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Original Article

The association of dietary patterns with latent tuberculosis infection among young adults: A case-control study in Shanghai

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Abstract
Introduction: In developing and underdeveloped countries, undernutrition plays a major role in subverting the immune system, leading to an increase in TB infections; this study investigated the associations between dietary patterns and latent tuberculosis infection risk among young adults in Shanghai.
Methodology: In a case-control study, 96 cases of latent tuberculosis infection and 192 healthy controls were studied among contacts of students in clusters of tuberculosis epidemics in colleges from January 2021 to March 2023. A standardized questionnaire assessing sociodemographic, lifestyle, and dietary characteristics was applied. Food intake was estimated using a 95-item semiquantitative Food Frequency Questionnaire. Using the principal component analysis to extract dietary patterns from food groups intake. Logistic regression models were applied.
Results: Four dietary patterns were identified: “traditional balanced” pattern, “unsaturated fatty acid” pattern, “snack” pattern, and “protein and fruit” pattern. Four components explaining 64.52% of the total variation in consumption were derived. In a conditional logistic regression analysis, three models were created. After adjusting for various confounders, compared to “snack” pattern, the risk of latent TB infection was 91% lower in the “traditional balanced” pattern (OR 0.05, 95% CI 0.01, 0.38, $p = 0.004$).
Conclusions: To prevent TB infection among young adults living in high TB burden areas, a balanced dietary pattern rather than a "snack” pattern should be promoted in school settings. Future research should explore the risk of developing active tuberculosis in Mtb-infected people with different dietary patterns and the prevention of this risk by healthy dietary patterns.

Key words: Tuberculosis infection; dietary patterns; balanced dietary; snack dietary; young adults.

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Introduction

TB, one of the ten leading causes of death worldwide, is caused by the *Mycobacterium tuberculosis* (Mtb). The relative incidence and mortality were reduced by effective interventions worldwide up to 2021 [1]. However, the incidence rate of tuberculosis increased by 3.6% in 2021 relative to 2020, with an estimated 10.6 million people becoming ill with tuberculosis and 1.6 million people dying from it in 2021, suggesting reversal from the trend of a nearly 2% decrease per year in the past two decades [2]. It has been estimated that in ~5% of patients, the disease progresses from latent infection to active disease within 2 years after infection, and an additional 5% develop active disease at some period in their lives [3]. A total of 30% of the world’s population has latent tuberculosis infection (LTBI), forming a large reservoir for disease reactivation [2]; hence, exploring the factors that affect Mtb susceptibility is vital in the control of TB epidemics.

Malnutrition is recognized as one of the important drivers of TB epidemics [4]. The relationship between TB and nutrition is bidirectional. The number of people with malnutrition is increasing, including those with an unbalanced and inadequate intake of nutrients, which is likely to have been further exacerbated by the COVID-19 pandemic during the past three years [5]. As TB is disseminated through the sputum of infected people, contacts who maintain close relations with a TB patient are at increased risk of being infected; this risk is higher when contacts show an unbalanced or inadequate nutritional situation, as their immune system is compromised [6]. Household contacts are defined as individuals who maintain relations with a TB patient [7], and the same concept applies equally to the epidemiological investigation of tuberculosis in boarding colleges and universities. Consequently, the early diagnosis of an unbalanced and unreasonable nutritional status is necessary to prevent infection in the population that is in contact with TB patients [8], especially in young adults in boarding colleges and universities.

Although many public health issues have been solved by intervening with a single nutrient, evaluating associations with TB susceptibility by focusing on single foods or nutrients is not sufficient since people consume diets consisting of a variety of foods with highly related combinations of micro- and macronutrients, not single nutrients [9]. An alternative method is to focus on overall dietary patterns (DPs), which express many different facets of the diet [10]. Although there are several studies on dietary patterns and Mtb infection risk, the findings are inconclusive [10], especially in young adults at boarding colleges and universities in China. It is necessary to use multiple methods to explore dietary patterns and their associations with Mtb infection among close contacts in boarding colleges and universities to obtain a complete picture. The most common techniques used for dietary pattern extraction are *a posteriori* analyses, mainly principal component analysis (PCA), which takes observed correlations as the basis among dietary variables [4,10,13,14].

