

**Article Type: main research article**

**Title:** Epidemiology of infertility in China: a population-based study

**Running title:** Epidemiology of infertility in China

**Authors:** Zehong Zhou<sup>1,2,3,15</sup>, Danni Zheng<sup>1,2,3,15</sup>, Hongping Wu<sup>1,2,3</sup>, Rong Li<sup>1,2,3</sup>, Suxin Xu<sup>4</sup>, Yuefan Kang<sup>5</sup>, Yunxia Cao<sup>6</sup>, Xiujuan Chen<sup>7</sup>, Yimin Zhu<sup>8</sup>, Shuguang Xu<sup>9</sup>, Zi-Jiang Chen<sup>10</sup>, Ben Willem Mol<sup>11,12</sup>, and Jie Qiao<sup>1,2,3,13,14,\*</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Reproductive Medical Center, Peking University Third Hospital, Beijing 100191, China <sup>2</sup>Key Laboratory of Assisted Reproduction, Ministry of Education, Beijing 100191, China <sup>3</sup>Beijing Key Laboratory of Reproductive Endocrinology and Assisted Reproductive Technology, Beijing 100191, China <sup>4</sup>Reproductive Medical Center, The Second Hospital of Hebei Medical University, Shijiazhuang 050000, China <sup>5</sup>Reproductive Medical Center, Maternal and Children's Health Hospital of Fujian Province, Fuzhou 350001, China <sup>6</sup>Department of Obstetrics and Gynecology, Reproductive

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1471-0528.14966

This article is protected by copyright. All rights reserved.

Medical Center, First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

<sup>7</sup>Reproductive Medical Center, Affiliated Hospital of Inner Mongolia Medical University,

Huhhot 010059, China <sup>8</sup>Department of Reproductive Endocrinology, Women's Hospital,

School of Medicine, Zhejiang University, Hangzhou 310006, China <sup>9</sup>Population and Family

Planning Research Institute of Heilongjiang Province, Harbin 150020, China <sup>10</sup>Center for

Reproductive Medicine, Shandong Provincial Hospital Affiliated to Shandong University,

Jinan 250001, China <sup>11</sup>The Robinson Research Institute, School of Medicine, University of

Adelaide, Adelaide, 5000 SA Australia <sup>12</sup>The South Australian Health and Medical Research

Institute, Adelaide, 5000 SA Australia <sup>13</sup>Beijing Advanced Innovation Center for Genomics,

Beijing 100871, China <sup>14</sup>Peking-Tsinghua Center for Life Sciences, Peking University,

Beijing 100871, China <sup>15</sup>Co-first authors

**\*Correspondence address:** Department of Obstetrics and Gynecology, Reproductive

Medical Center, Peking University Third Hospital, No.49 North Huayuan Road, Haidian

District, Beijing 100191, China. Tel: +86-010-82265080; Fax: +86-010-82266849; E-mail:

jie.qiao@263.net.

## Abstracts

**OBJECTIVE:** To assess the current prevalence of and risk factors for infertility among couples of reproductive age in China.

**DESIGN:** Population-based cross-sectional study.

**SETTING:** We approached 25,270 couples in 8 provinces/municipalities, of whom 18,571 (response rate 74%, 18,571/25,270) were interviewed.

**POPULATION:** Couples living together and married for more than 1 year, of whom the female spouse was 20-49 years old.

**METHODS:** Women were approached via telephone and face-to-face conversation to complete the standardized and structured questionnaire by trained interviewers.

**MAIN OUTCOME MEASURES:** Prevalence and risk factors of infertility.

**RESULTS:** Among women 'at risk' of pregnancy, the prevalence of infertility was 15.5% (2,680/17,275). Among 10,742 women attempting to become pregnant, the prevalence of infertility was 25.0% (2,680/10,742), which increased with age in the second population. Among women who failed to achieve pregnancy in the last 12 months, 3,470 finished our questionnaire about fertility care, and 55.2% (1,915/3,470) of them had sought medical help.

Socio-demographic risk factors for infertility included lower educational level (aOR=3.4, 95%CI: 2.0-5.5) and employment (aOR=2.3, 95%CI: 1.9-2.9). Clinical risk factors were irregular menstrual cycle (aOR=1.8, 95%CI: 1.2 -2.5), light menstrual blood volume (aOR=1.6, 95%CI: 1.2-2.0), history of cervicitis (aOR=1.5, 95%CI: 1.2-2.0) and

This article is protected by copyright. All rights reserved.

Accepted Article

endometriosis (aOR=3.1, 95%CI: 1.1-9.3), previous stillbirth (aOR=2.1, 95%CI: 1.3-3.3) and miscarriage (aOR=2.7, 95%CI: 2.1-3.5). In addition, history of operation was a significantly risk factor of infertility.

**CONCLUSIONS:** Among couples of reproductive age in China, the prevalence of infertility was 25%, and almost half of the couples experiencing infertility had not sought medical help.

**FUNDING:** Assisted Reproductive Technology Development Cooperation Projects (No. (2010)237), National Key Technology R&D Program (No.2012BAI32B01), Research Fund of National Health and Family Planning Commission of China (No.201402004).

**Tweetable abstract:** 25% of couples actively attempting to become pregnant suffered infertility in China.

**Keywords:** Infertility / Epidemiology/ Prevalence / Medical help/ Risk factors

## Introduction

Infertility is a heavy burden on countless families, with important implications for individuals and public health,<sup>1-4</sup> including psychological distress,<sup>5</sup> social stigmatization,<sup>6</sup> economic constraints,<sup>7</sup> and later onset adult diseases.<sup>8,9</sup> In the last decades, the trend of delaying marriage and childbearing has further exacerbated the burden of infertility.<sup>10-12</sup>

Couples aiming to conceive through unprotected sexual intercourse have an 85-90% chance of achieving pregnancy within 1 year, reaching over 90% in 2 years,<sup>13</sup> while difficulties in conception are encountered by about 10-15% of these couples.<sup>14</sup> The prevalence of infertility, defined as the inability to conceive after 12 months of unprotected intercourse, ranges from 3.5% to 16.7% in high-resourced countries, and 6.9% to 9.3% in low-resourced countries.<sup>2</sup> The differences in prevalence partially results from the differences of region, race and culture, while differences in the definition of infertility may contribute more essential part of it.<sup>14</sup> The causes of infertility are wide ranged, including socioeconomic factor, lifestyle, reproductive history, and childbearing status.<sup>15</sup> All factors above can contribute to the appearance of infertility through different pathways.<sup>16</sup>

