

# BMJ Open Association between obesity-related anthropometric indices and multimorbidity among older adults in Shandong, China: a cross-sectional study

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## ABSTRACT

**Objectives** Whether the association between obesity-related anthropometric indices and multimorbidity differs by age among Chinese older adults (aged 65+) is unclear. We aimed to investigate the association between body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR) with multimorbidity among the young-old (aged 65–79) and old-old (aged 80+) adults.

**Design** Cross-sectional population-based study.

**Setting** Shandong province on the eastern coast of China.

**Participants** 5493 subjects aged 65 years or above.

**Measurements** Details on sociodemographics, lifestyle characteristics and chronic conditions were collected using a structured questionnaire. The respondents were assessed with anthropometric measurements including height, weight, WC, hip circumference.

**Results** The overall prevalence of multimorbidity in older adults (aged 65+) was 35.2%. The BMI-obesity, WC-obesity and WHR-obesity rates were 7.4%, 57.5% and 80.4%, respectively. In the young-old adults (aged 65–79), the likelihood of multimorbidity was more than two times higher among the BMI-obese than the BMI-normal population (OR 2.08, 95% CI 1.66 to 2.60). Similar but less strong associations were found for the WC-obese and WHR-obese young-old population (OR 1.60, 95% CI 1.42 to 1.81; OR 1.31, 95% CI 1.10 to 1.56, respectively). For the old-old group (aged 80+), the BMI-obese, WC-obese and WHR-obese had a higher likelihood of having multimorbidity compared with the normal weight category (OR 2.10, 95% CI 0.96 to 4.57; OR 1.75, 95% CI 1.21 to 2.54; OR 2.15, 95% CI 1.18 to 3.93, respectively).

**Conclusion** BMI-obesity, WC-obesity and WHR-obesity were associated with a greater risk of multimorbidity, and the associations were different between the young-old and the old-old adults. These age differences need to be considered in assessing healthy body weight in old age. These findings may be vital for public health surveillance, prevention and management strategies for multimorbidity in older adults.

## INTRODUCTION

Multimorbidity, defined as the simultaneous occurrence of two or more chronic conditions within an individual, is an emerging public health concern due to its increasing prevalence and impact on individual health status,

## Strengths and limitations of this study

- The prevalence of multimorbidity in the young-old (aged 65–79) and the old-old (aged 80+) adults was estimated using a large number of population survey sample.
- This study examined the associations between obesity-related anthropometric indices and multimorbidity in Chinese older adults, and further explored the age-stratified patterns of the associations.
- Chronic diseases could be under-reported, which would affect the observed multimorbidity prevalence.
- The use of cross-sectional data that does not allow for exploration of causal pathways underlying the reported associations.

especially for the elderly.<sup>1 2</sup> Multimorbidity affects more than half of the elderly population globally with increasing prevalence in very old persons.<sup>3</sup> People with multimorbidity increased the burden on primary care services,<sup>4</sup> and require higher levels of healthcare utilisation resulting in increased costs.<sup>5 6</sup> As such, knowledge of risk factors associated with multimorbidity, stratified by age, will be needed to enable the delivery of high-quality healthcare adapted to patient needs. Evidence has indicated that being overweight or obese represents a major risk factor for multimorbidity.<sup>7 8</sup> Moreover, obesity can exacerbate the age-related decline in physical function and lead to a higher risk of developing multimorbidity for elderly persons, thus, obesity must be identified early so that a better quality of life can be provided to this older age group. More sensitive anthropometric instruments can assist with better comprehension of the dynamics involving physiological alterations in the ageing process, thereby enhancing an obesity diagnosis and preventing the multimorbidity associated with it.

