The burden and predictors of latent tuberculosis infection among elder adults in high epidemic rural area of tuberculosis in Zhejiang, China

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Diagnosis and treatment of latent tuberculosis infection (LTBI) is critical to tuberculosis (TB) control. Identifying the risk factors associated with LTBI can contribute to developing an optimized strategy for LTBI management. We conducted a survey of adults aged 65 years and older living in rural areas in Zhejiang Province during July 2021, followed by a one-year follow-up period to determine TB incidence. Participants underwent a physical examination and 5–6 mL of blood was drawn to test for Mycobacterium tuberculosis infection. A total of 1856 individuals participated in the study, of whom 50.5% were men and 80.1% were married. Most participants (96.8%) often opened windows for ventilation at home. One-third (33.4%) of participants had abnormal chest radiographs and 34.9% had LTBI. Nine participants (0.5%) developed active TB patients during the one-year follow-up period. People who frequented closed entertainment places such as chess and card rooms had a relatively high percentage of LTBI (39.5%). Factors associated with a higher risk of LTBI in multivariable logistic regression analysis included being male (odds ratio [OR]: 1.32; 95% confidence interval [CI] = 1.01–1.72), smoking (OR: 1.43; 95% CI: 1.04–1.97), not opening windows for ventilation at home frequently (OR: 1.88; 95% CI: 1.10–3.22), and abnormal chest radiographs (OR: 1.48; 95% CI: 1.20–1.81). LTBI was prevalent among the elder adults living in high-epidemic rural areas of TB in Zhejiang province. Men, people who smoke, and people without the habit of ventilating at home should be targeted for LTBI screening to accelerate the decline of the TB epidemic in Zhejiang Province.

KEYWORDS

tuberculosis, latent tuberculosis infection, risk factors, older adults, observational study
Introduction

Tuberculosis (TB) is caused by the bacteria *Mycobacterium tuberculosis* (Mt) and is responsible for 1.5 million deaths each year worldwide (World Health Organization, 2021). Mt is often in a quiescent state in an infected person and does not cause disease quickly. The state in which people are latently infected with Mt and without clinical evidence of active TB is referred to as latent tuberculosis infection (LTBI). The risk of LTBI developing into active TB could be 5%-10% over a lifetime (Andrews et al., 2012). About a quarter of the global population (approximately 2 billion individuals) have LTBI (World Health Organization, 2021), which is the precursor to TB disease and poses a great threat to TB control and the End TB Strategy, launched by the World Health Organization (WHO). The End TB Strategy aimed to achieve the ambitious goal of 90% and 95% reduction respectively in TB incidence and mortality by 2035 (Executive Board, 2014). Early diagnosis and treatment of LTBI might reduce the risk of developing TB disease and interrupt the spread of TB. Based on this, WHO advocates screening for LTBI and preventive treatment in high-risk groups (World Health Organization, 2018).

China is only one of the 30 countries with a high TB burden in the world and is also one with a high burden of LTBI (Gao et al., 2022). In order to reach the goal of the End TB Strategy, China is facing the challenge of developing a national strategy to address the further development of LTBI, including understanding the epidemiological characteristic of LTBI, identifying the target population for early screening and diagnosis, and development of preventive treatment regimens appropriate for the Chinese people (Xin et al., 2019). The fifth national TB prevalence survey conducted in China showed that TB prevalence increased with age (Technical Guidance Group of the Fifth National TB Epidemiological Survey, 2012). Studies found older adults were vulnerable to Mt infection due to factors such as reduced immune function, complications, and malnutrition. (Donald et al., 2010; Pratt et al., 2011; Rajagopalan, 2016). Recently published articles showed the rate of LTBI in people aged 15 years and above was 20.3%, and the infection rate also increased with age (Gao et al., 2022). Several multicenter studies have reported that the burden of LTBI and annual Mt infection rate were both significantly higher in older people compared with younger individuals in rural areas of China (Gao et al., 2015; Gao et al., 2016). Hence, intensifying efforts should be enhanced to prioritize LTBI detection and preventive treatment in high-risk groups, particularly in older adults. Modeling analysis also suggested that successful preventive therapy for the elderly population would reduce the incidence of TB in China by 84% (Huynh et al., 2015).