Due to the changes such as marital status, educational attainment, unfavorable lifestyle and pollution, the prevalence of infertility in China has been increasing: a large-scaled survey was conducted nationwide in 1988 and reported the prevalence of 2-year infertility was 6.7% among women of reproductive age. A similar population-based study conducted 15 years later in 39,586 women of reproductive age showed the prevalence of 1-year infertility to be 18%.<sup>17, 18</sup>

However, little is known about the overall prevalence and risk factors of infertility in recent years. We performed a population-based survey in northern and eastern China to assess prevalence and risk factors of infertility in a sample of thousands of married couples of childbearing ages. This information can be used to establish appropriate strategies for prevention treatment, and management of infertility.

## Materials and methods

### *Design and study population*

From February 2010 to November 2011, we conducted a large-scale population-based cross-sectional study in northern and eastern China. The provinces/municipalities included Zhejiang, Anhui, Fujian, Shandong, Beijing, Hebei, Heilongjiang and Nei Mongol, which due to the largest population and the highest population mobility can be considered representable for the rest of China. The target population consisted of couples who had been married for more than 1 year, and of which the female spouse was 20-49 years old. Couples who ever used birth control and who had lived apart longer than 3 months in the past year were excluded. This survey was reviewed and approved by the Ethics Committee of Peking University Third Hospital (No. 2006FC001).

### *Sample and data collection*

Sample sizes were determined by the assumed prevalence of infertility in 8 provinces/municipalities, with an allowable error of 1.0% and a confidence level of 95%. Using this assumption, a total sample size of 21,876 would be required. To minimize the sampling error, we calculated a final sample size which was 1.5-fold of previous one, resulting in a required sample size of 32,813. The sample size assigned in every province/municipality is shown in Table S1.

Accepted Article

A multistage stratified cluster sampling strategy was performed from each stratum by district, province/municipality, town/township and village/street order (Figure S1). In primary sampling units, the districts were categorized into two strata, representing high and low prevalence of infertility according to the prevalence in each district reported in 1988, and then two provinces/municipalities were randomly selected from each stratum. In secondary sampling units, townships in every province/municipality were ranked according to local per capita gross domestic product (GDP) and number of women at childbearing age and divided into nine strata, then three townships were randomly selected from the highest, moderate and lowest stratum respectively. In third sampling units, participants aged 20-49 years were identified in the selected townships, among these townships, every village/street was investigated as a unit.

Couples were approached by professional investigators with the assistance from the local National Health and Family Planning Commission of the People's Republic of China (NHFPC) and communities. The family planning policy requires women to get NHFPC-approval before aiming pregnancy, which allowed us to approach all women at reproductive age aiming to conceive via telephone. Informed consent was obtained from every participant accepted our survey. Before our investigation, the standardized and structured questionnaire was developed. Face to face interviews were conducted by trained interviewers consisted of local community leaders and health workers. In the process of investigation, women were interviewed to recall information about their partners and themselves in private to assure the confidentiality of the information obtained.

This article is protected by copyright. All rights reserved.

The questionnaire requested details regarding general demographic and socioeconomic status, physical measurements, lifestyle habits and toxic contacts for both women and their partners, such as birth date, ethnicity, height, weight, educational level, occupation, toxic contact history and category, smoking (defined as currently smoking at least once a week), drinking (defined as currently drinking at least once a week), exercise and annual household income, female reproductive health (e.g. age at menarche, last menstrual period, menstrual regularity, menstrual cycle, menstrual blood volume, medical history, operation history), male reproductive health (e.g. medical history, operation history), marriage and bearing status (e.g. length of marriage and cohabitation, pregnancy history including information concerning live births, miscarriage, induced abortions and stillbirths, frequency of sexual intercourse, time to pregnancy), seeking of medical help.

#### *Definition of infertility*

Infertility was defined according to the WHO manual as failing to achieve pregnancy after at least 12 months of unprotected regular sexual intercourse.<sup>19</sup> Primary infertility was defined as infertile couples without any previous pregnancy, whereas secondary infertility refers to couples in this situation after a previous pregnancy achieved without treatment.<sup>20</sup>

Four questions were utilized to identify infertile couples. First, women were asked whether they wanted to become pregnant in the previous year, on their frequency of intercourse with their partner in the previous year, whether they had a spontaneous pregnancy in the previous year, and how long they had been trying to become pregnant. Women who wanted to become



pregnant, who had unprotected sexual intercourse at least once a month, and who were trying to achieve pregnancy longer than 12 months were considered to be infertile.

### *Statistical analysis*

Extremes outside the 0.5-99.5 percentile of continuous variables (BMI of women and men, age at menarche, duration of menstruation, count of pregnancy, and number of uterine curettage), women aged <20 or >49 years, and couples who had lived separately longer than 3 months as logic error were excluded for the criteria of our study and avoiding unlikely ranges. In addition, missing data for the variables analyzed were excluded. Continuous variables were described by mean and standard deviation (SD), and categorical variables were checked out for percentages.

Infertility rate was calculated on the basis of the definition of infertility: the number of infertile women represented the numerator and the number of women exposed to the risk of pregnancy or women attempting to pregnant represented the denominator. Distribution of infertility among women 'at risk' of pregnancy in different region was presented. In addition, we calculated the prevalence of infertility by two different denominators in age groups continuously with the moving average per 5 years for both women and men.

For statistical test, distributions were compared using Pearson's chi-square test and Fisher's exact test when appropriate. Differences with  $p$  value <0.05 were considered statistically significant. Unconditional Multivariable logistic regression was used to examine the associations between potential risk factors and infertility. Variables considered as potential

This article is protected by copyright. All rights reserved.

Accepted Article

confounders were those had shown a univariate association at p value  $<0.2$ . A forward stepwise procedure was employed and the significant levels in the model were set with a  $p < 0.2$  as entry and  $p > 0.1$  to stay in the model <sup>21</sup>. Multivariable logistic regression analyses were then performed within each subgroup, adjusting for confounders. Odds ratios (OR) and 95% confidence intervals (95% CI) were used to approximate associated risks of infertility. Individual-level ORs were calculated for each category in comparison to a reference category. All statistical analyses were performed with the SAS software package V.9.4.

