The status of serum vitamin A/E and its effect on Recurrent Respiratory Tract Infections in children aged 2 to 17 years in Beijing, China, based on cross-sectional study

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Abstract

Objective

To test the association between serum vitamin A and vitamin E and the prevalence of recurrent respiratory tract infections (RRTIs) of children and adolescents.

Method

A total amount of 5780 children and adolescents aged 2 to 17 were involved, who were classified into:A) Control group ;B) Diagnosed as RRTI with RTI symptoms; C) With RRTI but currently no RTI symptoms being noticed, and D) Not RRTI but showing respiratory disease symptoms. The correlation between serum vitamin A/E level and the presence of RRTIs were analyzed.

Results

Comparing with the prevalence of RRTI in children with normal vitamin A level, the Odds Ratio(OR) of vitamin A deficiency for RRTIs with symptoms was 8.32 (95%CI: 6.15 ▯ 11.27), while the OR of marginal vitamin A deficiency was 1.30 (95%CI: 1.10 ▯ 1.55). The OR of vitamin A deficiency or marginal vitamin A deficiency for asymptomatic RRTIs were 1.52 (95%CI: 1.00 ▯ 2.32) and 1.30 (95%CI: 1.10 ▯ 1.55) respectively, while the OR of vitamin A deficiency or marginal vitamin A deficiency for other respiratory diseases were 7.09 (95%CI: 5.37 ▯ 9.37) and 1.60 (95%CI: 1.38 ▯ 1.86). Whereas, the OR of vitamin E deficiency or marginal vitamin E deficiency for RRTIs or normal respiratory infections were showed without statistical significance.

Conclusion

The low level of vitamin A in serum is a risk factor for children and adolescents getting RRTIs or RTIs, indicating a possibly regulatory role of vitamin A in the respiratory diseases. In comparison, the vitamin E deficiency seems to have a weaker but still positive effect on the RRTIs or RTI

Background

Respiratory tract infections (RTIs) are the most widespread type of infections associated with high morbidity and mortality which threaten the children's health. Typically, the preschool-aged children who were documented for more than eight episodes of airway infections per year or the elder children who suffered from more than 6 times of respiratory infections were considered as RRTIs[1].In China, the average frequency of the infection episodes in children having RRTIs aged 0–2, 3–5, 6–14 are respectively to be more than 7, 6, and 5 times a year[2]. In 2008, the Editorial Committee of Chinese Journal of Pediatrics, together with Department of Respiratory in Chinese Pediatric Society of Chinese Medical Association, established the official criteria to diagnose RRTIs [3], which also has been developing the principle for diagnosis and classification in our research.

According to the previous research, the potential risk factors of RRTIs include the parental education level, family medical history of respiratory disease, parental smoking status, nutrition, uptake of microelements, immunity status, life style, diet, exercising, and environmental factors [4]. Previous researches showed serum vitamin A and vitamin E level associated with the morbidity of RRTIs. Multiple studies indicated that lack of vitamin A/E would increase the risk of respiratory infection [5–7]. Moreover, most of the young patients with bronchopneumonia were observed to have vitamin A deficiency as well, meanwhile, the patients with chronic infections presented a severer vitamin A deficiency than the acute infections[8]. Additionally, the clinical trials conducted in 100 RRTI children without acute phase response demonstrated that the exogenous supplement of vitamin A/E might decrease the morbidity of RRTIs [9].

Nowadays the supplement of vitamin nutrition is getting valued, studies focusing on the connection between vitamin A/E and pediatric disease were encouraged to be constructed. At present, most of the researches focusing on the prevention of the occurrence or recurrence of RRTIs, especially in pre-school children. However, a comprehensive study of RRTI in children and adolescents aged 2–17 considering the factors such as the infectious severity, the serum vitamin A/E level and social demography with a large sample size is still lacking, especially with the rapid development and transition of lifestyle and bebavior in Beijing China, which exert subtle influence to children's vitamin nutrition intake. Therefore, a large sample study is needed to explore the effect of the factors such as the serum vitamin A/E level, BMI and residential distribution on the prevalence of pediatric RRTIs which can provide a reference for establishing strategy and measures to reduce the occurrence of respiratory tract infections in children.

Methods

Study population

The involved children in this study was recruited from the patients or the healthy children who were given a physical examination in the following institutes. The institutes participating in this study include the Department of Pediatrics and the Department of Children Health Care from Capital Institute of Pediatrics, Beijing Shouer Liqiao Children's hospital, Beijing Fangshan District Maternal and Child Health Hospital,The Civil Aviation General Hospital▯Beijing Shijingshan District Maternal and Child Health Care Hospital▯Beijing Pinggu District Maternal and Child ealth Care Hospital▯Tsinghua University Yuquan Hospital, Beijing Huairou Hospital.

