More than adequate iodine intake may increase subclinical hypothyroidism and autoimmune thyroiditis: a cross-sectional study based on two Chinese communities with different iodine intake levels

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Abstract

Objective: With the introduction of iodized salt worldwide, more and more people are exposed to more than adequate iodine intake levels with median urinary iodine excretion (MUI 200–300 μg/l) or excessive iodine intake levels (MUI >300 μg/l). The objective of this study was to explore the associations between more than adequate iodine intake levels and the development of thyroid diseases (e.g. thyroid dysfunction, thyroid autoimmunity, and thyroid structure) in two Chinese populations.

Design: A population-based cross-sectional study was conducted in two areas in which people are exposed to different levels of iodine intake (Rongxing, MUI 261 μg/l; Chengshan, MUI 145 μg/l). A total of 3813 individuals were recruited by random sampling. Thyroid hormones, thyroid autoantibodies in serum, and iodine levels in urine were measured. B-mode ultrasonography of the thyroid was also performed for each participant.

Results: The prevalence of subclinical hypothyroidism was significantly higher for subjects who live in Rongxing than those who live in Chengshan (5.03 vs 1.99%, P < 0.001). The prevalence of positive anti-thyroid peroxidase antibody (TPOAb) and positive anti-thyroglobulin antibody (TgAb) was significantly higher for subjects in Rongxing than those in Chengshan (TPOAb: 10.64 vs 8.4%, P < 0.02; TgAb: 10.27 vs 7.93%, P = 0.01). The increase in thyroid antibodies was most pronounced in the high concentrations of TPOAb (TPOAb: >500 IU/ml) and low concentrations of TgAb (TgAb: 40–99 IU/ml) in Rongxing.

Conclusions: More than adequate iodine intake could be a public health concern in terms of thyroid function and thyroid autoimmunity in the Chinese populations.

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Introduction

Iodine is essential to maintain a normal thyroid function. Iodine deficiency can result in thyroid goiter and hypothyroidism (1). On the other hand, excessive iodine intake can also lead to thyroid dysfunction. For instance, high iodine intake in China due to the presence of high iodine in drinking water or in Japan due to high seaweed consumption (milligram of iodine intake per day) has been linked with thyroid disorders such as goiter, hypothyroidism, and autoimmune thyroiditis (2–6). In iodine-deficient areas, increase in iodine intake might precipitate iodine-induced hyperthyroidism (7–10).

In 1990, the goal of the World Summit for Children at the United Nations was to eliminate iodine deficiency diseases and recommended universal salt iodization (USI) as the main strategy (11). The introduction of iodine fortification of salt and the appearance of various iodine fortifications in food greatly improved the iodine nutritional status worldwide. In 2003, the WHO released a report on using USI from 126 countries. There were 54 countries reporting iodine deficiency, 43 reporting adequate (median urinary iodine excretion (MUI) 100–200 μg/l), 24 reporting more than adequate (MUI 200–300 μg/l), and five reporting excessive iodine intake level (MUI >300 μg/l). Of the 72 countries that reported having sufficient iodine intake levels, 40.3% had MUI levels exceeding the optimal range recommended by international organizations (12). USI was initially introduced in China in 1996. National monitoring data show that Chinese inhabitants
experienced excessive iodine intake during the period 1997–2001 and more than adequate iodine intake after 2001 (13, 14).

In 2001, WHO/UNICEF/ICCIDD reported that ingestion of iodine at a more than adequate level may lead to the development of iodine-induced hyperthyroidism in susceptible groups within 5–10 years following the introduction of iodized salt (7, 9, 15). Other effects such as iodine-induced hypothyroidism and iodine-induced autoimmune thyroiditis were not reported. We conducted a 5-year follow-up study (from 1999 to 2004), and our data showed that among three communities in China with an MUI of 84 μg/l (a mildly deficient iodine intake area), 243 μg/l (a more than adequate iodine intake area), and 651 μg/l (an excessive iodine intake area), the incidence of either hypothyroidism or autoimmune thyroiditis increased with the increased intake levels (16, 17). Unfortunately, at that time, we had no data from an area with adequate iodine intake.