We utilized PCA, *data*-driven method, to investigate the correlation of Mtb susceptibility with certain dietary patterns in nutritional epidemiology among close contacts of students in clusters of tuberculosis epidemics in colleges in Pudong New Area, Shanghai, China. Our study may provide evidence to support the recommendation of an optimal diet pattern for close contacts of tuberculosis patients in colleges and universities.

Methodology

This was a case-control study conducted with face-to-face interviews among young adult close contacts of tuberculosis patients who were identified in clusters of tuberculosis outbreaks at colleges and universities in Pudong New Area, Shanghai, in 2021-2023. When we received reports of students with signs and symptoms compatible with TB (index cases, all of them were culture confirmed), we immediately conducted a field epidemiological investigation at the colleges or universities. We investigated the index case to identify close contacts. Close contact was defined as being in the same class or dormitory who had shared indoor airspace in school settings with a patient with pulmonary TB for more than 15 hour/week during 1 or more weeks or a total of more than 180 hours during a defined infectious period [15]. Then, the venous blood of all contacts was drawn, and interferon (IFN)-γ was measured by QuantiFERON® TB-Gold In-Tube assay (QFT-GIT) for the screening of Mtb infection. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All subjects gave their written informed consent for inclusion before participating in the study.

Subjects who did not have any clinical symptoms or medical history of tuberculosis were included in the study. Close contacts who tested positive for QFT-GIT were included in the LTBI group. For the case–control matching, the baseline information of all close contacts was reviewed, and 2 controls who tested negative for QFT-GIT were selected for each case, matched by age (+ 1 year), sex, and body mass index (BMI). In total, the LTBI and control samples included 288 subjects. Trained epidemiologists used a structured questionnaire to gather information on food frequency consumption, sociodemographic variables, and lifestyle factors for all enrolled participants. The anthropometric indicators consisted of body height and body weight, which were measured using standardized procedures. Body height was measured with an accuracy of ±0.5 cm, and weight was measured in light clothes with an accuracy of ±0.5 kg. Body mass index (BMI; kg/m^2) was calculated based on criteria from the World Health Organization and analyzed as a continuous variable [16]. Subjects were asked to recall whether they engaged in physical activity of different intensities for at least 10 minutes for more than 3 days per week and the time spent sitting and sleeping each day. Data on smoking and alcohol drinking habits, family history of tuberculosis, *per capita* monthly household income, and chronic disease history were recorded during the interview. Parental education level was categorized as completed primary education, secondary school, and higher vocational training or university degree.

Dietary data were collected by a 95-item semiquantitative Food Frequency Questionnaire (FFQ), using the previous year as the reference period [17]. Close contacts were asked to report the frequency of consumption and portion size for every food group. To minimize inaccuracies, an indicative photograph atlas was used to estimate the portion size of every food item. Frequencies of food consumption were classified into nine categories, ranging from "almost never" to "three or more times a day". Portion size was classified into five categories, ranging from "less than or equal to 50 grams" to "greater than or equal to 250 grams". The food intakes derived from the FFQ were calculated by multiplying the frequency of consumption with the daily portion size of each food item.

To reflect the dietary exposure of the subjects, several *a posteriori* dietary patterns were extracted using PCA, and factor loadings were then applied [18]. The 95 FFQ items were first classified into 13 noncorrelated food groups based on the similarity of nutrient profiles. We should note that the purpose of PCA was to derive a series of independent linear combinations of a set of food groups that retained as much of the original dietary habit information as possible. From the entire database of the 95 food variables, 12 food groups and a beverage group (i.e., grains, potatoes, beans and products, vegetables, thallophytes, fruits, dairy products, red meat and products, fish and shrimp, eggs, pastry biscuits and crackers, nuts, and sweet beverages) were ultimately used in the analysis, mainly due to their macronutrient compositions. The number of retained dietary patterns was determined according to eigenvalues (eigenvalues > 1.0), scree plot examination, and interpretability, since these patterns explained more information than the single food items. Factor loadings with an absolute value ≥ 0.5 were retained to define food items that characterized dietary patterns, which indicated that the food item contributed most to the construction of the pattern, and the food patterns were named according to their scores; moreover, the significance of Bartlett's Test of Sphericity was < 0.001, which implied high interrelationships between food items, and the Kaiser-Meier-Oklin criterion was 0.68 > 0.5. Therefore, PCA was effective for assessing meaningful food patterns in this study.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 22.0 (IBM, Armonk, USA). Descriptive statistics were used to characterize the population using frequencies and means ± standard deviations (SDs). Categorical variables are presented as frequencies. The normality of food variables was tested using P-P plots. The two-tailed chi-squared test was used for the statistical comparison of proportions, whereas continuous variables were tested between cases and controls using Student's t tests. Factor scores for each dietary pattern were computed as the sum of products between observed food group intakes and their factor loadings. The references (odds ratios [OR] = 1.00) were the control sample and the bottom tertile of each dietary pattern. Conditional logistic regression models were used to estimate ORs and corresponding 95% confidence intervals (95% CIs) of LTBI associated with PCA-derived dietary patterns using the following models: a crude model, a model adjusted for age, sex,