Criteria for recruitment

Children or teenagers aged 2–17 admitted into the previously mentioned departments from April 2012 to May 2017 who was diagnosed with rhinitis, influenza, pharyngitis, amygdalitis, trachitis, bronchitis, pneumonia or other respiratory tract diseases was recruited as the affected cases. Meanwhile, all those children including affected ones at the same age group were all given a physical examination in these departments, but healthy children were invited as the

healthy control in this study. Patients with inflammation involving other systems, or patients having a severe medical history (including congenital diseases and abnormal immune system diseases) or history of surgery were not considered as the objective in this study. Children without family consent for complete clinical data record were also excluded. Besides, 25 cases were excluded because of outliers in vitamin A or vitamin E level, and 2942 cases were not considered due to lack of Body Mass Index (BMI) record. Ultimately, 5780 cases were collected for statistics and analysis.

Research strategy

All information was collected after obtaining the parental consent to participate. The basic information of the participants was obtained from the participants' parents through a pre-designed and pre-tested questionnaire. The questionnaire included information regarding residential conditions and medical histories. Based on the medical records of the participants, all cases were grouped into 4 categories according to the criteria in Clinical Concept and Management of Recurrent Respiratory Tract Infections in children edited by Chinese Pediatric Society of Chinese Medical Association in 2008 [2]: A) The healthy control without RRTI history or any respiratory tract infection (RTI) symptoms, B) Diagnosed RRTI patients with RTI symptoms, C) Diagnosed RRTI patient but currently presenting no RTI symptom upon enrollment, i.e. the RRTI patients who were in the asymptomatic phase between infection episodes, and D) Not RRTI patients but currently presenting respiratory disease symptoms. The amount of positive cases in total including group B, C, and D, was 2845, and the proportion of different grades of RRTIs was respective to be group B 14.64% (n = 846), group C 13.37% (n = 773), and group D 21.21% (n = 1226). Whereas cases in the healthy control group A occupied 50.77% (n = 2935) of all 5780 participants in the study.

All individuals underwent physical examination, which includes the measurement of height, weight, body temperature and blood routine examination. To establish the concentration of vitamin A and vitamin E in serum, 3 ml of peripheral venous blood was collected into orange top (thrombin) blood collection tube from participant after overnight fasting. Collected blood samples were centrifuged at 3000 rpm/min for 10 min and settle down. Supernatant was transferred into a clean Eppendorf tube. Collected serum was store in -20 °C till analysis. The concentration of serum vitamin A and vitamin E were detected by Beijing Harmony Health Medical Diagnostics Co., Ltd. using HPLC (LC-20A; Shimadzu, Japan).All procedures in this study including doing the questionnaire, physical examination and classification were performed by professional pediatric doctors.

Standards of grading and classification

In this study, a concentration of vitamin A higher than 0.3 mg/ml was defined as normal, concentration lower than 0.3 mg/ml was defined as suspected subclinical deficiency, while serum vitamin A concentration lower than 0.2 mg/L was graded as deficiency. Meanwhile a vitamin E level higher than 7 mg/L was evaluated as normal, level between 5 mg/L to 7 mg/L was graded as subclinical deficiency while vitamin E level lower than 5 mg/L was classified as deficiency [10].

Participants were also classified based on their height and weight according to the criteria from Body Mass Index cut-offs for overweight and obesity in Chinese children and adolescents aged 2–18 years.Children was graded as normal, overweight and obesity by BMI [11].

Quality control

The pediatric doctors worked for this study were professional and well trained before the project. Diagnosis criteria and note formula were standardized and normalized. Cases should be record accurately, particularly and seriously following demand to insure the reality and reliability. Labs should follow the judgmental criteria and obey the rules in clinical research institution. Observed results were double checked to ensure that all conclusions were summarized from reliable and accurate data.

Results

Essential information

For 5780 individuals involving in this study, 59.2% were male and 40.8% were female; 6.4% of them were rural residents, 7.8% were residents in suburban area, while 85.8% were citizens; the mean age of all participants was 4.55 ± 2.63 years old (59.76 ± 31.58 months old). Individuals in group B, C, D were mostly aged 3–6, of which the proportion was respectively to be 60.40%, 59.77%, and 54.49%. The proportions of the 4 groups were respectively to be 50.77%, 14.64%, 13.37% and 21.21%. The prevalence of vitamin E deficiency in the groups was 20.78%, 33.22%, 22.64%, and 26.92%, respectively. With the increase of ages, the serum vitamin A level in children aged 2–17 in Beijing presented to be wavy increase (increase in the early phase, later decrease and then increase dramatically after age 15), while the serum vitamin E level keep decreasing. Group B had a large portion of country residents while group C included a higher portion of suburban residents. Essential information of age, sexuality, residence, BMI among those 4 groups all showed significant,difference, which mightly showed confounding effect on their Vitamin A and vitamin E level (Table 1–2, Fig. 2–3).