In China, about 71% of patients with TB live in rural areas (Wang et al., 2007; Technical Guidance Group of the Fifth National TB Epidemiological Survey, 2012; Wang et al., 2014). Therefore, rural must be the priority areas where a lot more investment and effective screening tools are needed to reduce the reservoir of potential TB cases. Zhejiang Province, located in southeastern China, has a relatively well-developed economy and a middle-level notification rate of TB in China (Ge et al., 2015). However, the western regions of the province are located in a mountainous area and still suffer from a high risk of TB. The burden of LTBI in these areas was unknown. This study aimed to identify the prevalence of and factors associated with LTBI in rural areas with a high TB incidence, which might contribute to optimizing intervention strategy for LTBI in rural areas of China, and provide a scientific basis for the development of TB prevention and control strategies.

Materials and methods

Study design and participants

We conducted an observational study in rural areas in Zhejiang Province. Two counties were selected in rural areas with high incidences of tuberculosis in Zhejiang Province. In each county, the township with the highest TB prevalence in the five years of 2016-2020 was selected. Three villages were randomly selected in each selected township. In selected villages, all eligible subjects were surveyed. Inclusion criteria: a. Local resident or permanent resident with at least 6 months of continuous residence in the latest year; b. Aged 65 or older at the time of the survey; c. Voluntarily participate in this study and sign informed consent. Exclusion criteria: a. Tuberculosis patient; b. History of tuberculosis; c. Unwilling to participate in the study. Only those who meet all inclusion criteria and none of the exclusion criteria could be included in the study. The baseline cross-sectional survey was conducted in July 2021, followed by one year of surveillance.

The sample size was calculated based on the following formula (Bacchetti et al., 2005),

\[ n = \left( \frac{Z_{0.025}}{p(1-p)} \right)^2 \]

in which *n* is the required sample size in one research county and *p* is the estimated prevalence of LTBI. δ is allowed a margin of error. The value of *p* was estimated to be 30% according to a study in China (Gao et al., 2015). After adding a 10.0% error for the study, a total of 354 individuals in each county site were needed for the analysis.

Data collection

According to the Basic Public Health Service Standards of Zhejiang Province (4th edition) (Zhejiang Provincial Health and...
Family Commission, 2017), the community health service institutions should provide physical health examinations for local residents aged 65 and above annually. The study was performed combined with the residents’ health physical examination by trained and qualified medical personnel and investigators. During the health physical examination, the basic demographic characteristics and social behavior which included sex, age, education, marriage, smoking status, alcohol consumption, and frequently open windows for ventilation at home were asked by trained investigators.

People who smoke was defined as an individual who smoked at least 1 cigarette per day for more than 6 months in the past year. Participants who had formerly smoked were defined as smokers who had been smoke-free for at least 6 months at the time of the survey. Alcohol consumption was defined as having consumed alcohol in the past 12 months and consuming more than 20 mL of alcohol. Daily alcohol consumption was defined as consuming at least 20 mL of alcohol per day. Frequent alcohol consumption was defined as consuming more than 20 mL of alcohol on average 1–3 times per week. Occasionally alcohol consumption is defined as drinking on average 1–3 times per month and consuming more than 20 mL of alcohol. Opening windows frequently for ventilation was defined as ventilating the family space or bedroom at least three times per week for at least 1 hour at a time. Places of frequent activity were defined as public places in which participants spent no less than 1 hour per time and at least 2 times a week.

The height, weight, and chest radiographs were conducted by medical personnel. In addition, about 5-6mL of blood from each participant was drawn to test for Mtb infection using IFN-γ release assays by professional medical staff. Participants in one county were tested for Mtb infection using T-SPOT.TB (CFDA20183400233) and participants in another county were tested with QuantiFERON-TB Gold (CFDA(I)20133405272). Both the methods had been registered and certified by the China State Food and Drug Administration, which could be used for auxiliary diagnosis of clinical tuberculosis and specific detection of tuberculosis infection caused by Mtb. Laboratory tests were carried out in strict accordance with the reagent instructions. Quality control of the laboratory testing process was carried out by the provincial laboratory workers. A normal chest radiograph was defined as having no abnormal lesions. An abnormal chest radiograph was defined as the presence of partial lesions, in which the possibility of active pulmonary TB was excluded by a radiographer. The state of people latently infected with Mtb but without clinical evidence of active TB is to be referred to as LTBI. The diagnosis of LTBI was also carried out by professional community health service personnel.