Several anthropometric indicators have been proposed to assess obesity among older

adults. These indicators provide an indirect evaluation of body composition and a subsequent risk of chronic diseases. In studies assessing the effects of obesity on multimorbidity, the most widely used measure for obesity is body mass index (BMI).<sup>9 10</sup> However, it is known that ageing is related to poor energy regulation, reduced hormonal levels and changes in body composition, which in turn affects anthropometric measurements and risk of chronic diseases.<sup>11</sup> BMI is criticised for its impaired validity to describe the amount of adipose tissue, especially in the abdominal region, in older adults.<sup>12</sup> Alternative approaches are needed for older adults, and measures such as central adiposity in addition to BMI are valuable for assessing disease risk.<sup>13</sup> Other anthropometric measurements such as waist circumference (WC) and waist-to-hip ratio (WHR) are recommended for the assessment of central obesity. Evidence indicates that there is a strong positive association between cardiovascular risk factors with measures of WC or WHR rather than BMI alone.<sup>14 15</sup>

Changes in body composition and fat distribution with ageing are poorly captured by standard anthropometric data.<sup>16</sup> Recent evidence recommended that determination of the optimal body mass and composition for older adults should consider the age and health condition of the individual.<sup>17</sup> Different anthropometric indices may have distinct meanings for older people of different age groups. Although some studies have explored the association between anthropometric indices and multimorbidity,<sup>18 19</sup> surprisingly few of them focused on older people and considered variation across different age groups. Therefore, this study aims to ascertain the associations between anthropometric indices (BMI, WC and WHR) and multimorbidity in older adults (aged 65+) and whether the associations vary among young-old (aged 65–79) versus old-old (aged 80+) adults.

## METHODS

### Study population

Data of this study are derived from the Survey of the Shandong Elderly Family Health Service, which was conducted by Shandong University in 2017. The detailed sampling and quality assurance measures have been described in a previously published paper.<sup>20</sup> In brief, a three-stage, stratified, random sampling scheme was used to ensure that samples were representative of the whole population of Shandong province. In the first stage, six counties/districts were selected in Shandong province. In the second stage, 18 villages and 18 communities were selected in sampled counties/districts. In the last stage, a total of 5643 households consisting of 7088 individuals aged 60 years and above were identified. Of these, 18 did not complete the survey. In total, 7070 individuals were included in the final sample. After obtaining the verbal informed consent of respondents, all participants were interviewed individually using a structured questionnaire. There were no missing data for the dependent

and independent variables, except for income (n=26), which were replaced with values obtained through mean imputation. In this study, all analyses were based on 5493 subjects aged 65 years or above.

### Chronic conditions and multimorbidity

A number of chronic conditions were collected via the following question: ‘Have you been diagnosed with any conditions by a doctor?’ The chronic diseases included hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease, asthma, cancer and other diseases. Respondents answered ‘yes’ or ‘no’ for each question. Each condition was assessed by trained investigators separately. Multimorbidity referred to the coexistence of two or more chronic diseases in the same person.<sup>21</sup>

### Anthropometric measurements

The anthropometric measurements included body height, weight, WC and hip circumference. Height was measured to the nearest 1 cm and weight to the nearest 1 kg. All subjects were measured wearing light clothing without hats or shoes. BMI was computed as weight in kilograms divided by height in metres squared ( $\text{kg}/\text{m}^2$ ) and classified according to WHO definitions.<sup>22</sup> The applied classifications were underweight (BMI <18.50  $\text{kg}/\text{m}^2$ ), normal weight (BMI 18.50–24.99  $\text{kg}/\text{m}^2$ ), overweight (BMI 25.00–29.99  $\text{kg}/\text{m}^2$ ) and obese (BMI  $\geq$ 30.00  $\text{kg}/\text{m}^2$ ). WC was measured midway between the level of the iliac crest and the lowest rib and the cut-off point for abdominal obesity were chosen as a WC >102 cm for males and >88 cm for females.<sup>23</sup> Hip circumference was measured from the widest part of pelvis. WHR was computed as the ratio of WC to hip circumference and the cut-off value for central obesity was considered  $\geq$ 0.90 for males and  $\geq$ 0.85 for females.<sup>23</sup> WC and WHR were used as categorical variables in the analysis.

### Other variables

Sociodemographic information included age (65–79, 80+), gender (male, female), residence (rural, urban), marital status (couple, single), education (no education, primary school, secondary school, high school and above), employment (employed, unemployed, retired), income ((four income quartiles: quartile 1 (q1) is the poorest and quartile 4 (q4) is the richest). Lifestyle characteristics included smoking (never-smoker, ex-smoker, current smoker), drinking (abstainer, ex-drinker, drinker), number of weekly exercise times ( $\leq$ 1,  $\geq$ 2).