Table 1

Essential information of the participants in study investigating the effect of serum vitamin A/E on Recurrent Respiratory Tract Infections in children aged 2 to 17 years in Beijing

Variate	Group	A(n = 2935)		B (n = 846)		C (n = 773)		D (n = 1226)		Please click here to download the original image file Click here to Correct	P value
		frequency	Proportion (%)	frequency	Proportion (%)	frequency	Proportion (%)	frequency	Proportion (%)		
Age	2□	734	25.01	159	18.79	122	15.78	281	22.92	152.17	< 0.001
	3□	1277	43.51	511	60.40	462	59.77	668	54.49		
	6□	809	27.56	167	19.74	177	22.90	259	21.13		
	12□	115	3.92	9	1.06	12	1.55	18	1.47		
gender	male	1711	58.30	511	60.40	448	57.96	753	61.42	4.49	0.213
	female	1224	41.70	335	39.60	325	42.04	473	38.58		
Residence	citizen	2580	87.90	655	77.42	644	83.31	1083	88.34	150.59	< 0.001
	country	126	4.29	119	14.07	36	4.66	90	7.34		
	floating	229	7.80	72	8.51	93	12.03	53	4.32		
BMI	normal	2326	79.25	583	68.91	584	75.55	848	69.17	80.20	< 0.001
	overweight	315	10.73	135	15.96	80	10.35	160	13.05		
	obesity	294	10.02	128	15.13	109	14.10	218	17.78		

Table 2

Serum vitamin A/E level in grouped children aged 2 to 17 years in Beijing

Variate	Group	A (n = 2935)		B (n = 846)		C (n = 773)		D (n = 1226)		Please click here to download the original image file Click here to Correct
		frequency	Proportion (%)	frequency	Proportion (%)	frequency	Proportion (%)	frequency	Proportion (%)	
Vitamin A	deficiency	87	2.96	145	17.14	33	4.27	197	16.07	446.27
	suspected subclinical deficiency	930	31.69	384	45.39	288	37.26	452	36.87	
	normal	1918	65.35	317	37.47	452	58.47	577	47.06	
Vitamin E	deficiency	33	1.12	25	2.96	11	1.42	16	1.31	69.95
	Subclinical deficiency	577	19.66	256	30.26	164	21.22	314	25.61	
	normal	2325	79.22	565	66.78	598	77.36	896	73.08	

Effect of vitamin A/E

Cases were graded and classified based on social demographic information and diagnosis criteria. To setup the logistic regression model, different groups were assigned and scored differently based on the severity of the judgmental condition. Details were described in Table 3.

Table 3. Scoring of multivariate for logistic regression model

Variate	Assigned	Description
Group	score	Healthy control
	1	RRTIs, attack period
	2	RRTIs, stable period
	3	Not RRTIs, with respiratory disease symptoms
Residence	1	Suburban area
	2	Country resident
	3	Citizen
BMI	1	Overweight
	2	Obesity
	3	Normal
Vitamin A	1	Deficiency
	2	Suspected subclinical deficiency
	3	Normal
Vitamin E	1	Deficiency
	2	Subclinical deficiency
	3	Normal

Multivariate logistic regression model was established and a series of Odd Ratio (OR) was calculated to indicate the association of vitamin A/E level to the presence of RRTIs. As a commonly used value for children health status indication, BMI of individuals and its related OR were also calculated. Comparing with the prevalence in children with normal vitamin A level, the OR of vitamin A deficiency for symptomatic RRTIs is 8.32 (95%CI: 6.1511.27), while the OR of vitamin A suspected subclinical deficiency for symptomatic RRTIs is 2.36 (95%CI: 1.982.80), which indicates a high risk of vitamin A deficiency. Comparing with the morbidity in children with normal vitamin E level, the OR of vitamin E deficiency for RRTIs is 1.56 (95%CI: 0.882.78), while the OR of vitamin E subclinical deficiency for symptomatic RRTIs is 1.37 (95%CI: 1.141.65). The vitamin E level seems to be a risk factor for symptomatic RRTIs as well. Comparing with the prevalence in children with normal BMI, the OR of overweight and obesity for symptomatic RRTIs are 1.73 (95%CI: 1.372.18) and 1.72 (95%CI: 1.362.18), respectively; comparing with the prevalence in permanent citizens, the OR of rural residence for symptomatic RRTIs is 3.26 (95%CI: 2.464.30), while the OR of suburban residence for symptomatic RRTIs is 1.22 (95%CI: 0.92 ~ 1.63), which indicates that the body weight and residential conditions might also affect the occurrence of RRTIs.