## Results

There was serious concern that the assigned locations were not sampled during the execution process in Shandong province (1,359 responses and 6,184 non-responses, response rate 18%), so the 7,543 couples in this province were excluded from our study. The subsequent analysis was restricted to the other 7 provinces. In these 7 provinces, a total of 25,270 couples was approached, of whom 18,571 (73.5%) couples responded and formed the study population. Main reasons for non-response were absence from the home and reluctance to spend time receiving investigation.

### *Study population*

Figure 1 shows the flowchart including the exclusion of ineligible data, screening of different denominator and extraction of infertile couples from our population. Among 18,571 couples, women aged <20 or >49 were excluded (n=125) to restrict the range of reproductive age in this study. The extreme values of the BMI of women (n=193, BMI <16.4 or >32.0) and men (n=173, BMI <17.3 or >32.3), age at menarche (n=61, <11 or >19), duration of menstruation (n=90, >10), count of pregnancy (n=33, >5) and number of uterine curettage (n=13, >3) were excluded to avoid the unlikely range. We also excluded 271 couples who had lived separately longer than 3 months, as well as 337 couples who did not become pregnant in the last 12 months but were trying to achieve pregnancy shorter than 12 months. Thus, 17,275 couples were included in the analysis (see Figure 1A). Women ‘at risk’ of pregnancy (i.e. having unprotected intercourse) were then identified, as the first denominator to explore the prevalence of infertility. Among them, women who actively trying to become pregnant were selected as the second denominator (see Figure 1B).

Demographic and socioeconomic characteristics of couples in the study are presented in Table 1. The mean  $\pm$ SD of age was  $29.3 \pm 6.7$  years for women and  $31.5 \pm 7.3$  years for men. More than 96% of couples were Han ethnic. The mean  $\pm$  SD of BMI was  $22.3 \pm 2.6$  for women and  $23.0 \pm 2.3$  for men. Only a few women in this study were current smokers or drinkers (0.5% and 2.1%, respectively). In contrast, almost half of men were current smokers or drinkers (43.4% and 44.3%, respectively).

*Prevalence of infertility and patterns of region*

Among women who could become pregnant (n=17,275), the overall prevalence of infertility was 15.5% (n=2,680), with the prevalence of primary and secondary infertility being 9.5% (n=1,644) and 6.0% (n=1,036), respectively. There was a pronounced regional pattern in the levels of infertility (Figure S2). The Fujian province stood out as the region with infertility rate lower than 8% (7.2%, n=130). The overall prevalence of infertility in Nei Mongol municipality (10.2%, n=170), Beijing municipality (11.3%, n=186) and Anhui province (14.5%, n=472) ranged in the moderate level. The overall prevalence of infertility in Heilongjiang province (15.6%, n=198) and Hebei province (17.2%, n=929) ranged from 15-20% in the study regions. Overall prevalence of infertility in Zhejiang province (26.7%, n=595) took up the highest setting among 7 provinces/municipalities.

In couples actively trying to conceive (n=10,742), the overall prevalence of infertility was 25.0% (n=2,680), with the prevalence of primary and secondary infertility 15.3% (n=1,625) and 9.7% (n=1,036), respectively (Figure S3). These couples were younger than couples 'at risk' of pregnancy, and had lower educational attachment and annual household income (Table S2). In addition, they tended to have more sexual intercourse than women 'at risk' of pregnancy (Table S3).

### *The patterns of age*

Figure 2 presents the overall prevalence of infertility calculated by two different denominators in age groups continuously with the moving average per 5 years for both women and men. In women who could become pregnant, the overall prevalence of infertility increased from 2.5% to 30.2% (test for trend,  $p < 0.001$ ) in women from 20 to 37 years old, to fell to 17.4% in women over the age of 37. As for the effect of men's age, from 20 to 43 years old, the overall prevalence of infertility increased from 0.0% to 25.8% (test for trend,  $p < 0.001$ ), whereas a fall to 15.5% was presented over the age of 43. Among couples actively trying to conceive, the overall prevalence of infertility increased with age in linear both in women and men before 45 years old, to drop slightly in groups aged over 45 years.

### *Clinical consultation by infertile couples*

For women who had not achieved pregnancy in the last 12 months but still wanted to get pregnant, we collected information about the behavior of seeking medical help and reasons of not to seek consultation (Table S4). Among these women, about 45% ( $n=1,555$ ) had not contacted a medical doctor or opted for treatment for infertility, since the majority of them still wanted to conceive naturally (44.1%,  $n=1,124$ ), and/or thought that they did not have a fertility problem (40.7%,  $n=1,038$ ).

### *Risk factors of infertility*

This article is protected by copyright. All rights reserved.

Table 2 shows both unadjusted and adjusted ORs with their 95% CIs for the association between infertility and risk factors among women actively trying to conceive. Both female age and male age were strongly associated with infertility: the risk of infertility was increased with advanced age of couples. There was a remarkable 'dose response' of decreasing risk of infertility along with the increasing levels of education in logistic regression analysis: compared with women who received education from college and above, the aOR for infertility of women with middle school education and above was 3.10 (95%CI: 2.07-4.64), and women with primary school and below was 3.35 (95%CI: 2.03-3.52). Compared with women who were not employed, working women were more likely to suffer from infertility (aOR=2.34, 95%CI: 1.87-2.93). Duration of cohabitation of infertile couples was significantly longer than that of fertile couples (aOR=1.08, 95%CI: 1.05-1.11). The proportions of women with irregular menstruation (aOR: 1.76, 95%CI: 1.24-2.49), and heavy (aOR: 0.89, 95%CI: 0.59-1.35) or light menstrual blood volume (aOR: 1.58, 95%CI: 1.10-2.27) among the infertile women were all greater than those among the fertile women. Women with infertility were more likely suffered from cervicitis (aOR=1.53, 95%CI: 1.17-2.00) and endometriosis (aOR=3.12, 95%CI: 1.05-9.24), and had experienced more adverse pregnancy outcomes such as stillbirth (aOR=2.06, 95%CI: 1.28-3.31) and miscarriage (aOR=2.67, 95%CI: 2.07-3.46). In the meanwhile, there was a significant higher percentage of female having operation history among couples with infertility: Surgery of ovary or fallopian tube (aOR=3.19, 95%CI: 1.51-6.75) and pelvic or abdomen (aOR=3.10, 95%CI: 1.86-5.16) were all significantly risk factors of infertility.

