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Association of antibiotics use in preschool age with atopic and allergic skin diseases in young adulthood

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Association of antibiotics use in preschool age with atopic and allergic skin diseases in young adulthood

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Abstract

Background: Overuse and misuse of antibiotics is a public health problem in low- and middle-income countries. Although the association of antibiotics with atopic and allergic diseases has been established. most studies focused on prenatal exposure and the occurrence of disease in infants or young children.

- Objective: To investigate the association of preschool use of antibiotics with atopic and allergic skin diseases in young adulthood for the association of antibiotics use with eczema.
- Design: Population-based retrospective cohort.

Setting and participants: The first-year college students (n=20138) from five universities were investigated. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively.

Methods: We conducted a dermatological field examination and a questionnaire survey inquiring the participants about frequency of upper respiratory tract infection (URTI) and the preschool antibiotics use (prior to 7 years old). The two-level Probit model was used to estimate the associations, and adjusted risk ratio (aRR) and 95% confidence interval (CI) were presented as the effect size.

Results: A total of 20138 participants with complete information was included in the final analysis. The frequent antibiotics use intravenously (aRR 1.36, 95% CI 1.14–1.62) and orally (aRR 1.18, 95% CI 1.01–1.38) prior to 7 years old was significantly associated with atopic dermatitis in young adulthood. Similar trends could be observed in allergic skin diseases among those who use antibiotics orally and intravenously, with RRs of 1.16 (1.01, 1.34) and 1.33 (1.13, 1.57), respectively.

Conclusions: Preschool URTI and antibiotics use significantly increases the risk of atopic and allergic skin diseases in young adulthood.

- Strengths and limitations of this study
 - The main outcomes were diagnosed by specialists instead of self-report. •
 - This study provides a relatively large and representative sample, and sufficient variations in • geographic regions and sociodemographic subgroups, as well as the random effect at the university level was fitted by the 2-level models, resulting in an unbiased estimation of associations.
 - Recall bias in the measurement of exposure to antibiotics might have been introduced, which • could not be ignored in most retrospective studies.
 - We lacked the information about the type and dose of antibiotics, and there might be a reversed causal relationship because antibiotics could be used in the treatment of AD and other conditions accompanied by a bacterial infection.

Introduction

The incidence and prevalence of atopic and allergic conditions such as asthma, allergic rhinitis, food allergies, and atopic dermatitis (AD) among the worldwide population have significantly increased during the past several decades.[1-3] An area of environmental change that may be responsible for the increase of allergic and atopic diseases is the growing use of medications which may alter the development of human microbiome.[4] It also seems that use of some antibiotics, which can directly cause intestinal dysbiosis and affect human microbiome and increase the risk for allergy development, is of particular concern in light of accumulating evidence.[5-7]

Furthermore, overuse and misuse of antibiotics is a severe public health problem worldwide, especially in low- and middle-income countries. In the last decade, prescriptions of broad-spectrum antibiotics increased by 49% in children under five years and doubled in children aged 5–17 years, concomitant with the increasing prevalence of allergic diseases.[8, 9] In China, 70% of outpatients attending primary care facilities with colds were inappropriately treated with antibiotics, often by intravenous infusion. The situation is even worse in children because many parents demand treatment with antibiotics[10]. However, most upper respiratory tract infections (URTI) in children are viral, for which antibiotics are unnecessary.[11-13]

The association between the use of antibiotics and atopic and allergic diseases has been observed in longitudinal studies. But most studies focused on antibiotics use during pregnancy or infancy when early colonization is initiated by maternal microbes.[14-17] With the childhood microbiome transition owing to alterations in food and exposure to more diverse microbes in external environments, children in preschool age (<7 yrs) are at higher risks of URTI infection and antibiotics treatment. However, the effect of antibiotics used during this period on atopic and allergic skin diseases that occurred in their young adulthood is not clear. The objective of this study was to evaluate the hypothesis that exposure to antibiotics in preschool age is associated with an increased risk of allergic and atopic skin diseases in young adulthood. We tested this hypothesis by conducting a retrospective study in college students.