Moreover, the vitamin A level is also positive correlated with asymptomatic RRTIs (between the infection episodes) with an OR of 1.52 (95%CI: 1.002.32) and 1.30 (95%CI: 1.101.55) for deficiency and suspected subclinical deficiency respectively. However, the correlation is weaker than for the symptomatic RRTIS. The association of vitamin E level and asymptomatic RRTIs is relatively weak. The OR of vitamin E deficiency and subclinical deficiency are 1.14 and 1.04 respectively. The OR of obesity for asymptomatic RRTIs is 1.52 (95%CI: 1.201.93), while the OR of overweight is 1.04. The OR of rural residence and suburban residence for asymptomatic RRTIs are 1.64 (95%CI: 1.272.12) and 1.13 (95%CI: 0.771.65), respectively. This time the effect of body weight and residence seems to be weaker than on the symptomatic RRTIs.

For other acute respiratory infections, the vitamin A level strongly associated with the RTIs again. The OR of vitamin A deficiency is 7.09 (95%CI: 5.379.37), while the OR of vitamin A suspected subclinical deficiency is 1.60 (95%CI: 1.381.86). Whereas the vitamin E level appears to be not completely associated with the RTIs this time. The OR of vitamin E deficiency is 0.69 (95%CI: 0.361.32), while the OR of vitamin E subclinical deficiency is 1.17 (95%CI: 0.991.38). The OR of overweight and obesity for respiratory symptoms are 1.43 (95%CI: 1.161.77) and 2.02 (95%CI: 1.662.47), indicating a risk of getting respiratory symptoms. The OR of rural and suburban residence are respectively to be OR = 1.56 (95%CI: 1.162.08) and OR = 0.55 (95%CI: 0.400.76). Only settling down in the countryside might be a risk factor of getting acute RTIs. The OR of age are all 0.99 (95%CI: 0.990.99) or 1.00 (95%CI: 0.991.00) in all groups, indicating that the age distribution did not significantly affect the result when taking all effect factors into consideration (Table 4).

Table 4
Results of multivariate for logistic regression analysis

Group	Score	B	Wald value	P	OR	95%CI
B	intercept	-1.63	238.13	0.000		
	[VA = 1]	2.12	187.85	0.000	8.32	6.15~11.27
	[VA = 2]	0.86	94.16	0.000	2.36	1.98~2.80
	[VA = 3]	0^b	.	.	.	.
	[VE = 1]	0.44	2.27	0.132	1.56	0.88~2.78
	[VE = 2]	0.31	10.82	0.001	1.37	1.14~1.65
	[VE = 3]	0^b	.	.	.	.
	[body shape = 1]	0.55	21.36	0.000	1.73	1.37~2.18
	[body shape = 2]	0.54	20.19	0.000	1.72	1.36~2.18
	[body shape = 3]	0^b	.	.	.	.
	[residence = 1]	0.20	1.84	0.175	1.22	0.92~1.63
	[residence = 2]	1.18	68.93	0.000	3.26	2.46~4.30
	[residence = 3]	0^b	.	.	.	.
	Age (month)	-0.01	31.14	0.000	0.99	0.99~1.00
C	Intercept	-1.38	204.72	0.000		
	[VA = 1]	0.42	3.86	0.05	1.52	1.00~2.32
	[VA = 2]	0.27	9.35	0.002	1.30	1.10~1.55
	[VA = 3]	0^b	.	.	.	.
	[VE = 1]	0.13	0.14	0.711	1.14	0.57~2.30
	[VE = 2]	0.04	0.16	0.688	1.04	0.85~1.27
	[VE = 3]	0^b	.	.	.	.
	[body shape = 1]	0.04	0.08	0.773	1.04	0.80~1.35
	[body shape = 2]	0.42	11.67	0.001	1.52	1.20~1.93
	[body shape = 3]	0^b	.	.	.	.
	[residence = 1]	0.50	14.23	0.000	1.64	1.27~2.12
	[residence = 2]	0.12	0.37	0.544	1.13	0.77~1.65
	[residence = 3]	0^b	.	.	.	.
	Age (month)	0.00	5.15	0.023	1.00	0.99~1.00
D	Intercept	-0.84	93.20	0.000		
	[VA = 1]	1.96	190.80	0.000	7.09	5.37~9.37
	[VA = 2]	0.47	37.93	0.000	1.60	1.38~1.86
	[VA = 3]	0^b	.	.	.	.
	[VE = 1]	-0.37	1.24	0.265	0.69	0.36~1.32
	[VE = 2]	0.16	3.26	0.071	1.17	0.99~1.38
	[VE = 3]	0^b	.	.	.	.
	[body shape = 1]	0.36	10.91	0.001	1.43	1.16~1.77
	[body shape = 2]	0.71	47.97	0.000	2.02	1.66~2.47
	[body shape = 3]	0^b	.	.	.	.