Statistical analysis

Descriptive statistics were used to describe the participants’ characteristics. A Chi-square test was conducted to detect the association between LTBI and participants’ characteristics. Variables with a p-value less than 0.1 in the chi-square tests were included in the multivariable analysis. Factors associated with LTBI were analyzed using multivariable logistic regressions, with the estimation of their odds ratios (ORs) and 95% confidence intervals (CIs). The “Enter” method was used in logistic regressions. The cumulative incidence risk of participants with LTBI positive compared to LTBI negative participants was also explored by multivariable logistic regressions when adjusted for sex, age, education, marital status, BMI, smoking, drinking, the habit of opening windows often for ventilation, and the chest radiograph result. A P value less than 0.05 was considered statistically significant. All statistical analysis was conducted using SPSS version 19.0 (IBM Corp, Armonk, NY, USA).

Results

Social-demographic characteristics of participants

Of the 2054 people aged 65 or older in the 6 selected villages, 1903 consented to participate in this study; 47 individuals were excluded due to active TB disease or a history of active TB. Finally, 1856 (90.4%) individuals were enrolled in the study.

The characteristics of all the 1856 participants included in the study are shown in Table 1. Approximately half of the participants were men (50.5%). The age ranged from 65 to 99 years with a mean age of 72.86 years. About 48.5% of participants had a primary school education level, and 38.1% were illiterate or semiliterate. More than two-thirds of participants reported they had never smoked (70.0%) and never drank alcohol (74.8%). Most participants (96.8%) frequently opened windows for ventilation at home. About two-thirds of participants had normal chest radiographs, and 33.4% of participants had abnormal chest radiographs. Among all the participants, 34.9% were diagnosed with LTBI.

Prevalence of LTBI according to participant characteristics

Table 2 shows the association between participant characteristics and LTBI. No statistically significant differences were observed in different age groups, education levels, marriage status, and body mass index (BMI). The chi-square test found that 5 variables were associated with LTBI infection: sex, cigarette consumption, alcohol consumption, the habit of opening windows frequently for ventilation or not, and chest radiographs. The percentage that were LTBI positive in men was higher than in women (40.6% versus 29.4%), the difference between the 2 groups was significant (p<0.01). More percent
of people who smoke (45.5%) were LTBI positive than participants who never smoke (31.7%) and formerly smoked (39.7%). The proportion of LTBI positive in participants with alcohol consumption was higher than in participants without alcohol consumption. About 48.3% of participants who did not often open windows for ventilation at home were LTBI positive, which was higher than that of participants who often opened windows for ventilation at home (34.5%). Participants with abnormal chest radiographs had a higher LTBI positive proportion than participants with normal chest radiographs (41.0% versus 31.9%, p<0.001). People who frequented closed entertainment places such as chess and card rooms had a relatively high prevalence of LTBI (39.5%).

Factors associated with latent tuberculosis infection

Five characteristics were found to be associated with LTBI in the multivariate model, as shown in Table 3. Male had a greater chance of LTBI infection than Female (OR: 1.32; 95% CI: 1.01–1.72). Participants who smoke had a greater chance of LTBI-positive infection than participants who never smoke (OR: 1.43; 95% CI: 1.04–1.97). Participants who did not often open windows for ventilation at home had a greater risk of TB infection than participants who often opened windows for ventilation at home (OR: 1.88; 95% CI: 1.10–3.22). Participants with abnormal chest radiographs had a greater chance of TB infection than participants with normal chest radiographs (OR: 1.48; 95% CI: 1.20–1.81).

Annual incidence of tuberculosis among study participants

Of all the participants, 0.5% developed active TB cases during the one-year follow-up period. As shown in Table 4, the multivariable logistic regressions indicated the cumulative incidence rate of participants with LTBI positive was higher than that of LTBI negative participants (p<0.001). During the one-year observation period, the cumulative risk of developing TB disease in LTBI participants was nine times that of non-infected participants.