## Discussion

### *Main Findings*

This study provides estimates of infertility prevalence, clinical consultation, and risk factors in married couples of reproductive ages in China. The overall prevalence of infertility among women could be pregnant was 15.5%, and the prevalence of primary and secondary infertility were 9.5% and 6.0%, respectively. Among women actively trying to conceive, the according prevalence was 25.0%, 15.3% and 9.7%, respectively. The changes of prevalence with age in the two selected population presented different patterns, and only 55.2% of women who failed to conceive in the last 12 months would seek medical help. Besides of this, associated risk factors of infertility were analyzed.

We can see that it makes no explicit reference to intent to conceive in the definition from WHO, but, given the availability of contraception, this definition implies that women meeting the criteria for infertility were trying to conceive. However, a study re-analyzed the data from the National Survey of Family Growth (NSFG) found there were a large number of women who fit the definition of infertility but did not having tried to become pregnant at that time, and there also existed many differences between the two populations.<sup>22</sup> This was the reason why we introduced the combined definition to our study.

### *Strengths and limitations*

Our study has several strengths. First, a multistage stratified cluster sampling strategy was conducted in a large sample size establishing substantial power. Second, standardized and structured questionnaires were designed to collect the information. By doing so, an accurate estimation of infertility rates was obtained. Thirdly, we extracted two denominators to calculate the prevalence of infertility, which perfectly revealed the importance of the intent to conceive in estimating infertility rate and the severity of fertility decline.

Our study has also several limitations. First, had to exclude data from the Shandong province as we found serious errors during data collection. The data from other provinces/municipalities were checked to ensure reliability. Second, information about infertility was self-reported, which could be subject to recall bias. To overcome this issue, we listed a series of question to identify infertility, and the logical errors were excluded from our analysis. Thirdly, participants stated their will to become pregnant according their intension at the time of investigation, however, it did not represent the sustained will during the last 12 months, which might lead to underestimation of the prevalence of infertility to some extent.

### *Interpretation*

The prevalence of infertility among women 'at risk' of pregnancy was 15.5%. Using the same analysis method, a population-based study in France sampled 15,810 women aged 18-44 years from 2007-2008, resulting in infertility rate of 24%.<sup>23</sup> Among women attempting to become pregnant in our study, the prevalence of overall infertility, primary and secondary

This article is protected by copyright. All rights reserved.



infertility was comparable with the results from a study in Scotland, of which the infertility rate was 19.3%, 9.8% and 7.0% accordingly.<sup>24</sup> Similar studies in Australia and Iran among women intending to conceive<sup>25,26</sup> reported infertility rates of 17% and 17.3%, respectively.

Not unexpectedly, we found a clearly raise of infertility with increasing age. However, among women 'at risk' of pregnancy, the prevalence of infertility fell in women over 40 years. This pattern was consistent with the study in France,<sup>23</sup> which is obviously related to the intent to conceive, as many women above 40 years might not want to conceive anymore, while not taking any contraception. These women could be included in the denominator but be excluded in the numerator, resulting a drop of infertility rate in this group. When we restricted the denominator to women attempting to be pregnant, the prevalence of infertility increased with age as expected (see Figure 2 (C) and (D)). Reviews showed that fecundity drops progressively with increasing age.<sup>11</sup> According to our analysis, 6 out of 10 women over 40 years old suffer from infertility. Therefore, more health improvement strategies should be carried out on older pregnancy.

Among women failed to conceive in the last 12 months, 55% had sought consultation or treatment for infertility, almost similar to the 57% reported in a previous Chinese study in 2002,<sup>27</sup> and higher than the 34% reported in UK in 1997.<sup>28</sup> Studies in Iran (67.6-72%) and Australia (72%) have reported higher rates.<sup>25,26,29</sup> A previous systematic review conducted by Boivin, J and colleagues summarized that only about half of the people who experienced fertility problems decided to seek fertility medical care, no matter in developed countries or

developing ones.<sup>2</sup> About 85% of our studied couples did not seek medical help since they still wanted to conceive naturally or thought no fertility problem with themselves, while a small portion of them did so due to economic barriers and busy schedule, as infertility treatment would not be covered by health insurance and was time consuming in most cases.

Socioeconomic status (SES) has been well established as associated with an individual's reproductive health.<sup>30</sup> In our study population, educational level presented an inverse association with infertility, which was consistent with Safarinejad's study from Iran.<sup>31</sup> It attest to the fact that women with higher educational attainment usually have healthier lifestyle and better curative care.<sup>32,33</sup> We also found working women had a higher risk of infertility than unemployed women, which was consistent with previous studies.<sup>34-36</sup> Of them, Younglai E.V. *et al.*<sup>35</sup> stated that female fertility impairment may resulted from the physiological and psychological burden from current occupation. Results in our population revealed that high-income couples had the highest risk of infertility compared with the low-income group, as income acts as a proxy for the general concept of social class.<sup>37</sup> It could be explained by the fact that high-income couples in China tend to postpone the timing of pregnancy, with the experience of induced abortion, which may increase their risk encountering infertility.

Reproductive factors synthetically associated with infertility in our study included regularity of menstrual cycle, menstrual blood volume, previous stillbirth and miscarriage, history of cervicitis and endometriosis, pelvic or abdominal surgery, and surgery of ovary or fallopian

Accepted Article

tube. The mechanism underlying the observed associations were well established, including distorted pelvic anatomy, altered peritoneal function, altered hormonal function, endocrine and ovulatory abnormalities, genital infection, et al.<sup>38,39</sup> In brief, infertility is a complex medical condition that enroll lots of factors play synthetic roles in it.

### **Conclusion**

In conclusion, the overall prevalence of infertility was 15.5% among women 'at risk' of pregnancy, and 25.0% among women attempting to become pregnant in China. Half of couples experiencing infertility had not sought medical help. What's more, we have identified a variety of risk factors for infertility. More than 5 years had passed since this survey was conducted. There is a tremendous need to have a further investigation to know about the current status of fertility and related risk factors, which is essential to health professionals and government in terms of planning healthcare services for infertility.