- **Materials and Methods**
- Study setting and design 2.1

This was a retrospective cohort study based on the data from the China College Student Skin Health Study (CCSSHS)[18]. The first-year college students from five universities were investigated. They underwent a health examination and completed a questionnaire survey. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively. The medical ethics committee of Xiangya Hospital, Central South University, approved the study (#201709993).

2.2 **Exposure** assessment

Two semi-quantitative questions served as the proxy measures of the frequency of antibiotics exposure in preschool age, with detailed explanations for the definitions of URTI and antibiotics. In our study, the definition of URTI refers to a series of acute illnesses that have an effect on the upper respiratory system including the common cold, acute otitis media, tonsillitis/tonsillopharyngitis, sinusitis and recurrent sinusitis.[19] The first question was "How often did you have URTI in your preschool age or before 7 years old", with three potential responses: ≤ 1 time/year, 2-3 times/year", and "4 or more

- 96 times/year". The second question was "How often did you receive antibiotics treatment when you had
 - a URTI", with four responses: "rare", "occasional", "often, orally; and "often, intravenously".

98 2.3 Outcome assessment

Diagnosis of skin diseases and inquiry of disease history were performed by dermatologists during the field survey. All subjects underwent skin examination by resident doctors in dermatology, and the diagnoses were further validated by senior dermatologists. Clinical manifestation, disease history, and family history were inquired about, and inspections were conducted to diagnose skin diseases. For recurrent skin diseases, only those with current symptoms and cutaneous lesions were diagnosed as cases. AD was diagnosed according to the Williams criteria.[20] Hand eczema was diagnosed according to eczema (rash) on the fingers, finger webs, palms, or back of hands, which had appeared once and continued for at least two weeks or had appeared several times or had been persistent. Allergies and urticaria were diagnosed by clinical manifestations, potential triggers, and histories. Asthma, allergic rhinitis, and allergic conjunctivitis were self-reported according to doctors' diagnoses. We also combined some of the outcomes. Atopic march is an apparent progression of allergic diseases from AD, to allergic asthma (AA) to allergic rhinitis (AR) and allergic conjunctivitis. [21, 22] We include the conditions of AD, AA, AR, and allergic conjunctivitis for the outcome of the atopic march. Allergic skin disease includes allergic reactions to food/drug/light, contact dermatitis, and urticaria. Participants with a history of atopic/allergic conditions but without the current disease are excluded.

²⁵₂₆ 114 **2.4 Covariates**

Demographic characteristics, socioeconomic status (annual family income and parental highest
 educational level), family history, behavioral factors (dietary and bathing habits) were inquired by the
 questionnaire.

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Categorical data were presented as number (%), and the between-group difference was tested using the chi-square test. Two-level Probit regression models (individual as level 1 and university as level 2) were used to estimate the associations of preschool exposure to antibiotics with atopic skin diseases in young adulthood, adjusting for level-1 covariates (gender, ethnicity, annual household income and parental education) and level-2 random effects. The effect size was presented as relative risk (RR) and 95% confidence interval (CI). P< 0.05 was considered statistically significant for all tests. Statistical analysis was performed in SAS 9.4 (SAS Institute Inc., Cary, USA).

43 126 **3 Results**

A total of 27144 registries for new enrolment was identified; among them, 21086 (77.7%) consented to participate, and 20138 (74.2%) who underwent the health examination and completed the online questionnaire survey were included in the final analyses. The mean age was 18.3 ± 0.8 years and 10289(51.1%) were men. The characteristics of participants in the study are shown in the Table 1. The prevalence rates of chronic urticaria, allergic reactions to food/drug/light, hand eczema, and AD were 1.89%, 2.27%, 3.35%, and 3.86%, respectively. The prevalence rates of AD and allergic skin disease were 3.86 % and 4.14%, respectively (Figure 1 and Table S1).

In general, URTI and the use of antibiotics were significantly associated with atopic and allergic
 diseases dose-dependently (Figure 1 and Table S1). For example, the prevalence of AD increased from
 3.39% to 4.11% and 4.79% in participants who reported rare or occasional use, frequent oral use, and

- frequent intravenous use of antibiotics, respectively. Consistent trends could be observed in all atopic
 and allergic diseases and their combinations
- ³ 138 and allergic diseases and their combinations.