Discussion

Few studies have been conducted to estimate the burden of LTBI in older adults living in rural areas and explore the potential target for LTBI control in high epidemic areas of TB in Zhejiang province, China. This study showed that there was a high prevalence (34.9%) of LTBI among older adults living in rural areas, which was in line with the findings of studies in Jiangsu (31.2-33.33%) (Liu et al., 2017), but was lower than the estimation of the national burden of LTBI among people aged 60 years and older based a multi-center epidemiological survey in China (38.36%) (Gao et al., 2022).

| TABLE 1 Characteristics of study participants. |
|--------|--------|--------|
| Items                           | n  | %     |
| Sex                             |     |       |
| Female                         | 938 | 50.5  |
| Male                           | 918 | 49.5  |
| Age (years)                     |     |       |
| 65-70                           | 661 | 35.6  |
| 70-75                           | 591 | 31.8  |
| 75-80                           | 317 | 17.1  |
| 80+                             | 287 | 15.5  |
| Education                      |     |       |
| Illiterate and semiliterate     | 708 | 38.1  |
| Primary school                 | 900 | 48.5  |
| Junior high school and above   | 248 | 13.4  |
| Marriage                       |     |       |
| Married                        | 1487| 80.1  |
| Unmarried                      | 46  | 2.5   |
| Widowed/divorced               | 323 | 17.4  |
| BMI                            |     |       |
| <18.5                          | 179 | 9.9   |
| 18.5–24                        | 1063| 58.8  |
| 24–28                          | 449 | 24.8  |
| 28+                            | 116 | 6.4   |
| Smoking status                 |     |       |
| People who never smoked         | 1283| 70.9  |
| People who smoke currently      | 336 | 18.6  |
| People who formerly smoked      | 190 | 10.5  |
| Alcohol consumption            |     |       |
| Never                          | 1384| 74.8  |
| Occasionally                   | 105 | 5.8   |
| Frequently                     | 22  | 1.2   |
| Daily                          | 328 | 18.1  |
| Open Windows frequently for ventilation at home | | |
| Yes                            | 1794| 96.8  |
| No                             | 59  | 3.2   |
| Chest radiograph results       |     |       |
| Normal                         | 1238| 66.7  |
| Abnormal                       | 618 | 34.3  |
| LTBI results                   |     |       |
| Negative                       | 1199| 64.1  |
| Positive                       | 644 | 34.9  |
| Developed active TB during the one-year follow-up period | | |
| No                             | 1844| 99.5  |
| Yes                            | 9   | 0.5   |

LTBI, latent tuberculosis infection; TB, tuberculosis; BMI, Body Mass Index.
The total is less than 1856 due to missing values.
| Items                        | Latent tuberculosis infection |        |        |        |        |        |        |
|-----------------------------|------------------------------|--------|--------|--------|--------|--------|--------|
|                             | Negative                     | Positive |        |        |        |        |        |
|                             | n   | %   | m   | %   | $\chi^2$ | P     |        |        |        |
| Age                         |     |     |     |     |        |        |        |        |        |
| 65-70                       | 438 | 66.7 | 219 | 33.3 | 2.91   | 0.406 |        |        |        |
| 70-75                       | 379 | 64.2 | 211 | 35.8 |        |       |        |        |        |
| 75-80                       | 207 | 66.6 | 104 | 33.4 |        |       |        |        |        |
| 80-                         | 175 | 61.4 | 110 | 38.6 |        |       |        |        |        |
| Sex                         |     |     |     |     |        |        |        |        |        |
| Female                      | 657 | 70.6 | 273 | 29.4 | 25.79  | <0.001|        |        |        |
| Male                        | 542 | 59.4 | 371 | 40.6 |        |       |        |        |        |
| Education                   |     |     |     |     |        |        |        |        |        |
| Illiterate and semiliterate | 471 | 67.2 | 230 | 32.8 | 3.89   | 0.143 |        |        |        |
| Primary school              | 579 | 64.7 | 316 | 35.3 |        |       |        |        |        |
| Junior high school and above| 149 | 60.3 | 98  | 39.7 |        |       |        |        |        |
| Marriage                    |     |     |     |     |        |        |        |        |        |
| Married                     | 966 | 65.1 | 517 | 34.9 | 4.21   | 0.122 |        |        |        |
| Unmarried                   | 23  | 51.1 | 22  | 48.9 |        |       |        |        |        |
| Widowed/divorced            | 210 | 66.7 | 105 | 33.3 |        |       |        |        |        |
| BMI                         |     |     |     |     |        |        |        |        |        |
| <18.5                       | 126 | 71.6 | 50  | 28.4 | 5.932  | 0.155 |        |        |        |
| 18.5-24                     | 668 | 63.3 | 388 | 36.7 |        |       |        |        |        |
| 24-28                       | 301 | 67.2 | 147 | 32.8 |        |       |        |        |        |
| 28-                         | 73  | 62.9 | 43  | 37.1 |        |       |        |        |        |
| Smoking status              |     |     |     |     |        |        |        |        |        |
| People who never smoke      | 872 | 68.4 | 403 | 31.6 | 24.47  | <0.001|        |        |        |
| People who smoke            | 182 | 54.5 | 152 | 45.5 |        |       |        |        |        |
| People who formerly smoked  | 114 | 60.3 | 75  | 39.7 |        |       |        |        |        |
| Alcohol consumption         |     |     |     |     |        |        |        |        |        |
| Never                       | 904 | 67.3 | 439 | 32.7 | 14.86  | 0.02  |        |        |        |
| Occasionally                | 59  | 56.2 | 46  | 43.8 |        |       |        |        |        |
| Frequently                  | 10  | 45.5 | 12  | 54.5 |        |       |        |        |        |
| Everyday                    | 195 | 59.5 | 133 | 40.5 |        |       |        |        |        |
| Open Windows frequently for ventilation at home |     |     |     |     |        |        |        |        |        |
| Yes                         | 1167| 65.5 | 615 | 34.5 | 4.68   | 0.030 |        |        |        |
| No                          | 30  | 51.7 | 28  | 48.3 |        |       |        |        |        |
| Chest radiograph results    |     |     |     |     |        |        |        |        |        |
| Normal                      | 836 | 68.1 | 392 | 31.9 | 14.78  | <0.001|        |        |        |
| Abnormal                    | 363 | 59.0 | 252 | 41.0 |        |       |        |        |        |
| Places of frequent activity (Multiple) |     |     |     |     |        |        |        |        |        |
| Chess and card room         | 181 | 60.5 | 118 | 39.5 | 3.24   | 0.07  |        |        |        |
| The cultural hall           | 33  | 62.3 | 20  | 37.7 | 0.29   | 0.66  |        |        |        |
| Corner shop                 | 96  | 66.7 | 48  | 33.3 | 0.27   | 0.68  |        |        |        |
| Nearby vegetable market     | 240 | 64.5 | 132 | 35.5 | 0.06   | 0.8   |        |        |        |
| Neighborhood                | 237 | 66.9 | 117 | 33.1 | 0.68   | 0.4   |        |        |        |
| Outdoor activity plaza      | 429 | 65.5 | 226 | 34.5 | 0.08   | 0.78  |        |        |        |
| Seldom go out               | 512 | 64.5 | 282 | 35.5 | 0.21   | 0.64  |        |        |        |