Table 1. Distribution of case and control characteristics.

Characteristics	Cases with Mtb infection (n = 96); n (%)	Controls (n = 192); n (%)	value	*p*
Age (y), mean ± SD	20.0 ± 4.7	20.0 ± 4.6	0.004	0.949
Male	22 (22.9)	44 (22.9)	0.026	0.872
Registration in Shanghai	22 (22.9)	84 (43.8)	6.306	0.020
Han ethnicity	88 (91.7)	191 (99.5)	5.345	0.254
Per capita monthly household income (Yuan), mean ± SD				
<6000	48 (50.0)	88 (45.8)		
6000~10000	28 (29.2)	64 (33.4)	0.544	0.762
>10000	20 (20.8)	40 (20.8)		
Body mass index (kg/m^2), mean ± SD	21.10 ± 4.17	21.11 ± 3.69	0.000	0.985
Smoking (ever)	4 (4.2)	0 (0.0)	2.169	0.141
Alcohol drinking (ever)	2 (2.1)	0 (0.0)	1.073	0.300
Tea drinking (ever)	8 (8.3)	20 (10.2)	0.065	0.799
Physical activity	50 (52.1)	92 (46.9)	0.501	0.479
Sleep duration (h), mean ± SD	7.1 ± 0.8	7.4 ± 1.6	0.175	0.677
Sitting time (h), mean ± SD	8.3 ± 6.3	6.7 ± 3.4	0.907	0.343
Chronic disease history	12 (12.5)	16 (8.3)	0.591	0.442
Paternal education level				
Primary education	24 (25.0)	16 (8.3)		
Secondary school	62 (64.6)	152 (79.2)	5.388	0.046
Higher vocational training or university degree	10 (10.4)	24 (12.5)		
Maternal education level				
Primary education	24 (25.0)	28 (14.6)		
Secondary school	64 (66.7)	140 (72.9)	1.764	0.414
Higher vocational training or university degree	8 (8.3)	24 (12.5)		

The reported *p* values were calculated using the *t*-test, the chi-square test, or the Mann–Whitney U test.

ethnicity, smoking, drinking, physical activity, sleep duration, sitting time, and registration in Shanghai, and a model adjusted for BMI, *per capita* monthly household income, chronic disease history, and parental educational level in addition to the above indices. All statistical tests were 2-sided, and p values less than 0.05 were considered statistically significant.

Results

Cases with LTBI and controls were of similar age, sex, and BMI (according to the protocol of the study) and had similar *per capita* monthly household incomes, maternal education levels, smoking rates, alcohol and tea drinking rates, and physical activity levels (Table 1); however, the rate of registration in Shanghai was higher in controls than in cases ($p < 0.05$), and the paternal educational level was lower in cases than in controls ($p < 0.05$). Cases were more likely to have a longer sitting time, shorter sleep duration, and higher rate of chronic disease, but there was no significant difference between the groups ($p > 0.05$).

Based on scree plot examination, we identified four major dietary patterns with eigenvalues ≥ 1.0, which explained 64.5% of the total variance among the 13 food groups (Figure 1).