### Statistical analysis

All data were analysed using SPSS V.24.0 (IBM). We first divided the participants into two age groups: the young-old (65–79) and the old-old (80+). Categorical variables were reported in number (percentage), and  $\chi^2$  tests and z-tests were used to analyse differences in sociodemographic factors, anthropometric indices and chronic conditions across the age groups.  $\chi^2$  tests were also used to compare the distribution of chronic conditions in different BMI,

**Table 1** Descriptive characteristics of study sample by age groups

Characteristic	Total	Young-old	Old-old	P value*
	n=5493	n=4884	n=609	
Gender n (%)				0.462
Male	2278 (41.5)	2017 (41.3)	261 (42.9)	
Female	3215 (58.5)	2867 (58.7)	348 (57.1)	
Residence n (%)				0.087
Rural	4242 (77.2)	3755 (76.9)	487 (80.0)	
Urban	1251 (22.8)	1129 (23.1)	122 (20.0)	
Marital status n (%)				<0.001
Couple	4291 (78.1)	3959 (81.1)	332 (54.5)	
Single†	1202 (21.9)	925 (18.9)	277 (45.5)	
Education n (%)				<0.001
No education	1808 (32.9)	1484 (30.4)	324 (53.2)	
Primary school	2438 (44.4)	2217 (45.4)	221 (36.3)	
Secondary school	877 (16.0)	847 (17.3)	30 (4.9)	
High school and above	370 (6.7)	336 (6.9)	34 (5.6)	
Employment n (%)				<0.001
Employed	1421 (25.9)	1393 (28.5)	28 (4.6)	
Unemployed	2931 (53.4)	2461 (50.4)	470 (77.2)	
Retired	1141 (20.8)	1030 (21.1)	111 (18.2)	
Income n (%)				<0.001
Q1	1460 (26.6)	1248 (25.6)	212 (34.8)	
Q2	1366 (24.9)	1213 (24.8)	153 (25.1)	
Q3	1292 (23.5)	1171 (24.0)	121 (19.9)	
Q4	1375 (25.0)	1252 (25.6)	123 (20.2)	
Smoking n (%)				0.104
Never-smoker	3883 (70.7)	3440 (70.4)	442 (72.6)	
Ex-smoker	748 (13.6)	659 (13.5)	89 (14.6)	
Current smoker	863 (15.7)	785 (16.1)	78 (12.8)	
Drinking n (%)				0.244
Abstainer	4143 (75.4)	3669 (75.1)	474 (77.8)	
Ex-drinker	465 (8.5)	414 (8.5)	51 (8.4)	
Drinker	885 (16.1)	801 (16.4)	84 (13.8)	
No of weekly exercise times n (%)				0.001
≤1	2159 (39.3)	1881 (38.5)	278 (45.6)	
≥2	3334 (60.7)	3003 (61.5)	331 (54.4)	
No of chronic conditions n (%)				<0.001
None	1578 (28.7)	1373 (28.1)	205 (33.7)	
1	1981 (36.1)	1749 (35.8)	232 (38.1)	
≥2 (multimorbidity)	1934 (35.2)	1762 (36.1)	172 (28.2)	
BMI n (%)				<0.001
Underweight	204 (3.7)	165 (3.4)	39 (6.4)	
Normal	2821 (51.4)	2441 (50.0)	380 (62.4)	
Overweight	2064 (37.6)	1905 (39.0)	159 (26.1)	
Obesity	404 (7.4)	373 (7.6)	31 (5.1)	
WC n (%)				<0.001

Continued



Table 1 Continued

Characteristic	Total	Young-old	Old-old	P value*
	n=5493	n=4884	n=609	
Normal	2335 (42.5)	2037 (41.7)	298 (48.9)	0.832
Central obesity	3158 (57.5)	2847 (58.3)	311 (51.1)	
WHR n (%)				
Normal	855 (15.6)	762 (15.6)	93 (15.3)	
Central obesity	4638 (84.4)	4122 (84.4)	516 (84.7)	

Young-old means aged 65–79, old-old means aged 80 or over.

\* $\chi^2$ .

†Single, not married/divorced/widowed or others.