The objective of this study was to answer the following question: compared with iodine adequacy, does intake of a more than an adequate level of iodine influence thyroid function, thyroid autoimmunity, and goiter? In 2007, we chose two areas with an MUI of 100–200 and 200–300 μg/l respectively, and conducted a cross-sectional epidemiological study to explore the relationship between more than adequate iodine intake levels and the spectrum of thyroid diseases in the two Chinese populations.

**Subjects and methods**

**Subjects**

In 2007, two representative areas with different iodine intake levels were chosen for the study. Chengshan, a rural community located in the south of Liaoning Province, had mildly deficient levels of iodine intake before salt iodization (iodine content in drinking water was 4.3 μg/l; MUI 61.67 μg/l in 1996) (18). However, the MUI during 1997–2007 was 120–155 μg/l due to the introduction of salt iodization, and the iodine intake of the local inhabitants has been adequate (i.e. MUI 100–200 μg/l) since salt iodization began. Rongxing, another rural community located in the west of Liaoning Province, had no history of iodine deficiency before the introduction of salt iodization because of high iodine content in drinking water (55.5 μg/l; MUI 154.5 μg/l in 1994) (19). However, the MUI was increased to 200–300 μg/l between 1996 and 2007 after salt iodization was instituted. Thus, it is possible that iodine intake has been more than adequate (i.e. MUI 200–300 μg/l) since salt iodization was introduced in the area. Geographically, there are more than 400 km between the two communities. The difference in iodine intake levels between the two areas is due to the different levels of iodine in drinking water (Table 1).

In the first part of this study, home visits were performed to register the local inhabitants who had lived in the study areas for more than 10 years, and one-third of the residents in each area participated in this study. Pregnant women, women who had given birth within the past year, and women taking oral contraceptives were excluded, as were persons receiving glucocorticoids, dopamine, or anti-epileptic drugs and persons diagnosed as having renal insufficiency or adrenocortical hypofunction. In total, 3813 people were enrolled in this study (1908 in Rongxing and 1905 in Chengshan). In Chengshan and Rongxing, 19 and 23 persons respectively, had a history of overt hyperthyroidism, who had received one or more of the treatments such as anti-thyroid drugs, radioiodine treatment, and thyroid surgery; one person in Chengshan and three persons in Rongxing were previously diagnosed as having overt hypothyroidism and had been taking levothyroxine; and 84 persons in Chengshan and 99 persons in Rongxing had the family history of thyroid diseases, with no significant difference found between the two populations (4.4 vs 5.2%, χ² = 1.27, P = 0.26). The demographic characteristics of the two populations with different levels of iodine intake are shown in Table 1 and Fig. 1. Both the sex and the age composition of the two populations were similar. Smokers accounted for 36% of the population in Rongxing and 35% in Chengshan (smoker: one or more than one cigarette per day, continuous or cumulative smoking for 6 months or more). People with a history of alcohol intake accounted for 36% of the population in Rongxing and 32% in Chengshan (drinker: 20 g or more than 20 g alcohol intake per day, continuous alcohol intake for 1 year or more). For each participant, both palpation and B-mode

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chengshan</th>
<th>Rongxing</th>
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<tbody>
<tr>
<td>Sample size</td>
<td>1905</td>
<td>1908</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>1:1.67</td>
<td>1:1.76</td>
</tr>
<tr>
<td>Age</td>
<td>47.26 ± 15.96</td>
<td>46.32 ± 15.85</td>
</tr>
<tr>
<td>U iodine (μg/l; median (IQR))</td>
<td>145 (88–229)</td>
<td>261 (201–342)</td>
</tr>
<tr>
<td>Schoolchildren</td>
<td>164 (95–245)</td>
<td>272 (203–355)</td>
</tr>
<tr>
<td>Iodine in salt (mg/kg; n = 20)</td>
<td>25.6 ± 4.3</td>
<td>24.3 ± 3.5</td>
</tr>
<tr>
<td>Iodine in drinking water (μg/l; n = 20)</td>
<td>1.7 ± 4.5</td>
<td>55.4–60.5</td>
</tr>
<tr>
<td>Serum selenium (μg/l; n = 60)</td>
<td>79.88 ± 13.09</td>
<td>80.75 ± 13.89</td>
</tr>
<tr>
<td>Serum zinc (mg/l; n = 60)</td>
<td>0.81 ± 0.14</td>
<td>0.79 ± 0.09</td>
</tr>
<tr>
<td>Urinary fluoride (mg/l; n = 100)</td>
<td>0.56 ± 0.12</td>
<td>0.62 ± 0.18</td>
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IQR, interquartile range; U iodine, urinary iodine.