The loadings for the four food patterns that represent the correlation of each food item with the corresponding component are presented (Table 2) (the coefficients with absolute loadings > 0.5 are in bold, which means that they are better correlated with the pattern). Since the higher absolute values indicate that the food variable contributes more to the characterization of the pattern [18], it could be suggested that the extracted patterns are (Factor 1) a "traditional balanced" pattern, which loaded heavily on grains, red meat, beans, vegetables, thallophytes, and potatoes; (Factor 2) an "unsaturated fatty acid" pattern, mainly characterized by the consumption of fish, shrimp, and nuts; (Factor 3) a "snack" pattern that represents the consumption of pastries, biscuits and crackers; and (Factor 4) a "high protein and fruit" pattern that represents the consumption of dairy products, fruits, and eggs. The "traditional balanced" pattern was the most dominant food pattern and explained 20.8% of the total variance. The "unsaturated fatty acid" pattern was the second dominant food pattern and explained 16.8% of the total variance. The remaining two patterns explained 13.6% ("snack" pattern) and 13.3% ("high protein and fruit" pattern) of the variance in consumption. Regarding the other 9 components that explained the rest of the variation in food and beverage consumption, none were characterized by a specific consumption pattern.

Figure 1. The scree plot, used to determine the appropriate number of principal components, shows the eigenvalues, which represent the partitioning of the total variation accounted for by each principal component against the PCA component number.

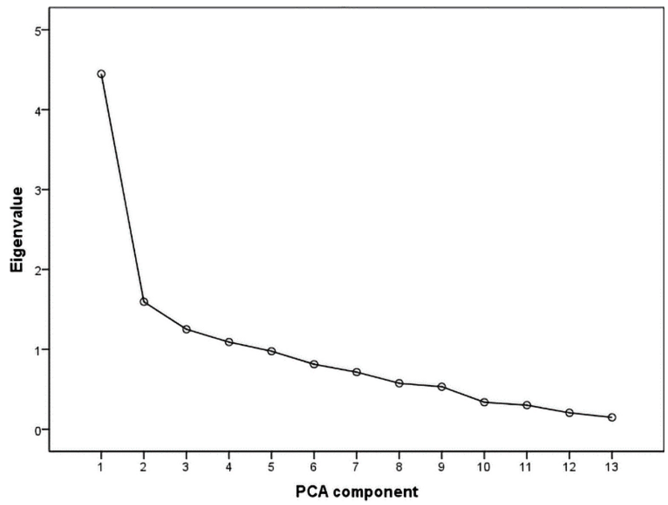

Table 2. Factor loadings that characterized the four dietary patterns identified by PCA in 288 study participants*.

	Factor 1	Factor 2	Factor 3	Factor 4
Grains	**0.765**	-0.257	-	-0.195
Potatoes	**0.518**	0.217	0.243	-
Beans	**0.670**	-0.317	-0.413	-0.227
Vegetables	**0.631**	-	-0.403	-
Thallophytes	**0.637**	-	-0.376	-
Fruits	0.483	0.376	-0.164	0.434
Dairy products	**0.569**	-	0.285	**0.599**
Red meat and products	**0.746**	-0.409	-	-
Fish and shrimp	0.438	**0.617**	-	-0.293
Eggs	0.498	0.400	-0.145	0.341
Pastries, biscuits and crackers	0.490	-0.161	**0.539**	-0.309
Nuts	0.351	**0.615**	0.193	-0.339
Sweet beverages	0.463	-0.357	**0.593**	0.128
Variance explained (%) #	20.812	16.843	13.556	13.306

*Values are factor loadings; Dietary patterns are classified according to factor loadings; Absolute values of <0.10 are not listed; # Percentage variance of total food intake explained by the patterns.