### **Acknowledgements**

We thank thousands of health workers who have contributed to data collection in the provincial, city, township, and village levels. We appreciate Professor He-Feng Huang (the chairman of the Department of Reproductive Endocrinology, Women's Hospital, School of Medicine, Zhejiang University during the time period of the survey) for her coordination of the investigation in Zhejiang province. We thank Professor Canquan Zhou (the chairman of

This article is protected by copyright. All rights reserved.

Accepted Article

CSRM during the time period of the survey) for his coordination and organization throughout the implementation of the project. We also appreciate for the efforts from Doctor Geng Yu during the preparation and execution phase of this study.

### **Disclosure of Interests**

None declared. Completed ICMJE disclosure of interests forms are available to view online as supporting information.

### **Contribution to Authorship**

Z.Z. was mainly in charge of drafting the article and revising it. D.Z. contributed to the data analysis and drafting the article. H.W. conducted the organization and implementation of project as secretary and participated in the investigation of Beijing. R.L. contributed to the acquisition of Beijing's data, and revising the article for important intellectual content. S.X., Y.K., Y.C., X.C., Y.Z., S.X. and Z.C. did the specific data interpretation of Hebei, Fujian, Anhui, Nei Mongol, Zhejiang, Heilongjiang and Shandong provinces, respectively. B.M. provided critical comments and critical review for important intellectual content. J.Q. contributed to conception and design, final approval of the version to be published as corresponding author.

## Details of Ethics Approval

This survey was reviewed and approved by the Ethics Committee of Peking University Third Hospital in March 23, 2006. The approval number is No. 2006FC001. Informed consent was obtained from every participant accepted our survey.

## Funding

This study was supported by Assisted Reproductive Technology Development Cooperation Projects from the Center for international exchanges and cooperation in National Health and Family Planning Commission of the People's Republic of China (No. (2010)237), National Key Technology R&D Program in the Twelfth Five-Year Plan (No.2012BAI32B01) and Research Fund of National Health and Family Planning Commission of China (No.201402004). The study funders had no rule in the study design, implementation, analysis, manuscript, preparation, or decision to submit this article for publication.

## References

- 1 Bhattacharya S, Porter M, Amalraj E, Templeton A, Hamilton M, Lee AJ, et al. The Epidemiology of Infertility in the North East of Scotland. *Hum Reprod* 2009;24:3096-107.
- 2 Boivin J, Bunting L, Collins JA, Nygren KG. International Estimates of Infertility Prevalence and Treatment-Seeking: Potential Need and Demand for Infertility Medical Care. *Hum Reprod* 2007;22:1506-12.
- 3 Schmidt L, Sobotka T, Bentzen JG, Nyboe AA. Demographic and Medical Consequences of the Postponement of Parenthood. *Hum Reprod Update* 2012;18:29-43.

- 4 Duron S, Slama R, Ducot B, Bohet A, Sorensen DN, Keiding N, et al. Cumulative Incidence Rate of Medical Consultation for Fecundity Problems--Analysis of a Prevalent Cohort Using Competing Risks. *Hum Reprod* 2013;28:2872-9.
- 5 Bak CW, Seok HH, Song SH, Kim ES, Her YS, Yoon TK. Hormonal Imbalances and Psychological Scars Left Behind in Infertile Men. *J Androl* 2012;33:181-9.
- 6 Slade P, O'Neill C, Simpson AJ, Lashen H. The Relationship Between Perceived Stigma, Disclosure Patterns, Support and Distress in New Attendees at an Infertility Clinic. *Hum Reprod* 2007;22:2309-17.
- 7 Wu AK, Elliott P, Katz PP, Smith JF. Time Costs of Fertility Care: The Hidden Hardship of Building a Family. *Fertil Steril* 2013;99:2025-30.
- 8 Jensen TK, Jacobsen R, Christensen K, Nielsen NC, Bostofte E. Good Semen Quality and Life Expectancy: A Cohort Study of 43,277 Men. *Am J Epidemiol* 2009;170:559-65.
- 9 Merritt MA, De Pari M, Vitonis AF, Titus LJ, Cramer DW, Terry KL. Reproductive Characteristics in Relation to Ovarian Cancer Risk by Histologic Pathways. *Hum Reprod* 2013;28:1406-17.
- 10 Te VE, Pearson PL. The Variability of Female Reproductive Ageing. *Hum Reprod Update* 2002;8:141-54.
- 11 Evers JL. Female Subfertility. *Lancet* 2002;360:151-9.
- 12 Petraglia F, Serour GI, Chapron C. The Changing Prevalence of Infertility. *Int J Gynaecol Obstet* 2013;123 Suppl 2:S4-8.
- 13 Cabrera-Leon A, Lopez-Villaverde V, Rueda M, Moya-Garrido MN. Calibrated Prevalence of Infertility in 30- To 49-Year-Old Women According to Different Approaches: A Cross-Sectional Population-Based Study. *Hum Reprod* 2015;30:2677-85.
- 14 Gurunath S, Pandian Z, Anderson RA, Bhattacharya S. Defining Infertility--A Systematic Review of Prevalence Studies. *Hum Reprod Update* 2011;17:575-88.
- 15 Balen AH, Rutherford AJ. Management of Infertility. *BMJ* 2007;335:608-11.
- 16 Te VE, Pearson PL. The Variability of Female Reproductive Ageing. *Hum Reprod Update* 2002;8:141-54.
- 17 Liu J, Larsen U, Wyshak G. Prevalence of Primary Infertility in China: In-Depth Analysis of Infertility Differentials in Three Minority Province/Autonomous Regions. *J Biosoc Sci* 2005;37:55-74.