°Adequate iodine intake.

*bMore than adequate iodine intake.

*bData from schoolchildren aged 8–10 years old in each community (n = 80).

*bData from study populations in each community (n = 585 in Rongxing; n = 582 in Chengshan).
ultrasonography of the thyroid were performed, and samples of fasting urine and blood were obtained. The research protocols were approved by the medical ethics committee of China Medical University. All subjects provided written informed consent after the study was explained to them during the recruitment process.

Assays

Serum TSH, thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb) were measured in all participants, and free thyroxine (FT₄) and free tri-iodothyronine (FT₃) levels were determined in subjects with abnormal TSH. These were measured using a solid-phase, enzyme-labeled, chemiluminescent sequential immunometric assay (IMMULITE 1000 Analyzer, Diagnostic Products Corporation, Los Angeles, CA, USA). The reference range of serum TSH (0.3–4.8 mIU/l) was derived from the 2.5th–97.5th percentile in 2503 normal subjects with no family or personal history of thyroid disease, normal serum thyroid autoantibody values, and no goiter or nodules detected under B-mode ultrasound (16). The sensitivity of serum TSH was 0.002 mIU/l. The intra- and inter-assay coefficients of variation for serum parameters were as follows: TSH: 2.5%, 1.2% at 0.26 mIU/l and 3.2%, 1.2% at 4.06 mIU/l; TPOAb (reference range: 7–50 IU/ml defined by our laboratory); 3.3%, 4.3% at 42.5 IU/ml and 5.7%, 2.9% at 516.5 IU/ml; TgAb (reference range: 10–40 IU/ml defined by our laboratory); 4.1%, 3.4% at 33.7 IU/ml and 4.6%, 2.9% at 517.6 IU/ml; FT₄ (reference range of kit: 10.3–24.5 pmol/l): 5.7%, 3.2% at 10.65 pmol/l and 3.4%, 3.1% at 30.55 pmol/l; and FT₃ (reference range of kit: 2.3–6.3 pmol/l): 5.5%, 1.7% at 4.85 pmol/l and 4.2%, 3.9% at 17.38 pmol/l respectively.

Urinary iodine concentration was determined in all participants by the ammonium persulfate method based on the Sandell–Kolthoff reaction (20). Considering that some other trace elements such as selenium, zinc, and fluorine are involved in the development of thyroid function, thyroid autoimmunity, and goiter (21–24), 60 serum samples from each population were randomly selected and the levels of serum selenium, serum zinc, and urinary fluorine were measured. Urinary fluorine concentrations were measured by fluorine ion-selective electrode. Serum selenium concentrations were measured by inductively coupled plasma atomic emission spectrometry, and serum zinc concentrations were measured by atom absorption method. No significant difference was found in the levels of serum selenium, serum zinc, and urinary fluorine between the two populations (Table 1). We also did not find an association between serum selenium levels and the titers of thyroid autoantibodies. The inter- and intra-assay coefficients of variation for serum selenium, serum zinc, and urinary fluorine were < 6%.

Thyroid ultrasonography was performed by two trained observers using a portable instrument (LOGIQx50, GE, Milwaukee, WI, USA with 7.5 MHz linear transducers). The normal thyroid volume was obtained from healthy subjects residing in Chengshan (MUI 14.5 µg/l) without known thyroid disease; without a family history of thyroid disease; without anti-thyroid antibodies; and without goiter, nodules, or an abnormal echo pattern on B-mode ultrasonography. Goiter was defined as a thyroid volume exceeding 22.5 ml for women and 25.4 ml for men, which corresponded to the mean (+2 s.d.) in 478 healthy male subjects and 596 female subjects. The diagnostic criteria for thyroid diseases are listed in Table 2 (16, 25).
Table 2 Diagnostic criteria for thyroid diseases. The reference range of serum TSH (0.3–4.8 mIU/l) was derived from the 2.5th–97.5th percentile in 2503 normal subjects (16) (no family or personal thyroid disease, normal serum thyroid autoantibody values, and no goiter or nodules under B-mode ultrasound).