Three conditional logistic regression models were estimated to evaluate the association between each of the extracted dietary patterns and LTBI (Table 3). The use of these models helped explore the potential effect of various confounders in the investigated relationship more deeply. The "traditional balanced" pattern has a high consumption of vegetables and fruits, the "unsaturated fatty acid" pattern has a high consumption of fish, shrimp, and nuts, and the "high protein and fruit" pattern has a high consumption of dairy products and fruits, which are all considered to be healthy diets. Therefore, the "snack" pattern is set as the reference. Based on Model 1, compared with the "snack" pattern, mainly characterized by the consumption of pastries, biscuits, crackers and sweet beverages, the risk of latent TB infection in the "traditional balanced" pattern which was mainly characterized by the consumption of grains, red meat, beans, vegetables, thallophytes, and potatoes, and the "unsaturated fatty acid" pattern which was mainly characterized by the consumption of fish, shrimp, and nuts, was 77% and 55% lower, respectively, and the differences were statistically significant (OR 0.23, 95% CI 0.06, 0.88, $p = 0.032$; OR 0.45, 95% CI 0.14, 1.45, $p = 0.041$); In the second set of models, age, sex, ethnicity, smoking, drinking, physical activity, sleep duration, sitting time, and registration in Shanghai were considered. Compared with the "snack" pattern, the risk of TB infection was 91% and 80% lower in the same two dietary patterns, respectively (OR 0.09, 95% CI 0.01, 0.52, $p = 0.008$; OR 0.20, 95% CI 0.04, 0.96, $p = 0.044$); In the third nested model, BMI, *per capita* monthly household income, chronic disease history, and parental educational level were additionally included. It was observed that the subject's adherence to the "traditional balanced" pattern could reduce the risk of TB infection by 95%, and the difference was statistically significant (OR 0.05, 95% CI 0.06, 0.38, $p = 0.004$). In all the three models, compared with the "snack" pattern, the risk of TB infection was reduced by 15%, 51%, and 62% in the "high protein and fruit" pattern, which represented the consumption of dairy products, fruits, and eggs, but the differences were not statistically significant (OR 0.85, 95% CI 0.25, 2.84, $p = 0.790$; OR 0.49, 95% CI 0.10, 2.32, $p = 0.365$; OR 0.38, 95% CI 0.06, 2.46, $p = 0.313$).

Discussion

Four components explaining most of the total variation in consumption were derived in this study. Among those four components, compared with "snack" pattern, which was mainly characterized by the consumption of pastries, biscuits, crackers, and sweet beverages, the risk of LTBI was 91% and 80% lower in the "traditional balanced" pattern group and "unsaturated fatty acid" pattern group, respectively. China has a heavy burden of TB and LTBI, accounting for 8.5% of the tuberculosis incidence, which was the second highest incidence globally in 2020 [4]. Previous studies have revealed that if the contacts of TB patients present with some type of malnutrition, their risk of being infected increases because their immune system is weakened [6].

Good nutrition requires an adequate and balanced intake of macro and micronutrients [19]. In clusters of tuberculosis epidemics in colleges and universities in Pudong New Area, Shanghai, China, the relationship between *a posteriori* extracted dietary pattern adherence based on the dietary reports of close contacts of students and LTBI was studied in this work. The "traditional balanced" pattern, mainly characterized by the consumption of grains, red meat, beans, vegetables, thallophyte, and potatoes, as well as the "unsaturated fatty acid" pattern, mainly characterized by the consumption of fish, shrimp, and nuts, were recognized as healthy diet, had features similar to those of the Mediterranean diet pattern.

A study has revealed that dietary patterns characterized by a balanced diet rich in high-quality protein, sufficient energy, marine omega-3 polyunsaturated fatty acids (n-3 PUFAs), phytochemicals, B vitamins, and fiber are associated with mild initial clinical manifestations of TB [4], suggesting the importance of balance in dietary habits according to the "traditional balanced" pattern in this study. Similar to the Mediterranean diet's favorable fatty acid profile, the "unsaturated fatty acid" pattern

Table 3. Results of the conditional logistic regression models that were applied to evaluate the association between dietary patterns derived by principal component analysis and the risk of LTBI in cases (n = 96) and controls (n = 192).