The total is less than 1856 due to missing values.
The high prevalence of LTBI is a great threat to TB prevention and control. Studies showed that people with LTBI have a relatively high risk of developing active TB, especially within 5 years of the initial infection (Andrews et al., 2012). Our study also found a higher cumulative incidence rate in participants with LTBI positive than that of LTBI negative participants during our one-year follow-up period. Studies indicated that implementation of active case finding for LTBI and tuberculosis preventive treatments nationwide or in areas with high incidence and in older adults could greatly reduce the number of TB cases, which may contribute to achieving the target of the "End TB Strategy" in China (Huynh et al., 2015; Wen et al., 2022). The WHO developed a series of recommendations for screening LTBI in developed countries with low incidence levels of active TB (Godoy, 2021). A study in Australia demonstrated that screening and management of LTBI patients can be achieved within the primary care setting, considering barriers and enablers at the patient, provider, and clinical levels (Kunin et al., 2022). The formulation of tuberculosis prevention and control strategies in rural areas with a high TB incidence should be tailored to local conditions, including available public health resources. China had established a relatively complete primary care system. Most community health service institutions could provide health physical examinations for the local residents annually, which made it possible to conduct screening and management of participants with LTBI in these primary care settings.

Although the incidence of TB had declined in recent years with the implementation of the DOTS strategy (Wang et al., 2007; Wang et al., 2014), about 800 thousand TB cases were still

TABLE 3 Factors associated with latent tuberculosis infection among the elderly in rural area, Zhejiang, China.