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

WC and WHR categories among the young-old and old-old adults. The associations between each anthropometric measure (BMI, WC and WHR as independent variables) and multimorbidity were estimated via logistic regression, providing ORs and 95% CIs. In all analyses, BMI, WC and WHR were modelled as categorical variables. The regression models were adjusted for gender, residence, marital status, education, employment, income, smoking, drinking and number of weekly exercise times.

### Patient and public involvement

No patients or member of the public were involved in the conception, design and planning of this study.

## RESULTS

### Characteristics of participants

Table 1 shows the age-stratified characteristics of the study sample. In total, 5493 elderly people were enrolled, 11.1% of them were aged 80+, 58.5% were female and most of them lived in a rural area (77.2%) and were couples (78.1%). As expected, in contrast to the young-old, most of the old-old were unemployed, had a lower level of education and income, and did less weekly exercise. As for chronic conditions, 28.7% of older adults reported no chronic disease, 36.1% reported having one chronic condition and 35.2% reported multimorbidity. The prevalence of multimorbidity in the young-old was higher than that in the old-old (36.1% vs 28.2%). Regarding obesity-related anthropometric indices, the young-old were more likely to be BMI-obese and WC-obese compared with the old-old (7.6% vs 5.1% and 58.3% vs 51.1%). No difference was observed in the distribution of WHR-obesity between the two age groups.

### The prevalence of multimorbidity by BMI, WC and WHR categories

The prevalence of multimorbidity according to BMI, WC and WHR categories is shown in table 2. The prevalence of multimorbidity was 49.3%, 65.2% and 36.7% among BMI-obese, WC-obese and WHR-obese population, respectively. The increase in multimorbidity prevalence which was mirrored by an increase in BMI (overweight

and obesity), both for the young-old and old-old but more pronounced in young-old adults. Also, those with central obesity (WC-obesity and WHR-obesity) reported a higher mean number of chronic conditions and a higher prevalence of multimorbidity, both in the young-old and old-old population.

### Association of BMI, WC and WHR with multimorbidity

Table 3 shows, for each age group separately, results of the logistic regressions that estimated the association of BMI, WC and WHR with multimorbidity. Overall, the BMI-obese or central obese had a higher likelihood of having a chronic condition compared with those normal weight. In young-old adults, after multivariable adjustment, the likelihood of multimorbidity was still more than two times higher among the BMI-obese than the BMI-normal population (OR 2.08, 95% CI 1.66 to 2.60). Similar but less strong associations were found for the WC and WHR young-old populations (OR 1.60, 95% CI 1.42 to 1.81; OR 1.31, 95% CI 1.10 to 1.56, respectively). With regard to the old-old, BMI-obesity was no longer associated with multimorbidity whereas WC-obesity and WHR-obesity remained positively associated with multimorbidity (OR 1.75, 95% CI 1.21 to 2.54; OR 2.15, 95% CI 1.18 to 3.93, respectively). An analysis of potential gender differences in obesity measures and multimorbidity was undertaken, however, it was found that men and women were similar in both outcomes.

## DISCUSSION

This study was performed to assess the association between obesity-based anthropometric indices and multimorbidity in older adults. To our knowledge, this is the first study to examine whether the association varied across two age groups among older adults (65+) in China. We controlled for many confounders, including sociodemographic, socioeconomic characteristics and living habits.

The prevalence of multimorbidity was 35.2% in the sample of Shandong, China, with a higher prevalence of multimorbidity in the young-old (aged 65–79) than that in the old-old (aged 80+). Numerous studies regarding

**Table 2** Mean number of chronic conditions and prevalence of multimorbidity (%) for overall (n=5493), young-old (n=4884) and old-old (n=609) adults by BMI, WC and WHR categories