After adjustments for sociodemographic factors (Figure 2 and Table S2), URTI and the use of antibiotics were significantly associated with atopic/allergic skin diseases in dose-response manners. For instance, compared to those reporting rare or occasional use of antibiotics, the RRs for AD in participants who reported frequent oral administration and intravenous injection of antibiotics was 1.18 (95% CI: 1.01, 1.39) and 1.36 (95% CI: 1.14, 1.62), respectively. For other allergies or atopic disease of skin or beyond skin, the correlations were highly consistent despite some variations in the magnitude of the association.

Because our study was not a prospective cohort, it was difficult to know if antibiotic use was ahead of suffering from AD. We further evaluated the joint effect of URTI and antibiotics on AD by including an interaction term in the model. As shown in Figure 3, in each category of antibiotic use, the frequency of URTI was positively associated with the risk of AD. Vice versa, in each category of URTI, antibiotic use was positively associated with AD according to the effect size, despite some insignificant results in categories with a small sample size.

²² 152 **4 Discussion**

This retrospective cohort study demonstrated that preschool exposure to antibiotics, either through oral
 administration or intravenous infusion, was associated with increased risks of having allergic and
 atopic skin diseases in young adulthood. Participants who reported frequent URTI in preschool-age
 also had higher risks of allergies and atopy.

Similar trends were identified in previous observational studies that early-life antibiotic use was associated with an increased risk of eczema, but there were still some inconsistent results.[23, 24] Meta-analysis including 22 studies with 394,517 patients concluded that children with antibiotics exposure in the first two years had increased odds of atopic eczema with an OR of 1.26 (95%CI: 1.15-1.37). Notably, the onset age of the outcomes in the included studies was the period of childhood (<12) vears old). [7] A large population-based retrospective cohort study in twins showed that antibiotic use was also associated with an increased risk of eczema; however, it is likely that the relationship between early-life antibiotic use and eczema was confounded by shared familial environment and genetic factors.[25] However, current data lacked the information regarding the atopic and allergic skin diseases occurred in late adolescence to early adulthood, while we firstly investigated the effects of preschool antibiotic in a retrospective study and revealed a positive association.

Evidence showed that AD was the first manifestation of an atopic phenotype which begins in early childhood and the progression from AD to the diseases such as food allergy, asthma, and allergic rhinitis were more likely to be shown in adolescence.[22, 26, 27] The mechanisms behind the march from AD to allergic airway diseases and allergic conjunctivitis likely arise from initial epicutaneous allergen sensitization inducing robust local and systemic type 2 immune responses with increased production of type 2 cytokines including interleukin (IL)-4, IL-13, IL-31, and thymic stromal lymphopoietin. [28, 29] Most studies were prone to make these responses responsible for the commonly shared pathogenesis of cutaneous, airway, and conjunctiva inflammation, supporting the view that AD is not merely a disease confined to the skin, but is in fact, a systemic disease.[30, 31] Therefore, it could be explained that the increased risks beyond skin manifestations in young adulthood were consistent with those of skin diseases and some with even greater effect sizes. While not fully understood, the underlying mechanism of the association between antibiotics and atopic and allergic

diseases can be elucidated by microbial diversity. The gut microbial community is dynamic and variable during the first 3 years of life, before stabilizing to an adult-like state.[32] Studies have demonstrated continued development through childhood into the teenage years.[33, 34] Dietary intake plays a key role in the development period of the gut microbiome. Breast-fed infants have microbiota enriched in Lactobacillus, Staphylococcus, and Bifidobacterium. Studies have shown that human milk symbiotic and potentially probiotic isolates contain microbes. and supplementation of *Bifidobacteria* was found to be effective in primary preventing allergic diseases.[35-37] But among children of preschool age, the dominance of *Bifidobacterium* diminishes with the alteration in dietary intake.[15] On the other hand, the high prevalence of antibiotic use may also lead to a concurrent increase in antibiotic-resistant bacteria.[38, 39] Antibiotic-treated children have a less diverse gut microbiota and less stable communities. Antibiotic therapy affects microbiome variety and thus may increase the risk of atopic diseases.[40, 41]

In our study, increased risks of atopic march or allergic diseases were observed in students who reported frequent URTI. Another potential explanation was related to the infections which could also affect microbial conditions. Except for the change in diet, children of preschool age tend to be exposed to more diverse microbes and infectious diseases including URTI in kindergarten or external environments. Respiratory viral infections, in particular, have been shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut, [42] which could further shape atopic microenvironments.

