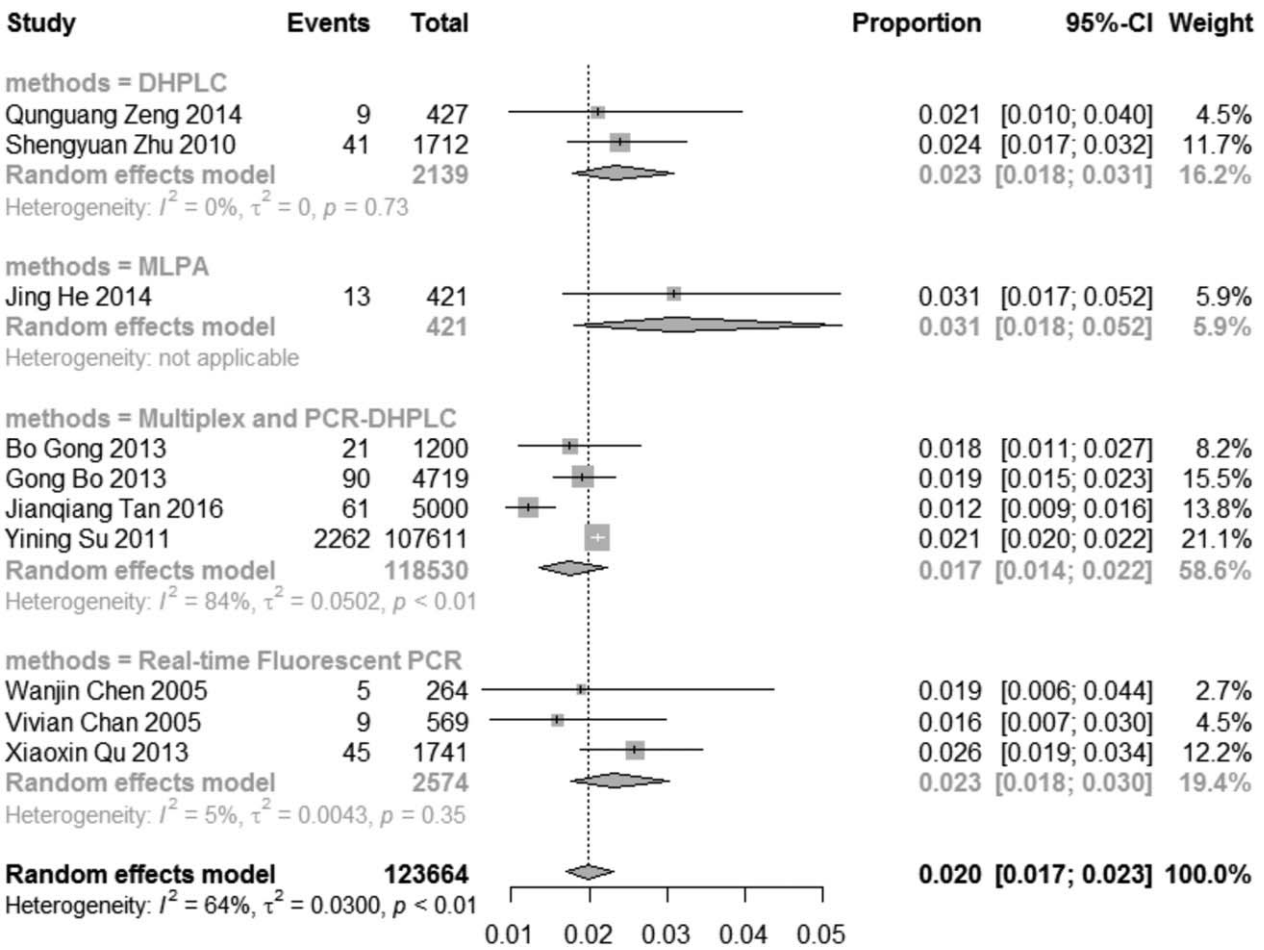

Figure 7. Results of carrier rate of SMA in China by subgroup analysis, based on diagnostic methods.

Table 3

Influential analysis (Random effects model).

Study	Proportion	95%-CI *P* value	tau^2	I^2
Omitting Jing He 2014	0.0193	[0.0165; .0226]	0.0292	65.2%
Omitting Bo Gong 2013	0.0201	[0.0170; .0237]	0.0329	67.3%
Omitting Wanjin Chen 2005	0.0199	[0.0169; .0233]	0.0323	68.1%
Omitting Qunguang Zeng 2014	0.0198	[0.0168; .0233]	0.0328	68.1%
Omitting Gong Bo 2013	0.0200	[0.0166; .0241]	0.0432	67.2%
Omitting Vivian Chan 2005	0.0201	[0.0171; .0236]	0.0315	67.2%
Omitting Jianqiang Tan 2016	0.0211	[0.0203; .0219]	0.0000	0.0%
Omitting Shengyuan Zhu 2010	0.0194	[0.0163; .0230]	0.0349	67.0%
Omitting Xiaoxin Qu 2013	0.0191	[0.0162; .0226]	0.0324	65.0%
Omitting Yining Su 2011	0.0197	[0.0159; .0244]	0.0619	64.4%
Pooled estimate	0.0199	[0.0170; .0232]	0.0300	64.2%

Details on meta-analytical method: Inverse variance method; DerSimonian-Laird estimator for tau^2.
Logit transformation.

5. Conclusions

To sum up, the SMA carrying rate of 2% of the population could no longer be neglected, both domestically and globally. Considering that the prevalence may be on a slow upward trend, the authorities should take active and effective measures to conduct routine prenatal screening and health genetic counseling as early as possible to guide people to develop healthy lifestyle behaviors and reduce the occurrence of birth defect of SMA disease eventually.

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Author contributions

The research idea was derived from XL Guo and CL Xia, and C Li designed the study. LH Zhang, ZT Hong and XD Zhu participated in data collection and analyzed the data. C Li wrote the paper and YF Geng revised it. All the authors helped with article review, and they had read and approved the final manuscript.

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