- 18 Junqing W, Qiuying Y, Jianguo T, Wei Y, Liwei B, Yuxian L, et al. Reference Value of Semen Quality in Chinese Young Men. *Contraception* 2002;65:365-8.
- 19 Nygren KG, Sullivan E, Zegers-Hochschild F, Mansour R, Ishihara O, Adamson GD, et al. International Committee for Monitoring Assisted Reproductive Technology (Icmart) World Report: Assisted Reproductive Technology 2003. *Fertil Steril* 2011;95:2209-22, 2221-2.
- 20 Larsen U. Research On Infertility: Which Definition Should we Use? *Fertil Steril* 2005;83:846-52.
- 21 Mark J, Goldberg M. Multiple Regression Analysis and Mass Assessment: A Review of the Issues. *Appraisal Journal* 1988;56:89.
- 22 Greil AL, McQuillan J, Johnson K, Slauson-Blevins K, Shreffler KM. The Hidden Infertile: Infertile Women without Pregnancy Intent in the United States. *Fertil Steril* 2010;93:2080-3.
- 23 Slama R, Hansen OK, Ducot B, Bohet A, Sorensen D, Giorgis AL, et al. Estimation of the Frequency of Involuntary Infertility On a Nation-Wide Basis. *Hum Reprod* 2012;27:1489-98.
- 24 Bhattacharya S, Porter M, Amalraj E, Templeton A, Hamilton M, Lee AJ, et al. The Epidemiology of Infertility in the North East of Scotland. *Hum Reprod* 2009;24:3096-107.
- 25 Herbert DL, Lucke JC, Dobson AJ. Infertility, Medical Advice and Treatment with Fertility Hormones and/Orin Vitro Fertilisation: A Population Perspective From the Australian Longitudinal Study On Women's Health. *Australian and New Zealand Journal of Public Health* 2009;33:358-64.
- 26 Kazemijaliseh H, Ramezani TF, Behboudi-Gandevani S, Hosseinpanah F, Khalili D, Azizi F. The Prevalence and Causes of Primary Infertility in Iran: A Population-Based Study. *Glob J Health Sci* 2015;7:226-32.
- 27 Che Y, Cleland J. Infertility in Shanghai: Prevalence, Treatment Seeking and Impact. *J Obstet Gynaecol* 2002;22:643-8.
- 28 Buckett W, Bentick B. The Epidemiology of Infertility in a Rural Population. *Acta Obstet Gynecol Scand* 1997;76:233-7.
- 29 Ahmadi ABY, Madaen K, Haj ES, Ehsan NA, Koushavar H. Prevalence of Infertility in Tabriz in 2004. *Urol J* 2006;3:87-91.

- 30 Baker DP, Leon J, Smith GE, Collins J, Movit M. The Education Effect On Population Health: A Reassessment. *Popul Dev Rev* 2011;37:307-32.
- 31 Safarinejad MR. Infertility Among Couples in a Population-Based Study in Iran: Prevalence and Associated Risk Factors. *Int J Androl* 2008;31:303-14.
- 32 Mackenbach JP. The Persistence of Health Inequalities in Modern Welfare States: The Explanation of a Paradox. *Soc Sci Med* 2012;75:761-9.
- 33 Partridge S, Balayla J, Holcroft CA, Abenheim HA. Inadequate Prenatal Care Utilization and Risks of Infant Mortality and Poor Birth Outcome: A Retrospective Analysis of 28,729,765 U.S. Deliveries Over 8 Years. *Am J Perinatol* 2012;29:787-93.
- 34 Homan GF, Davies M, Norman R. The Impact of Lifestyle Factors On Reproductive Performance in the General Population and those Undergoing Infertility Treatment: A Review. *Hum Reprod Update* 2007;13:209-23.
- 35 Younglai EV, Holloway AC, Foster WG. Environmental and Occupational Factors Affecting Fertility and Ivf Success. *Hum Reprod Update* 2005;11:43-57.
- 36 Kumar S. Occupational Exposure Associated with Reproductive Dysfunction. *J Occup Health* 2004;46:1-19.
- 37 Logie C. The Case for the World Health Organization's Commission On the Social Determinants of Health to Address Sexual Orientation. *Am J Public Health* 2012;102:1243-6.
- 38 Hanson B, Johnstone E, Dorais J, Silver B, Peterson CM, Hotaling J. Female Infertility, Infertility-Associated Diagnoses, and Comorbidities: A Review. *J Assist Reprod Genet* 2017;34:167-77.
- 39 Lee RM, Silver RM. Recurrent Pregnancy Loss: Summary and Clinical Recommendations. *Semin Reprod Med* 2000;18:433-40.

#### **Table/Figure Caption List**

**Table 1.** Demographic and socioeconomic characteristic of study participants.

**Table 2.** Risk factors of infertility among couples actively trying to conceive.



**Figure 1.** Flow charts of data according to eligibility for inclusion in the analysis (A) and the process of identifying two denominators and infertile couples (B).

**Figure 2.** The prevalence of overall infertility in different age groups for both women and men. A and B represent the changes of infertility rate with age for women (A) and men (B) among couples could be pregnant. C and D represent the changes of infertility rate with age for women (C) and men (D) among couples actively trying to conceive. The hidden line represents the moving average per 5 years.

**Table S1.** The sample size assigned in every stratum.

**Table S2.** Demographic and socioeconomic characteristics between two denominators.

**Table S3.** Sexual intercourse between two denominators.

**Table S4.** Percentage of women seeking medical help among all women attempting to conceive for at least 12 months.

**Figure S1.** Flow chart of multi-stage stratified cluster sampling strategy during participant selection.

**Figure S2.** The prevalence of overall infertility among 7 regions in northern and eastern China was classified as <5%, 10-15%, 15-20% and >20% by different shades of colors.