Several limitations should be noted, and the results should be interpreted with caution. First, recall bias in the measurement of exposure to antibiotics might have been introduced. While recall bias on the frequency of antibiotics use and URTIs should not be ignored, this is a limitation in most retrospective studies. Second, there was a lack of information about the type and dose of antibiotics, and we could not attribute the association to specific antibiotics. Third, there might be a reversed causal relationship, because antibiotics could be used in the treatment of AD and other conditions accompanied by bacterial infection. Last but not least, we assessed the role of URTI and antibiotics separately, because the two variables were significantly correlated (contingency coefficient=0.4, P < 0.001) and were therefore not included in the same model to avoid collinearity and biased estimation of parameters. It is possible that the association of URTI with AD and allergies is confounded by antibiotics, and vice versa.

However, both infection and antibiotics may be correlated with allergies/atopies, with different mechanisms. Although under the hygiene hypothesis, exposure to pathogens during infancy and early childhood has been proposed to explain the lower prevalence of asthma and other atopic diseases among children in developing countries, [43, 44] some studies showed that early respiratory infections could not protect against atopic eczema or recurrent wheezing, but could drive the development of atopic disease. [45-49] Atopic sensitization, a process of generation of specific immunoglobulin E (sIgE) when exposed to an innocuous antigen, was common to all allergic diseases. As preschool URTI most probably represent viral infections in the majority of cases, some studies investigated a potential mechanistic explanation for how a respiratory viral infection could drive the development of atopic sensitization and disease. Martorano et al. used a Sendai virus to establish the mouse model mimicking a human limited respiratory syncytial virus infection and found that Sendai virus infection could promote the crosslinking of high-affinity IgE receptor (FceRI) on the lung conventional dendritic cells (cDC), which led to the production of the chemokine CCL28, recruiting IL-13 and driving the development of mucous cell metaplasia and airway hyperreactivity.[50] Another animal study found that except for the increase of sIgE against Sendai virus in mice, there was also a large increase in total IgE and it remained elevated long after the viral infection being resolved.[51] This notion has further been fuelled by findings that mice infected with flu virus developed virus-specific mast cell

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degranulation in the skin, indicating a possible pathway of viral infections that could mediate allergic symptoms.[52] Besides, the respiratory viral infections were shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut.[42, 53] However, we cannot ignore that infections that do not require antibiotics are not captured in our design, such that it is difficult to assess whether the observed association is caused by a specific infection or antibiotics because they occur simultaneously in many cases.

Our study also has strengths. The primary strength is that the sample size for the retrospective cohort study was large. Second, the outcomes were diagnosed by specialists. In contrast, some previous studies used self-reported diagnoses that might introduce misclassification bias. Third, the study had a relatively large and representative sample, and sufficient variations in geographic regions and sociodemographic subgroups. The random effect at the university level was fitted by the 2-level models, resulting in an unbiased estimation of associations.

To conclude, preschool children exposed to URTI or antibiotics may be at higher risks of atopic and allergic skin diseases in their young adulthood, especially among those who frequently had URTI or received antibiotics by intravenous infusion. Our study implies that unnecessary antibiotics treatment in children should be avoided to prevent the occurrence of atopic and allergic diseases in their later life. Prospective studies that consider the type and dose of antibiotics are warranted.

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This study was conducted according to the guidelines established in the Declaration of Helsinki. All procedures involving patients were approved by the institutional research ethics boards of Xiangya Hospital, Central South University (Changsha, China). Informed consent was obtained from all the

Dr. Minxue Shen, Dr. Xiang Chen, and Dr. Yi Xiao are joint corresponding authors and have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy

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Data Availability Statement 5

Ethics statement

students before the investigation.

Author contributions

Drafting of the manuscript: Y.J. Li

Concept and design: Shen, Chen, and Xiao.

Statistical analysis: Shen, Xiao, and Y.J. Li.

of the data analysis.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supervision: Chen **Conflict of interest** The authors declare no conflict of interest.

Acquisition, analysis, or interpretation of data: Y.J. Li, Jing, and Huang

Critical revision of the manuscript for important intellectual content: All authors.