	Snack pattern	Traditional balanced pattern	Unsaturated fatty acid pattern	High protein and fruit pattern
Model 1	1.000 (reference)	0.233 (0.062-0.881)*	0.454 (0.142-1.454)*	0.848 (0.254-2.838)
Model 2	1.000 (reference)	0.087 (0.014-0.522)*	0.196 (0.040-0.955)*	0.486 (0.102-2.316)
Model 3	1.000 (reference)	0.046 (0.006-0.382)*	0.201 (0.032-1.255)	0.384 (0.060-2.462)

All odds ratios and their corresponding 95% CIs were calculated by conditional logistic regressions. * Statistically significant p values ($p < 0.05$). Model 1 was not adjusted. Model 2 was adjusted for age, sex, ethnicity, smoking, drinking, physical activity, sleep duration, sitting time, and registration in Shanghai. Model 3 was adjusted for the same variables included in Model 2 plus BMI, per capita monthly household income, chronic disease history, and parental educational level.

with high monounsaturated fatty acids (MUFAs) is associated with an anti-inflammatory effect by inhibiting eicosanoids derived from arachidonic acid [20]. Furthermore, Nienaber *et al.* used an animal experiment to reveal that eicosapentaenoic and docosahexaenoic acid have antibacterial and inflammation resolving effects in TB [21]. In addition, there was an evidence that whole grain cereals constitute an effective supplementary food for those suffering from the effects of food insecurity, poor health, and coping with TB infection [22].

However, the most vital advantage of identifying participants' eating habits by *a posteriori* approaches is that they are inherently capable of overcoming the high levels of intercorrelation and the synergistic effect of foods and nutrients compared to focusing on single nutrients or foods, representing a broader picture of food and nutrient consumption [23].

Frequently, TB disease is considered to be influenced by not only nutritional status but also several factors, such as sex, age, civil status, socioeconomic status, education level, living environment, and access to public health services [24]. In our study, there were no differences in these factors, except for paternal educational level and registration in Shanghai, between cases and controls since all contacts were from the same urban areas and the same boarding colleges or universities and had the same access to health services. It has been suggested that there is an association between TB and living in rural areas because people living in rural areas have lower incomes than those who live in urban areas [25]. Similar to our research, people with little or no formal education are socially, geographically and/or economically marginalized and present with a weakened health status associated with TB morbidity and mortality [26], which may also apply to the paternal education level.

According to previous studies, it is difficult to determine whether the presence of TB is due to poor nutritional status and then impaired immune status or if this condition is the result of Mtb infection. Inadequate and unbalanced nutrition leads to protein/energy malnutrition and micronutrient deficiencies that lead to immunodeficiency, increasing the risk for developing TB [27]. Moreover, several reports have also shown that deficiency of single or multiple nutrients can reduce people's resistance to infection [28]. Recently, outbreaks of tuberculosis in schools have occurred more frequently in China than in other areas of the world, posing a heavy public health burden to students and their families [29]. In our study, the "snack" pattern was mainly characterized by the consumption of pastries, biscuits, crackers and sweet beverages, which may be a diet pattern that was common among young college students during the COVID-19 pandemic from January 2020 to January 2023. This pattern was inadequate in protein, fiber, unsaturated fatty acids, and minerals, such as calcium, magnesium and zinc, which are considered to play fundamental roles in the control and prevention of several infections [30], including Mtb infection. Therefore, the determination of the nutritional status of close contacts among students in colleges and universities is very important to prevent TB infection.

Limitations

As in most case-control studies, the major limitation of this study was recall bias. Especially, food intakes were estimated by the FFQ, which does not preclude measurement error. However, an effort was given to minimize this limitation by choosing newly outbreak tuberculosis epidemics and collecting all close contacts in a small period of time. Furthermore, large prospective studies should be encouraged. Regarding the selection of the controls, selection bias may exist, but as mentioned in the Methodology section, an effort was given to reduce it by enrolling controls matched by age (+ 1 year), sex and BMI in the same university even in the same class, or dormitory and avoiding any "specific" sampling rule. All these procedures were applied to ensure that the control group reflected the distribution of the exposure characteristics of the referent population of the LTBI. Moreover, people who collected the data were commonly well-trained before the beginning of the study, limiting the intra-investigators bias.

Conclusions

The present study provides interesting insight into the strong harmful effects of adherence to a "snack" dietary pattern on LTBI risk among young adult close contacts in Shanghai, which should be avoided in high TB burden areas. This study reinforces the evidence that a balanced dietary pattern should be chosen to prevent Mtb infection. Future research should explore the risk of developing active tuberculosis in Mtb-infected people with different dietary patterns and the prevention of this risk by healthy dietary patterns, which may lead to the exploration of other interventions besides drug therapy among young students with Mtb infection.

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