	Total			Young-old			Old-old		
	Mean no of chronic conditions (95% CI)	Prevalence of multimorbidity (n, %)	Mean no of chronic conditions (95% CI)	Prevalence of multimorbidity (n, %)	Mean no of chronic conditions (95% CI)	Prevalence of multimorbidity (n, %)	Mean no of chronic conditions (95% CI)	Prevalence of multimorbidity (n, %)	
<b>BMI</b>									
Underweight	0.97 (0.83 to 1.10)	52 (25.5)	0.95 (0.80 to 1.09)	40 (24.2)	1.05 (0.75 to 1.36)	12 (30.8)			
Normal	1.08 (1.05 to 1.12)	854 (30.3)	1.10 (1.06 to 1.14)	756 (31.0)	1.01 (0.88 to 1.14)	98 (25.8)			
Overweight	1.30 (1.25 to 1.34)	829 (40.2)	1.32 (1.27 to 1.37)	780 (40.9)	1.39 (1.02 to 1.75)	49 (30.8)			
Obesity	1.55 (1.45 to 1.65)	199 (49.3)	1.57 (1.46 to 1.67)	186 (49.9)	0.99 (0.89 to 1.08)	13 (41.9)			
P value*	<0.001		<0.001			0.200			
<b>WC</b>									
Normal	0.95 (0.92 to 0.98)	673 (34.8)	0.96 (0.93 to 1.00)	607 (34.4)	0.83 (0.74 to 0.92)	66 (38.4)			
Central obesity	1.15 (1.12 to 1.18)	1261 (65.2)	1.16 (1.13 to 1.19)	1155 (65.6)	1.06 (0.97 to 1.15)	106 (61.6)			
P value*	<0.001		<0.001			0.001			
<b>WHR</b>									
Normal	1.01 (0.94 to 1.08)	234 (27.4)	1.04 (0.97 to 1.11)	218 (28.6)	0.74 (0.57 to 0.92)	16 (17.2)			
Central obesity	1.23 (1.20 to 1.26)	1700 (36.7)	1.25 (1.21 to 1.28)	1544 (37.5)	1.07 (0.99 to 1.15)	156 (30.2)			
P value*	<0.001		<0.001			0.010			

Young-old means aged 65–79, old-old means aged 80 or over.

\* $\chi^2$ .

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

**Table 3** Association between BMI, WC and WHR status and multimorbidity in young-old (n=4884) and old-old (n=609) adults

	Unadjusted		Covariates*	
	OR (95% CI)	P value	OR (95% CI)	P value
<b>Young-old</b>				
BMI				
Normal	Ref		Ref	
Underweight	0.71 (0.50 to 1.03)	0.071	0.70 (0.48 to 1.02)	0.060
Overweight	1.55 (1.36 to 1.75)	<0.001	1.48 (1.30 to 1.68)	<0.001
Obesity	2.22 (1.78 to 2.76)	<0.001	2.08 (1.66 to 2.60)	<0.001
WC				
Normal	Ref		Ref	
Central obesity	1.61 (1.43 to 1.82)	<0.001	1.60 (1.42 to 1.81)	<0.001
WHR				
Normal	Ref		Ref	
Central obesity	1.50 (1.26 to 1.77)	0.001	1.31 (1.10 to 1.56)	0.003
<b>Old-old</b>				
BMI				
Normal	Ref		Ref	
Underweight	1.28 (0.62 to 2.62)	0.502	1.46 (0.69 to 3.08)	0.320
Overweight	1.28 (0.85 to 1.93)	0.233	1.23 (0.81 to 1.88)	0.335
Obesity	2.08 (0.98 to 4.40)	0.056	2.10 (0.96 to 4.57)	0.063
WC				
Normal	Ref		Ref	
Central obesity	1.82 (1.27 to 2.61)	0.001	1.75 (1.21 to 2.54)	0.003
WHR				
Normal	Ref		Ref	
Central obesity	2.09 (1.18 to 3.69)	0.012	2.15 (1.18 to 3.93)	0.013

\*BMI, WC and WHR each separately adjusted for gender, residence, marital status, education, employment, income, smoking, drinking, number of weekly exercise times.