Note :0^b Reference

Group	Score	B	Wald value	P	OR	95%CI
	[residence = 1]	-0.59	13.59	0.000	0.55	0.40~0.76
	[residence = 2]	0.44	8.92	0.003	1.56	1.16~2.08
	[residence = 3]	0^b	.	.	.	.
	Age (month)	-0.01	51.03	0.000	0.99	0.99~0.99
Note :0^b Reference						

Discussion

Respiratory tract infections are a series of respiratory system diseases caused by infections resulting from proliferation of pathogenic microorganism. RTIs can be divided into upper respiratory infections and lower respiratory infections, the former one includes rhinitis, pharyngitis, and laryngitis while the latter one includes tracheitis, bronchitis, and pneumonia[12–13]. Possible complications like acute carditis, nephritis, and rheumatism may also happen to a few people. Children, most of whom with weaker immunity, are susceptible to RTIs and may even getting worse to RRTIs. RRTIs are a special form of RTIs which extremely popular in children. Delayed diagnosis or unthoroughly treatment would induce the severe complications and serious impact their healthy growth[14]. Scientists have been studying on the occurrence and development as well as risk factors of RTIs for years, wherein the status of vitamin A and vitamin E in children can be a topic in focus.

Association between vitamin A/E and RRTIs

Several independent reported double-blind, randomized trials indicated that supplement of vitamin A /vitamin E would boost the immunity system of infected patients who suffered from chronic vitamin deficiency [15–17]. Ma et al., set up a case-control study analyzed comparing the acute bronchiolitis group and uninfected/other respiratory disease group, to confirm the association between the infection of acute bronchitis and vitamin A/D level through independent risk factor analysis. Moreover, when using the multi-factor model, they also accidentally find another risk factor, vitamin [18]. Zhang et al studied RRTIs in children aged 0.5–14 in northern China (Harbin) demonstrated that low level of vitamin A/D/E had a positive association with RRTIs in children[19]. The concentration of serum vitamin E lower than 7,85 mg/L can be a risk factor of RRTIs[20]. Our study detected an even lower level of serum vitamin A/E in some young patients, and the vitamin A/E level showed a negative association with symptomatic RRTIs in children. Thus, children should be well fed with a balanced nutrition in their important developmental period to avoid vitamin A/E insufficiency and to prevent the attack of RRTIs.

Vitamin A plays a significant role in supporting body growth and immune response in mammals. Common infectious diseases such as measles, diarrhea and respiratory infection are comprised of different types of immune response[21]. IgA is one of the most important compounds in mucosal immunity system, which is confirmed associating with the respiratory infection[22]. Previous research indicated that vitamin A played a major role in the differentiation of T cells as well as the secretion and class switching of IgA [23–25]. Additionally, airway mucus, a protective barrier to against antigen, was consist of mucoprotein and glycoprotein[26]. Deficiency in vitamin A would impact the expression of mucoprotein and decrease the proliferation of lymphocytes following antigen activation, and indeed decrease the immune response in airway mucus in patient[27]. Besides, scientists had investigated that significant impair of virus-specific IgA and CD8 + T- cells were observed in the airway of vitamin A-deficient mice[28]. These studies demonstrated the deficiency of Vitamin A would reduce the status of immunity, thus increase the probability of infection. In this study, children with high vitamin A level displayed a much lower morbidity of symptomatic RRTIs, and serum vitamin A level showed a negative association with both symptomatic RRTIs and symptomatic acute RTIs, and a mild but not significant correlation with asymptomatic RRTIs in children, which is consist with the hypothesis mentioned before.

Vitamin E, as a lipid-soluble antioxidant, can protect cell membrane and prevent the oxidative damage induced by high metabolism and the accumulation of unsaturated fatty acid [29–30]. Vitamin E is also an important immunomodulator. BouGhanem,E.N. et al demonstrated that α-tocopherol, an active form of vitamin E, is an effective regulator of neutrophils [31]. Neutrophils are the most abundant white blood cells which are considered to be the first barrier attacking infections, including RTIs and RRTIs[32]. Therefore, there might be an association between vitamin E and RRTIs. Our study indicates a lower morbidity of symptomatic RRTIs in individuals with high vitamin E level, which is corresponding with early studies as well. However, it didn't display a significant correlation with asymptomatic RRTIs or symptomatic acute RTIs, which may probably due to the demand of vitamin E in immune response is lower than vitamin A.