Administrative, technical, or material support: Su, J. Li, Tao, Shan, Wang, Kang, and

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Figure legends

- Figure 1. The prevalence of atopic and allergic diseases in exposure vs. non-exposure group of antibiotics and URTI.
- Figure 2. Association of early-life exposure to antibiotics with the risk of atopic/allergic diseases later in life. RR: risk ratio; CI: confidence interval.

Figure 3. The joint effect of URTI and antibiotics on AD after including an interaction term in the model. RR: risk ratio; CI: confidence interval.

Supplementary file captions

- Table S1. The prevalence of atopic and allergic diseases in college students.
- tic and UR1. Table S2. Association of antibiotic and URTI exposure with atopic and allergic diseases in college students.

Characteristics	Ν	%
Gender		
Male	10289	51.1
Female	9849	48.9
Income (CNY)		
<10,000	2169	10.8
10,000–29,999	4378	21.7
30,000–49,999	3470	17.2
50,000–99,999	4419	21.9
100,000–199,999	4065	20.2
≥200,000	1637	8.1
Parental highest		
Primary school	2288	11.5
Middle school	5557	28
High school	4782	24.1
College and above	7233	36.4
Ethnicity		
Han Chinese	16230	80.6
Other ethnicities	3908	19.4
		4

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Frequency of URTI

Rare

Occasional

Frequent

15.0

Use of antibiotics

Rare / occasional

Often, intravenously

9.47

25.0

20.0

Often, orally

3.79

4.45

5.0

10.0

Prevalence (%)

15.0

1.08

0.61

Atopic dermatitis

Allergic reactions to

food/drug/light

Allergic skin disease

Chronic urticaria

Allergic rhinitis

Allergic conjunctivitis

Atopic march

Asthma

0.0

5.0

10.0

Prevalence (%)

Skin

Beyond skin

Hand eczema



20.0

22.34

25.0 0.0

The prevalence of atopic and allergic diseases in exposure vs. non-exposure group of antibiotics and URTI.

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4.0

5.0

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BMJ Open BMJ Open Supplementary file captions Table S1. The prevalence of atopic and allergic diseases in college students. Table S2. Association of antibiotic and URTI exposure with atopic and allergic diseases in college students and data m . diseases in college students. .1 exposure with atopic and allergic dise.

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S1. The prevalence of	atopic and allergic	diseases in coll	ege students URTI, %		n 21 Sep ling for	Antibiotics, %	
Disease	Prevalence ^a	Rare	Occasional	Frequent	uses Enseigr Kategor eiser	Often, or ally	Often, intravenou
Skin					2021 heme		
Atopic dermatitis	3.86	2.99	3.99	5.1	to the So ^{3.39}	4.11	4.79
Hand eczema	3.35	2.49	3.54	4.38	xt an D3.01	3.79	3.57
Allergic reactions to food/drug/light	2.27	2.08	2.22	2.85	aded ieur (AB d data n	2.37	2.69
Chronic urticaria	1.89	1.65	1.8	2.78	ninin 1.65	2.08	2.28
Allergic skin disease ^b	4.14	3.73	4	5.56		4.45	4.88
Beyond skin					omjo I trair		
Atopic march ^c	15.6	11.79	15.88	22.34	11 1 3 . 33	17.19	19.47
Allergic conjunctivitis	0.76	0.55	0.73	1.32	and 0.61	0.84	1.05
Allergic rhinitis	15.6	8.34	11.55	16.39	simi 9 .56	12.63	14.03
Asthma	1.51	0.79	1.49	3.06	art 0,1.08	1.83	2.19