**Figure S3.** The prevalence of overall, primary and secondary infertility among two selected populations.

**Table 1. Demographic and socioeconomic characteristic of study participants**

Characteristic	Women		Men	
	n	percentage (%)	n	percentage (%)
<b>Number of participants</b>	17,275	100.00	17,275	100.00
<b>Region</b>				
Anhui	3,256	18.9	3,256	18.9
Beijing	1,649	9.6	1,649	9.6
Fujian	1,802	10.4	1,802	10.4
Hebei	5,402	31.3	5,402	31.3
Heilongjiang	1,267	7.3	1,267	7.3
Nei Mongol	1,672	9.7	1,672	9.7
Zhejiang	2,227	12.9	2,227	12.9
<b>Age, years (mean (SD))</b>		29.3 (6.7)		31.5 (7.3)
<b>Ethnicity</b>				
Han ethnic	16,528	96.3	16,392	96.4
Minority <sup>a</sup>	629	3.7	617	3.6
<b>BMI, kg/m<sup>2</sup> (Mean (SD))</b>		22.3 (2.6)		23.0 (2.3)
<b>Education</b>				
Primary school and below	1,236	7.2	1,007	5.9
Middle school	9,958	57.9	9,835	57.9
High school	3,084	17.9	2,955	17.4
College and above	2,936	17.1	3,195	18.8
<b>Occupation</b>				
Clerk	1,337	7.8	1,473	8.6

Professional worker	1,214	7.1	2,267	13.3
Service worker	2,221	12.9	2,788	16.3
Agricultural & related workers	4,831	28.1	5,424	31.7
Factory worker	428	2.5	1,962	11.5
Unemployed	6,065	35.3	256	1.5
Other or not stated	1,083	6.3	2,921	17.1
<b>Annual household income, yuan</b>				
<10,000	9,641	56.7	9,641	56.7
10,000-19,999	3,721	21.9	3,721	21.9
>20,000	3,657	21.5	3,657	21.5
<b>Toxic exposure<sup>b</sup></b>				
Yes	361	2.2	560	3.5
No	16,241	97.9	15,419	96.5
<b>Smoking</b>				
Yes	90	0.5	7,447	43.3
No <sup>c</sup>	17,143	99.5	9,744	56.7
<b>Drinking</b>				
Yes	353	2.1	7,621	44.3
No <sup>d</sup>	16,847	97.9	9,565	55.7

**a.** Minorities included the Mongol nationality, the Hui nationality, and the Zang nationality, etc. **b.** Restricted to radioactive substance and toxic substance. **c.** Included people who never smoke and who used to smoke. **d.** Included people who never drink and who used to drink.

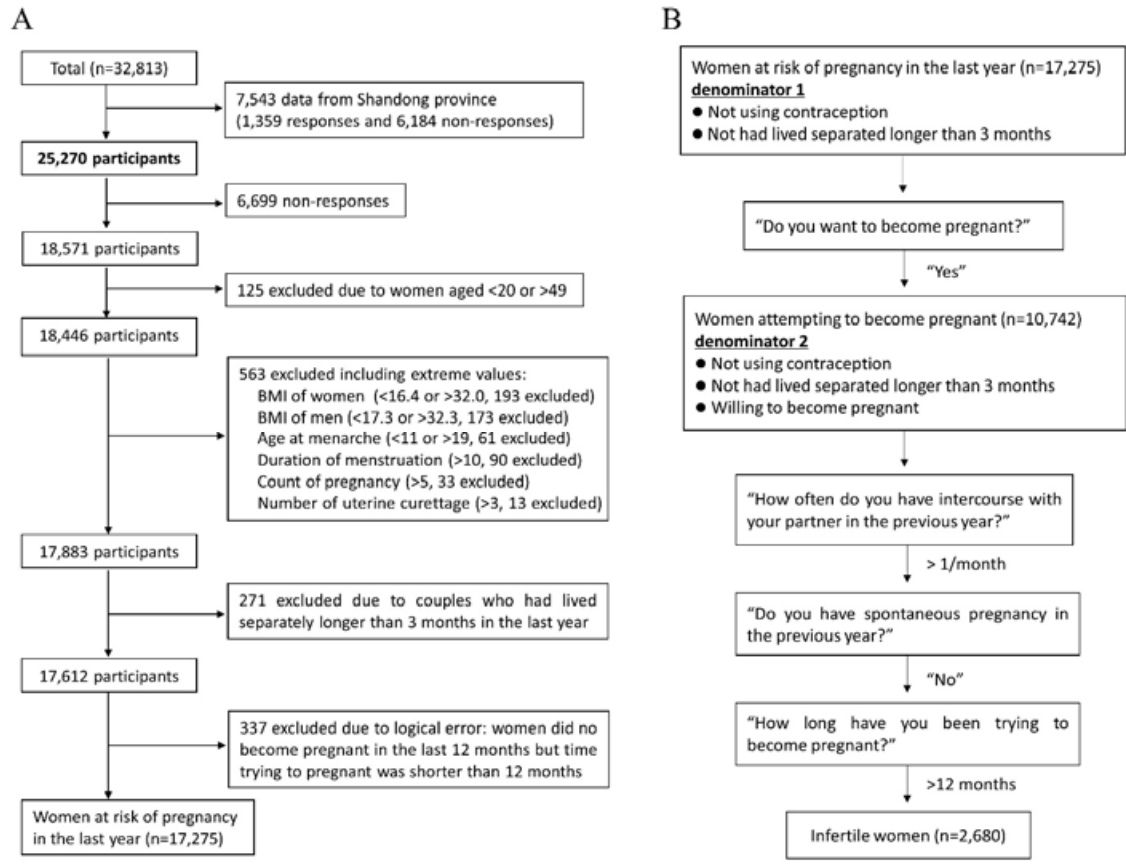
**Table 2. Risk factors of infertility among couples actively trying to conceive**

Characteristic	Fertile women n=8,062	Infertile women n=2,680		
		Overall infertility	Unadjusted OR (95% CI)	Model 2-adjusted OR (95% CI)
<b>Age, years (women) (%)</b>				
20-24	40.38	18.02	ref	ref
25-29	36.42	31.25	1.92 (1.70-2.17)	1.69 (1.16-2.46)
30-34	14.73	23.59	3.59 (3.13-4.11)	2.96 (1.89-4.65)
35-39	5.76	15.70	6.11 (5.19-7.19)	3.98 (2.28-6.95)
≥40	2.71	11.44	9.45 (7.76-11.54)	4.84 (2.38-9.85)
<b>Education (women) (%)</b>				
Primary school and below	6.33	10.18	1.92 (1.58-2.32)	3.35 (2.03-5.52)
Middle school	61.84	61.95	1.19 (1.04-1.36)	3.10 (2.07-4.64)
High school	17.13	15.53	1.08 (0.92-1.27)	1.79 (1.18-2.74)
College and above	14.70	12.35	ref	ref
<b>Employment (women) (%)</b>				
Employment <sup>a</sup>	48.93	63.95	2.45 (2.21-2.71)	2.34 (1.87-2.93)
Unemployment	45.84	24.49	ref	ref
<b>Annual household income, yuan (%)</b>				
<10,000	60.92	53.53	ref	ref
10,000-19,999	22.62	25.03	1.26 (1.13-1.40)	1.30 (1.04-1.64)
>20,000	16.46	21.44	1.48 (1.32-1.66)	1.40 (1.05-1.85)
<b>Age, years (men) (%)</b>				