Additionally, we also found a mild but not significant effect of age for RRTIs. In addition to the age, the morbidity of RRTIs in obesity or overweight group is also 0.72 ~ 0.73 times higher than normal, which indicate the accumulation of fatty acid may affect the status of immunity. Moreover, the morbidity in rural resident is 3.26 times higher than the citizen, which may probably due to the combination of effects including different economic level, sanity conditions, nutrition supplements, diversification or preference of diet, or different outpatient rate etc.

Further study

In this cross-sectional and analytical study, we enrolled an extremely large sample size, 5780 cases, which is unprecedented in respiratory disease study, which helps decreasing the sampling error and makes the result more convincing. However, there are still some unresolved questions. For example, our study is still hard to specify if the low serum vitamin A/E is the inducer or result of RRTI diseases since it is just a prevalence study focusing on the current status. If the decreasing of serum vitamin A/E is aroused by RRTIs which can be reversed automatically, supplementation of vitamin A/E may not be an effective therapeutic strategy, vice versa. Some presented studies demonstrated that the supplementation of vitamin A didn't produce a substantial reduction in

symptoms or morbidity of respiratory infections[33], only one publication displayed that vitamin A supply would decrease the mortality of young measles patients and decrease the severer status of measly infection, but it didn't work for other respiratory infections [34]. Dibley et al [35] investigated that high dose of supplementary vitamin A would oppositely increase the morbidity of lower respiratory infections, which is extremely significant in nutritionally adequate children. It was also suggested not giving vitamin A to all children to prevent the acute RTIs, except for those who was under nutrition[36]. We assume that the decreasing of serum vitamin A is a consequence of infections due to the consumption of vitamin A by immune response leading to rearrangement of vitamin A in body. But for the malnutritional children, chronic vitamin A deficiency could be an inducer of RRTIs due to the immunodeficiency. Suitable supplementation would assist the disease cure. This assumption could be supported by the research of Grobler et al. They observed that nutrient supplementation for patients with active tuberculosis didn't present any clinically benefits, but their serum vitamin A level increased rapidly following tuberculosis treatment regardless of supplementation[37]. Other scientists also demonstrated that inflammation would affect serum vitamin A level, but it is able to re-normalized without therapeutic intervention[36]. Similarly, the supplementation of vitamin E didn't demonstrate a consistent significant effect to human immunity, opposite effects were observed in some trials[38]. We assume than wavy serum vitamin E level might also due to the spending and replenishment of vitamin E. Once infected, vitamin E in serum would be used to support the regulation of neutrophils resulted in a low vitamin E level, while the reduction would be normalized later through body regulate system. However, assumptions described above are all speculated according to published conclusions and current study. Further exploration is requested to demonstrate the hypothesis by conducting the further cohort-study.

Another unresolved question of this study is if the pathogen of RRTIs associated with serum vitamin in children. Comparing with bacteria, virus induced infections would active different types of immune responses, of which the consumption of vitamins might be different as well. Vitamin A contribute in both T cell differentiation and class switch recombination of antibody expression [23–25], which helps against both bacteria and virus. However, vitamin E contribute more on proliferation and regulation of neutrophils, trending to control bacteria and fungal induced inflammation[39–40]. It is possible that most individuals involved in this study were attacked by virus, which explains the weaker association between RRTIs and vitamin E than the association between RRTIs and vitamin A. Besides, dietary structure of individuals, which may highly affect their physique and the recurrence of serum vitamin, is not included in this study as well.

In later cohort studies, we would like to monitor the immunity status, such as lymphocytes cell level or neutrophils level, as well as serum vitamin level in children with RRTIs to further investigate the mechanism of vitamins and its association between RRTIs. Patients infected by different pathogens would be classified and analyzed in different groups, and the relationship between different vitamins, pathogens and immune responses would be summarized and concluded. Other vitamins such as vitamin C and vitamin D would be considered to investigate if they display similar association with RRTIs. Optimized grading and classification criteria would be used. For instance, thin and emaciation group would be added when classify individuals through BMI, and residential environment could be graded based on the residential area and the hygiene status. Additional aimed risk factors, such as dietary structure and racism, would be included in the study as well. A comprehensive statistical logistic regression model would be set up to better investigate the risk factors of RRTIs.

Conclusion

Vitamin A and vitamin E level are negative risk factors of pediatric RRTIs. Their deficiency especially vitamin A deficiency are strongly associated with the disease morbidity. Body mass index is the positive risk factor of RRTIs, i.e. RRTIs are more frequently observed in children with overweight or obesity. Besides, the residential quality also related to the development of RRTIs as well. Consequently, in future governmental children health program, monitoring serum vitamin A and vitamin E level through periodically physical exanimation, evaluating the nutrition status of vitamin A/E objectively, screening out children suffering from long-term nutrition deficiency and supplying them adequate amount of vitamin though balanced diet or nutrition supplements can be valuable and worth popularized. Children should routinely do exercise and have less greasy food for a good body shape, they should also pay more attention on their personal hygiene to keep a healthy lifestyle.