| Items                                | Positive/All Participants | P       | OR (95%CI)       |
|--------------------------------------|---------------------------|---------|-----------------|
| Sex                                  |                           |         |                 |
| Female                               | 276/904                   | 1       |                 |
| Male                                 | 375/891                   | 0.043   | 1.32 (1.01-1.72) |
| Smoking status                       |                           |         |                 |
| People who never smoke               | 419/1273                  | 1       |                 |
| People who smoke                     | 154/334                   | 0.03    | 1.43 (1.04-1.97) |
| People who formerly smoked           | 78/188                    | 0.70    | 1.08 (0.74-1.57) |
| Alcohol consumption                  |                           |         |                 |
| Never                                | 458/1341                  | 1       |                 |
| Occasionally                         | 48/104                    | 0.181   | 1.34 (0.87-2.07) |
| Frequently                            | 12/22                     | 0.175   | 1.83 (0.77-4.36) |
| Everyday                              | 133/328                   | 0.957   | 1.01 (0.75-1.36) |
| Open Windows frequently for ventilation at home |           |         |                 |
| Yes                                  | 622/1738                  | 1       |                 |
| No                                    | 29/57                     | 0.022   | 1.88 (1.10-3.22) |
| Chest radiograph results             |                           |         |                 |
| Normal                               | 378/1180                  | 1       |                 |
| Abnormal                              | 273/615                   | <0.001  | 1.48 (1.20-1.81) |

The total is less than 1856 due to missing values.
reported annually in China (World Health Organization, 2021). To reach the “End TB Strategy”, more efforts should be intensified in TB control, particularly in how LTBI intervention is effectively conducted to achieve a rapid decline in TB incidence in some important areas. An accurate understanding of the LTBI burden and epidemic characteristics in these areas is conducive to identifying the intervention targets and developing appropriate intervention technical guidelines for LTBI. Age was found to be associated with LTBI in previous studies. A study showed age older than 50 years exhibits a higher incidence of LTBI than younger ages in Taiwan (Chang et al., 2022). The rate of Mtb infection were found to gradually increase with age. Older people were more likely to acquire Mtb infection, but no statistically significant difference was observed in participants aged 60 years and older (Gao et al., 2015), which was similar with our study results. The effect of age on LTBI was also seen in Brazil (De Jezus et al., 2021) and Japan (Ogawa et al., 2021). Compared to the younger participants with LTBI, the older adults showed a higher percentage of LTBI positive. Therefore, keeping the environment ventilated is one of the measures to reduce the risk of Mtb transmission.

In addition to the screening for LTBI, the chest radiograph was also performed in order to exclude active disease or to reveal signs of old tuberculosis infection TB cases. Our study results showed the percentage of LTBI among participants with abnormal chest radiographs was higher than that of participants with normal chest radiographs. Similar results were also reported that lesions on chest radiographs suggestive of previous infection with Mtb were significantly associated with positive tests for LTBI (Uzorka et al., 2019). The complementary roles between chest radiograph and immunological testing methods were also reported (Wang et al., 2020). Thus, people with abnormal chest radiographs should also be the focus of screening for TB infection. It could improve the effectiveness of screening for LTBI to combine immunological testing methods and chest radiographs.

Our study has several limitations. Firstly, the study was based on the cross-sectional baseline study, which just demonstrated the association between different factors with LTBI. Secondly, there were differences in the detection efficacy of Mtb infection between the two methods (T-SPOT.TB and Quantiferon-TB Gold) used in our study, but both the two methods had been certified by China State Food and Drug Administration, which could be used for specific detection of Mtb infection. Thirdly, the follow-up period was only one year, which was a little short, the incidence might vary with the length of follow-up. The initial infection time of the study subjects is unknown and different, which might also have an influence on morbidity. Despite the above deficiencies, our survey results can basically reflect the level of LTBI among older adults in areas of Zhejiang Province with a high TB incidence.

There was a high prevalence of LTBI among the older adults living in rural areas with a high burden of TB in Zhejiang province. Men, people who smoke and participants without the habit of ventilating at home were important targets for LTBI screening. Providing preventive intervention to people with LTBI would contribute to accelerating the decline of the TB epidemic.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.
**Ethics statement**

The studies involving human participants were reviewed and approved by the Ethics Committee of the Zhejiang Provincial Center for diseases control and prevention (2021-027-01). The patients/participants provided their written informed consent to participate in this study.

**Author contributions**

WW (1st author), PZ, and BC designed the study. WW (1st author) and XC wrote the manuscript. WW (1st author), BC, and SC modified the manuscript. WW (1st author), BC, and MZ did the statistics. XH, KL, QW, and YZ performed the investigation and collected data. WW (1st author), SC, MZ, and WW (5th author) were responsible for quality control of baseline investigation at the study sites. All authors contributed to the article and approved the submitted version.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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