<table>
<thead>
<tr>
<th>Thyroid disease</th>
<th>Diagnostic criteria</th>
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<tbody>
<tr>
<td>Overt hypothyroidism</td>
<td>TSH &gt; 4.8 mIU/l, free T4 &lt; 10.3 pmol/l</td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>TSH &gt; 4.8 mIU/l, free T4 levels within the normal range</td>
</tr>
<tr>
<td>High serum autoantibody values</td>
<td>TPOAb ≥ 50 IU/ml or TgAb ≥ 40 IU/ml</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>TSH &lt; 0.3 mIU/l, free T4 &gt; 24.5 pmol/l and/or free T3 &gt; 6.3 pmol/l</td>
</tr>
<tr>
<td>Graves’ disease</td>
<td>Overt hyperthyroidism, a diffuse goiter or normal thyroid volume on B-mode ultrasonography</td>
</tr>
<tr>
<td>Toxic nodular goiter</td>
<td>Overt hyperthyroidism with nodular goiter</td>
</tr>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>TSH &lt; 0.3 mIU/l, free T3 and free T4 within the normal ranges</td>
</tr>
<tr>
<td>Goiter</td>
<td>Thyroid volume &gt; 22.5 ml (women) or &gt; 25.4 ml (men)</td>
</tr>
<tr>
<td>Diffuse goiter</td>
<td>Goiter without nodules</td>
</tr>
<tr>
<td>Nodular goiter</td>
<td>Goiter with nodules &gt; 10 mm in diameter</td>
</tr>
</tbody>
</table>

Free $T_4$, reference range of kit: 10.3–24.5 pmol/l. Free $T_3$, reference range of kit: 2.3–6.3 pmol/l. TPOAb, thyroid peroxidase antibody, reference range: 7–50 IU/ml defined by our laboratory; TgAb, thyroglobulin antibody, reference range: 10–40 IU/ml defined by our laboratory.

Statistical analysis

All statistical analyses were performed using SPSS software (version 11.5; SPSS, Inc., Chicago, IL, USA). The proportions were compared using a $\chi^2$ test. The level of significance was set at 5% for both the $\chi^2$ test and the t-test.

Results

Hypothyroidism

In Chengshan, three patients were diagnosed as having overt hypothyroidism. Among them, one had a history of overt hyperthyroidism and the other two were first diagnosed as having spontaneous overt hypothyroidism. In Rongxing, six patients were diagnosed as having overt hypothyroidism. Among them, two had thyroid adenoma and the remaining four were diagnosed as having spontaneous overt hypothyroidism. In Chengshan and Rongxing, 38 and 96 patients respectively, were newly diagnosed as having subclinical hypothyroidism. Thus, the prevalence of subclinical hypothyroidism was higher in subjects from Rongxing than in subjects from Chengshan ($\chi^2 = 24.52, P < 0.000$; Table 3). Among the 38 patients from Chengshan, three (10%) were previously diagnosed as having clinical hypothyroidism and 16 (42%) had positive thyroid autoantibodies. Among the 96 patients from Rongxing, ten (10%) were being treated for hypothyroidism or receiving thyroid surgery for thyroid nodules and 35 (36%) had positive thyroid autoantibodies. In total, thyroid autoimmunity accounted for more than 40% of subclinical hypothyroidism in both the populations.