Abbreviations

Recurrent respiratory tract infections
RRTIs
Respiratory tract infection
RTI
Body Mass Index
BMI
Odd Ratio
OR

Declarations

Ethics approval and consent to participate: This research is approved by the Ethics Committee of Capital Institute of Pediatrics, with the ethics batch number of SHERLL2015001.Participants and participants' family were informed during the investigation, and children's parents have provided signed informed consent for research enrollment and data accessibility. **Consent for publication:** The authors declare that they consent for publication.

Availability of data and materials: we state that data will be shared.

Competing interest: The authors declare that they have no competing interests.

Fund： Not applicable.

Authors Contributions: XW,CJ and XL conceived the study design, conceptualized the ideas, and supervised the whole analytical procedure. JW,JW,LZ,NL,NJ and WS contributed to data collection and manuscript writing. XW and XL also provided technical support for drafting and revising the manuscript. All authors have read and approved the manuscript.

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Figures

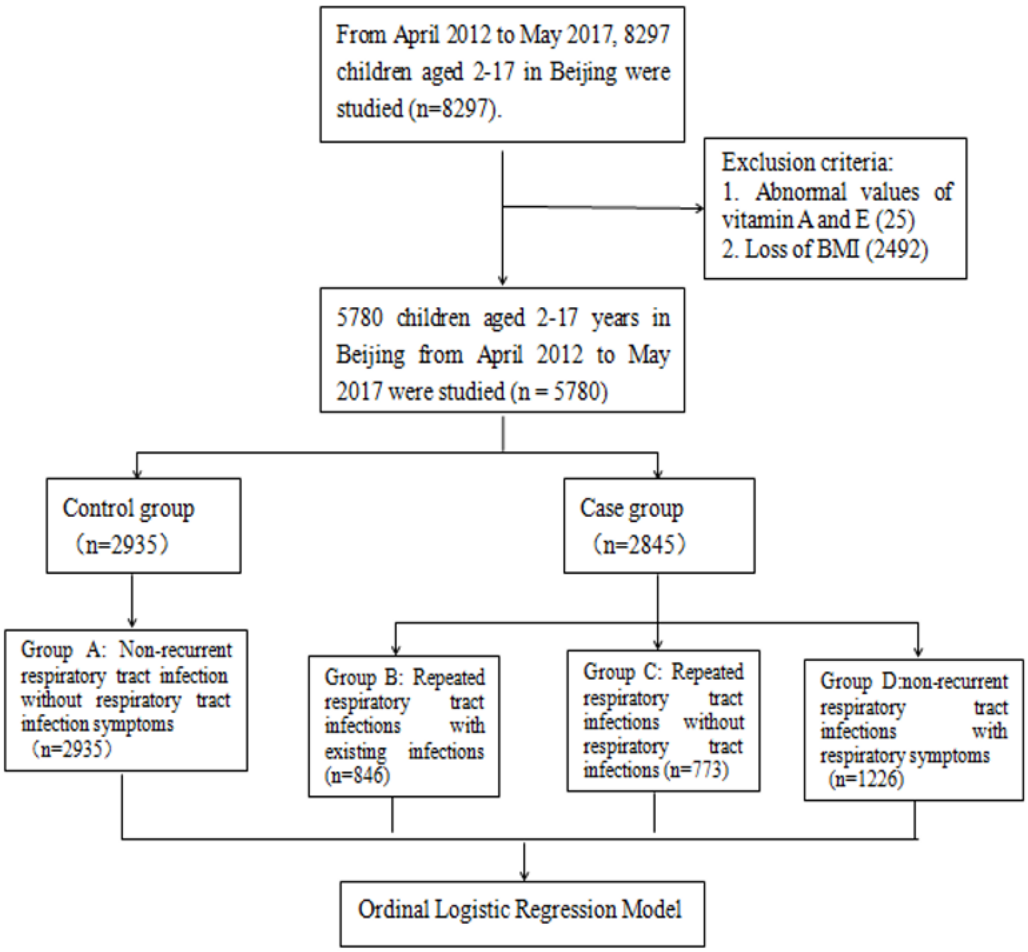

Figure 1

Flow chart of research strategy investigating the effect of serum vitamin A/E on Recurrent Respiratory Tract Infections in children aged 2 to 17 years in Beijing