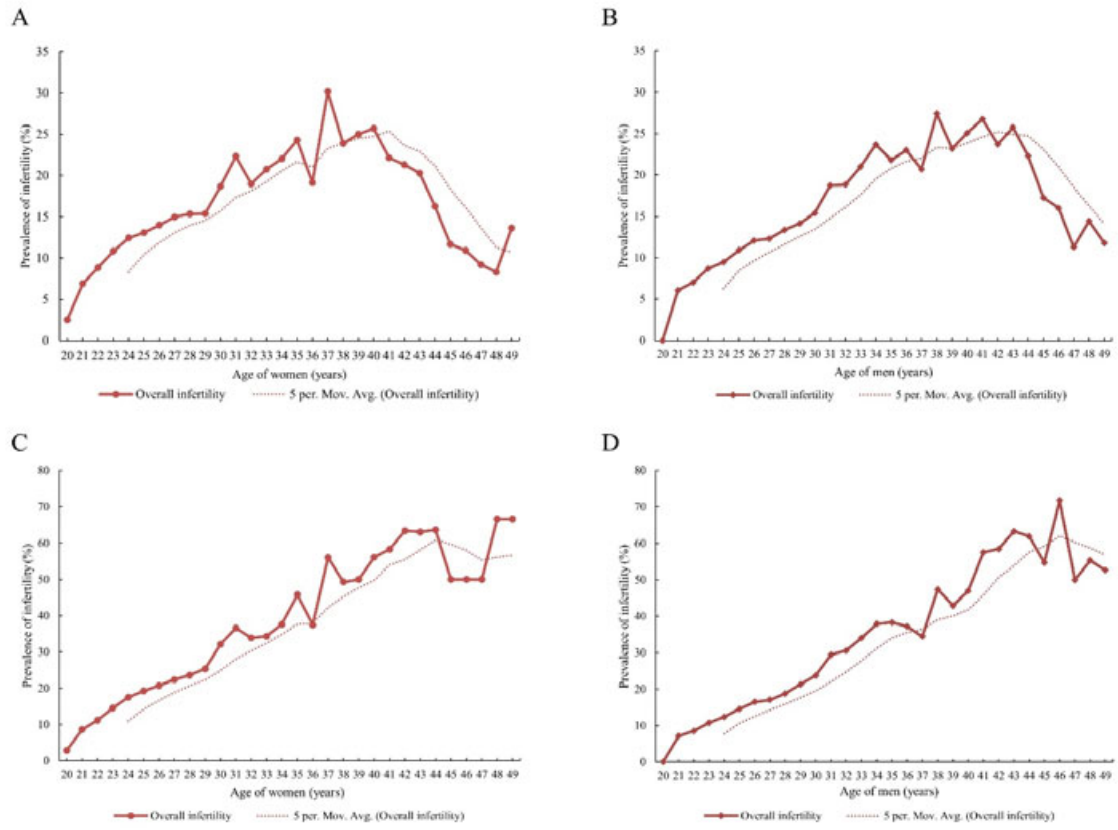
20-24	23.64	8.61	ref	ref
25-29	40.64	26.02	1.76 (1.47-2.10)	2.43 (1.43-4.13)
30-34	21.06	27.16	3.54 (2.96-4.24)	3.16 (1.76-5.66)
35-39	9.49	18.55	5.36 (4.41-6.53)	2.28 (1.18-4.40)
≥40	5.18	19.65	10.42 (8.46-12.83)	2.47 (1.15-5.28)
<b>Duration of cohabitation, years</b>	4.13 (4.38)	7.48 (5.95)	1.13 (1.12-1.14)	1.40 (1.05-1.85)
<b>Irregular menstrual cycle<sup>b</sup></b>	5.54	14.15	2.81 (2.43-3.26)	2.43 (1.43-4.13)
<b>Menstrual blood volume</b>				3.16 (1.76-5.66)
Heavy	5.94	7.38	1.37 (1.15-1.64)	2.28 (1.18-4.40)
Moderate	89.28	80.75	ref	2.47 (1.15-5.28)
Light	4.78	11.87	2.75 (2.34-3.22)	1.58 (1.10-2.27)
<b>Cervicitis<sup>b</sup></b>	0.26	1.06	1.97 (1.71-2.26)	1.53 (1.17-2.00)
<b>Endometriosis<sup>b</sup></b>	0.06	0.57	4.05 (2.30-7.15)	3.12 (1.05-9.26)
<b>Operation history</b>				
Surgery of ovary or fallopian tube <sup>c</sup>	0.39	2.14	5.61 (3.62-8.71)	3.19 (1.51-6.75)
Surgery of pelvic or abdomen <sup>d</sup>	1.39	2.82	2.06 (1.53-2.77)	3.10 (1.86-5.16)
None	92.27	90.98	ref	ref
<b>Previous stillbirth<sup>b</sup></b>	2.26	5.08	2.31 (1.66-3.21)	2.06 (1.28-3.31)
<b>Previous miscarriage<sup>b</sup></b>	7.96	24.77	3.81 (3.21-4.51)	2.67 (2.07-3.46)

All *p*-values test for difference between fertile women and infertile women were less than 0.01.

**a.** Included clerk, professional worker, service worker, agricultural & related workers, and factory worker. **b.** Make negative results as reference groups. **c.** Included oophorectomy, salpingectomy and tubal anastomosis. **d.** Included surgery for pelvic adhesion, appendicitis and ectopic gestation.



**Figure 1. Flow charts of data according to eligibility for inclusion in the analysis (A) and the process of identifying two denominators and infertile couples (B)**



**Figure 2. The prevalence of overall infertility in different age groups for both women and men. A and B represent the changes of infertility rate with age for women (A) and men (B) among couples could be pregnant. C and D represent the changes of infertility rate with age for women (C) and men (D) among couples actively trying to conceive. The hidden line represents the moving average per 5 years.**