Hypothyroidism

In Chengshan, 34 patients were diagnosed as having overt hyperthyroidism (previously diagnosed: seven cases and newly diagnosed: 27 cases), whereas in Rongxing, 24 patients were diagnosed with this disorder (previously diagnosed: seven cases and newly diagnosed: 17 cases). Table 3 shows the prevalence of overt hyperthyroidism and Graves’ disease (GD) in both the populations. GD was the main cause of overt hyperthyroidism, accounting for 53% of the cases in Chengshan and 66.7% in Rongxing. Toxic nodular goiter was the cause of hyperthyroidism in five cases in Chengshan and one case in Rongxing. Thus there was no significant difference between the two populations. The prevalence of subclinical hyperthyroidism was 1.73% in Chengshan and 0.63% in Rongxing ($\chi^2 = 9.95, P = 0.002$). Of the 142 cases with subclinical hyperthyroidism, no significant difference in the positive rate of TPOAb was found between the two areas.

Thyroid autoantibodies

The prevalence of both positive TPOAb and positive TgAb was higher in Rongxing than in Chengshan (TPOAb: $\chi^2 = 5.55, P = 0.02$; TgAb: $\chi^2 = 6.34, P = 0.01$; Table 3). Then we divided the positive TPOAb into low level (TPOAb: 50–99 IU/ml), middle level (TPOAb: 100–299 IU/ml), middle–high level (TPOAb: 300–499 IU/ml), and high level (TPOAb: ≥ 500 IU/ml), as well as positive TgAb into low level (TgAb:...
40–99 IU/ml), middle level (TgAb: 100–299 IU/ml), middle–high level (TgAb: 300–499 IU/ml), and high level (TgAb: ≥500 IU/ml). We found that high concentrations of TPOAb or low concentrations of TgAb were more frequent in Rongxing than in Chengshan (TPOAb: χ² = 4.48, P = 0.03; TgAb: χ² = 11.62, P < 0.001; Table 4).

**Goiter**

The prevalence of goiter was higher in Chengshan than in Rongxing (χ² = 4.85, P = 0.03). When we analyzed the cause of goiter, we found that the prevalence of nodular goiter was higher in Chengshan than in Rongxing (χ² = 12.44, P < 0.001), but no significant difference was found in diffuse goiter between the two populations (Table 3). In patients with diffuse goiter, the rate of positive thyroid autoantibodies was higher in Rongxing than in Chengshan (51.8 vs 35.4%, χ² = 4.43, P = 0.035), indicating that thyroid autoimmunity may be involved in the formation of diffuse goiter in more than adequate iodine intake areas. However, no significant difference was found in the rate of positive thyroid autoantibodies in 160 patients with nodular goiter (20.2% in Chengshan versus 19.1% in Rongxing, P > 0.05).

**Discussion**

This study focused on the impact of more than adequate iodine intake on thyroid diseases in the Chinese populations. Compared with the adequate iodine intake level recommended by WHO/UNICEF/ICCIDD MUI (100–200 μg/l), our data indicated that MUI 200–300 μg/l might be related to potentially increased risk of developing subclinical hypothyroidism or autoimmune thyroiditis. This result differs from the WHO's suggestion that MUI > 300 μg/l may increase the risk of developing autoimmune thyroid diseases (15).

In both the 5-year follow-up study and this study, we found that high iodine intake was associated with a significant increase in the prevalence of hypothyroidism. The acute Wolff–Chaikoff effect (26, 27) suggested that iodine-induced hypothyroidism, especially occurring in patients on amiodarone therapy, is caused by failure of the thyroid gland to escape from acute inhibition (28, 29). However, the exact mechanism by which chronic high iodine intake induces hypothyroidism remains unclear. Vitale et al. (30) and our previous experimental studies revealed that high iodine intake damages endogenous thyroid peroxidase and induces apoptosis in these cells through a mechanism that involves the generation of free radicals (30–32), but whether the iodine-induced apoptosis contributes to chronic iodine-induced hypothyroidism is unknown. It has been reported that iodine-induced hypothyroidism usually resolves quickly after iodine withdrawal, but if the administration of iodide continues, overt or subclinical hypothyroidism will persist (33). Even though the symptoms of subclinical hypothyroidism are less, complications can be severe. For example, subclinical hypothyroidism is not only an independent risk factor for coronary heart disease but it can also result in a poor neurodevelopmental outcome in a fetus or neonate during pregnancy (34–36). Thus, preventing high iodine-induced hypothyroidism is as important as preventing iodine deficiency-induced hypothyroidism.