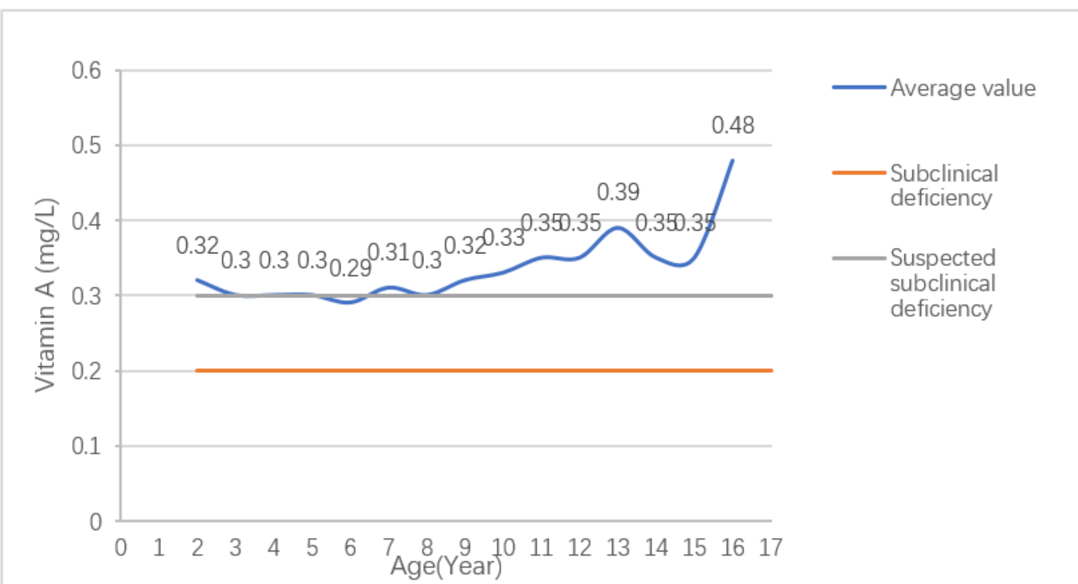

Figure 2

Concentration of serum vitamin A along age distribution in children aged 2-17 in Beijing

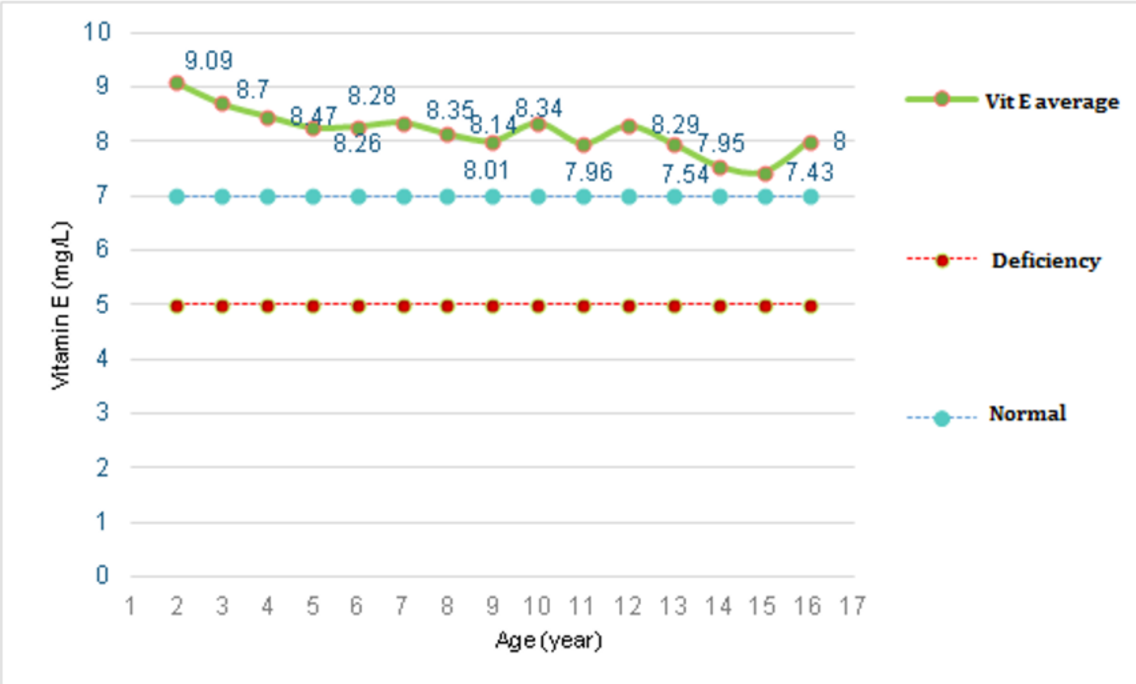

Figure 3

Concentration of serum vitamin E along age distribution in children aged 2-17 in Beijing

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