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

the prevalence of multimorbidity have been conducted in China.<sup>24–26</sup> These studies included different data sources, targeted age groups, definitions of multimorbidity and number of chronic conditions integrated in the analyses. Consequently, the estimated prevalence of multimorbidity varied. A previous systematic review reported that the overall prevalence of multimorbidity among older adults (aged 60+) ranged widely from 6.4% to 86.9% in China.<sup>27</sup> Regarding to the difference between young-old and old-old, a multicountry study showed that multimorbidity prevalence was high in older adults (aged 50+) across countries, and increased with age, although the rate of increase in the oldest age groups (80+) was modest at best in most countries with declines observed in some countries.<sup>28</sup> Moreover, evidence indicates that life expectancy is substantially lower in people with multimorbidity<sup>29–30</sup>; the most old-old people with multimorbidity may have already died, while those with less chronic diseases live longer, which may result in lower prevalence of multimorbidity in the old-old than that in the

young-old. It was shown that survey chronic conditions data from patients may not be entirely concordant with medical record documentation.<sup>31</sup> However, the difference attenuates with age, and the prevalence is similar in both data sources for elderly patients.<sup>32</sup> The prevalence of multimorbidity reported in this study, despite the difference between this study and others, is consistent with the literature, indicating that multimorbidity is a common occurrence in older population and should receive more attention, especially in the young-old adults.

Multimorbidity more often occurred in subjects with BMI-obesity/central obesity than in those with normal weight, which was aligned with previous reports that obesity was an important risk factor for chronic diseases, which can lead to multimorbidity.<sup>33–34</sup> With regard to the positive association between obesity and multimorbidity, our results were consistent with those of Jovic *et al*,<sup>19</sup> who reported that obesity was associated with increased prevalence of multimorbidity. Other research also showed that obesity was independently associated with the occurrence

of multimorbidity in adults from six low-income and middle-income countries (China, India, Mexico, Russia, South Africa and Ghana).<sup>18</sup> In these studies, however, obesity was assessed by BMI alone. Our results indicated that WC/WHR central obesity was also correlated with increased risk of multimorbidity. This may have important implications for the potential to delay onset of multimorbidity through earlier and more effective intervention on BMI-obesity and central obesity.

Furthermore, we found some different pattern between the young-old and old-old adults. More specifically, in young-old adults, BMI-obesity and central-obesity were associated with increased multimorbidity risk. In the old-old, however, a positive association was observed only in the case of central obesity. Our findings support the contention that abdominal obesity is associated with increased risk of multimorbidity independently of potential confounding factors.<sup>35</sup> WC or WHR may be the better screening measure for chronic conditions than other anthropometric indicators. For example, Wang *et al*<sup>36</sup> reported that WC was a better measure of central obesity than WHR for predicting the risk of type 2 diabetes, while other studies showed that among the anthropometric indices of obesity, WHR was better than BMI, bodyweight and WC in predicting chronic conditions, such as chronic kidney disease<sup>37</sup> and type 2 diabetes<sup>38</sup> in the elderly. Our study extends the previous findings because we found that both WC and WHR are more sensitive to screening for multimorbidity than BMI, especially in old-old (aged 80+) adults. Another possible reason for such variations in the associations of anthropometric indices with multimorbidity is that body composition changes as age advances, and BMI cannot accurately describe body fat distribution for those in old-old age compared with other indicators; this deserves further exploration. Based on these findings, multiple obesity-related indicators should be used to predict multimorbidity in the elderly population in order to avoid biases caused by the use of a single indicator. We recommend that WC and WHR are more important and necessary indicators.

There are still some limitations in this study. First, chronic diseases could be under-reported, which would affect the observed multimorbidity prevalence. Second, other anthropometric indicators, such as waist-to-height ratio and hip index, were not considered in this study. Therefore, further studies are required in the future. Third, because our study was a cross-sectional design, causality cannot be inferred. Despite these limitations, this study elaborates on the available evidence on multimorbidity in the Chinese older population.

## CONCLUSIONS

In conclusion, the prevalence of multimorbidity among Chinese aged  $\geq 65$  years was high and varied by age. The associations between BMI-obesity and WC, WHR central obesity and multimorbidity were different between the young-old and old-old adults. Further research on

investigating the underlying mechanisms linking BMI-obesity/central obesity and multimorbidity among older adults should consider different age subgroups. Our findings also highlight the importance of using multiple body mass indicators to predict chronic conditions in the older population.

**Contributors** JZ performed the statistical analysis and drafted the initial manuscript, LX and JL provided the concept and design of study. LS and WQ was involved in the analysis and interpretation of data and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** The Ethical Committee of Shandong University School of Public Health approved the study protocol (No. 20170110).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request. Data are available on reasonable request to corresponding author (email: lzxi@sdu.edu.cn).

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