Studies in both humans and animals have demonstrated that iodine administration may enhance autoimmune thyroiditis (4, 5, 37–46). Totally, three mechanisms (47) have been assumed for the development of iodine-induced autoimmune thyroiditis. First, iodine intake increases the immunogenicity of thyroglobulin (Tg), thereby precipitating an autoimmune process at both the T- and B-cell level (48–50). Secondly, iodine has a toxic effect on thyroid cells (51–53). Thirdly, iodine directly stimulates immune and immunopathy-related cells (54–56). Then what is the upper limit of iodine intake that could be considered a risk factor for iodine-induced autoimmune thyroiditis in humans? In Japan, the incidence of autoimmune thyroiditis is higher in areas with high dietary iodine intake (milligrams of iodine intake per day) than in areas with normal dietary iodine intake (4, 5). Our 5-year prospective study has found that the cumulative incidence of autoimmune thyroiditis was higher in subjects with more than adequate iodine intake than in those with mild deficient iodine intake (16). In this study, we again confirmed that the prevalence of positive thyroid autoantibodies was higher in subjects with more than adequate iodine intake than in those with adequate iodine intake. So we infer that more than adequate iodine intake would be a risk factor for autoimmune thyroiditis in humans.
In this study, the prevalence of both overt hyperthyroidism and GD was similar between the two communities with MUI of 145 and 261 μg/l respectively. GD was the main cause of overt hyperthyroidism in both the communities. Our 5-year follow-up study also reported that there was no difference in either the prevalence or the incidence of overt hyperthyroidism in areas with MUI of 84 μg/l (a mildly deficient iodine intake area), 243 μg/l (a more than adequate iodine intake area), and 651 μg/l (an excessive iodine intake area) \(^{57, 58}\). Thus, from our epidemiological studies, we infer that excess chronic iodine would not increase the prevalence of overt hyperthyroidism.

Another interesting result is that we found a higher prevalence of nodular goiter in Chengshan (MUI 145 μg/l), whereas higher positive thyroid autoantibodies were found in diffuse goiter in Rongxing (MUI 261 μg/l). The explanation for the higher prevalence of nodular goiter may be connected with the iodine-deficient history in Chengshan. Urinary iodine levels can be quickly increased by iodine supplementation, but disappearance of nodular goiter is difficult to achieve \(^{20, 59}\). The result that a higher positive thyroid autoantibodies were found in diffuse goiter in Rongxing indicated that when iodine nutrition shifted from iodine deficiency to more than adequate iodine, thyroid autoimmune will be the main cause of diffuse goiter rather than in iodine deficiency.

Considering the effects of some confounding factors on the thyroid diseases, this study chose the comparative method to study the effect of iodine on the thyroid diseases, which excludes the effects of the confounding factors such as the sex and age composition of the populations, social and economic condition, the personal and family history of thyroid diseases, the condition of taking alcohol and smoking, and other trace elements (selenium, zinc, and fluorine). But there was shortage in choosing the adequate iodine intake area in this study. Chengshan was an area shifting from mild deficient iodine intake levels to adequate iodine intake levels since 1996, but not a long-term adequate iodine intake area. Because of the USI in China, it is difficult to find a stably adequate iodine intake area at present.

In conclusion, compared with the population with MUI 145 μg/l in Chengshan, the population with MUI 261 μg/l in Rongxing had a higher risk to develop autoimmune thyroiditis and subclinical hyperthyroidism. Thus, more than adequate iodine intake might not be recommended for the general population in terms of keeping a normal function of thyroid.

### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Author contribution statement

The authors’ responsibilities were as follows – X Teng performed the study design, participated in the epidemiological study, and prepared the first version of the manuscript; Z Shan and W Teng performed the study design and participated in the discussion of the findings; Y Chen, Y Lai, J Yu, L Shan, X Bai, Y Li, N Li, and Z Li participated in the epidemiological study and performed the statistical analysis; S Wang, Q Xing, H Xue, L Zhu, and X Hou participated in the epidemiological study; C Fan performed the measurements. None of the authors declared a conflict of interest.

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