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ic and URTI expo	sure with atopic and a	allergic diseases in c	ollege standents				
	URTI, aRR (95%CI) ^a			or % Antibiotics, aRR (95%CI) a			
Rare	Occasional	Frequent	Rare occasional	Often, orally	Often, intravenously		
			elater				
Reference	1.32 (1.09, 1.54)	1.59 (1.27, 1.98)	Reference	1.18 (1.01, 1.39)	1.36 (1.14, 1.62)		
Reference	1.32 (1.08, 1.56)	1.60 (1.26, 2.02)	Reference	1.27 (1.08, 1.49)	1.17 (0.95, 1.44)		
Reference	1.10 (0.92, 1.28)	1.30 (1.04, 1.63)	Reference	1.15 (0.97, 1.37)	1.36 (1.12, 1.65)		
Reference	0.97 (0.76, 1.17)	1.58 (1.21, 2.05)	ar C d Retermence	1.13 (0.90, 1.40)	1.39 (1.09, 1.78)		
Reference	1.04 (0.89, 1.20)	1.46 (1.22, 1.76)	Res ance	1.16 (1.01, 1.34)	1.33 (1.13, 1.57)		
			g, Al				
Reference	1.39 (1.26, 1.52)	2.08 (1.85, 2.34)	Reference	1.35 (1.24, 1.48)	1.55 (1.40, 1.71)		
Reference	1.89 (1.13, 2.66)	3.49 (2.05, 5.96)	Reference	1.58 (1.08, 2.32)	2.72 (1.75, 4.23)		
Reference	1.43 (1.27, 1.59)	2.13 (1.86, 2.43)	Reference	1.39 (1.26, 1.53)	1.56 (1.39, 1.74)		
Reference	2.56 (1.69, 3.43)	4.89 (3.20, 7.47)	Reference	1.92 (1.52, 2.43)	2.10 (1.64, 2.70)		
ergic reactions to for matitis, allergic ast	bod/drug/light, contact hma, allergic rhinitis, a	dermatitis, and urtica	vitis. vitis.				
	Rare Reference Reference	c and URTI exposure with atopic and a URTI, aRR (95%CI) aRareOccasionalReference1.32 (1.09, 1.54)Reference1.32 (1.08, 1.56)Reference1.10 (0.92, 1.28)Reference0.97 (0.76, 1.17)Reference0.97 (0.76, 1.17)Reference1.04 (0.89, 1.20)Reference1.39 (1.26, 1.52)Reference1.89 (1.13, 2.66)Reference1.43 (1.27, 1.59)Reference2.56 (1.69, 3.43)gender, income, education, and ethnicity a ergic reactions to food/drug/light, contact matitis, allergic asthma, allergic rhinitis, a	c and URTI exposure with atopic and allergic diseases in c URTI, aRR (95%CI)* Rare Occasional Frequent Reference 1.32 (1.09, 1.54) 1.59 (1.27, 1.98) Reference 1.32 (1.08, 1.56) 1.60 (1.26, 2.02) Reference 1.32 (1.08, 1.56) 1.60 (1.26, 2.02) Reference 0.97 (0.76, 1.17) 1.58 (1.21, 2.05) Reference 0.97 (0.76, 1.17) 1.58 (1.21, 2.05) Reference 1.04 (0.89, 1.20) 1.46 (1.22, 1.76) Reference 1.39 (1.26, 1.52) 2.08 (1.85, 2.34) Reference 1.89 (1.13, 2.66) 3.49 (2.05, 5.96) Reference 1.43 (1.27, 1.59) 2.13 (1.86, 2.43) Reference 2.56 (1.69, 3.43) 4.89 (3.20, 7.47) gender, income, education, and ethnicity and the random effect ergic reactions to food/drug/light, contact dermatitis, and urtical matitis, allergic asthma, allergic rhinitis, and allergic conjunction	and URTI exposure with atopic and allergic diseases in college shorters URTI, aRR (95%CI)* Rare Occasional Frequent Rare Reference 1.32 (1.09, 1.54) 1.59 (1.27, 1.98) Reference Reference Reference 1.32 (1.09, 1.54) 1.59 (1.27, 1.98) Reference Reference Reference 1.32 (1.08, 1.56) 1.60 (1.26, 2.02) Reference Reference Reference 1.01 (0.92, 1.28) 1.30 (1.04, 1.63) Reference Reference Reference 0.97 (0.76, 1.17) 1.58 (1.21, 2.05) Reference Reference Reference 1.39 (1.26, 1.52) 2.08 (1.85, 2.34) Reference Reference Reference 1.39 (1.26, 1.52) 2.08 (1.85, 2.34) Reference Reference Reference 1.43 (1.27, 1.59) 2.13 (1.86, 2.43) Reference Reference Reference 2.56 (1.69, 3.43) 4.89 (3.20, 7.47) Reference Reference Reference 2.56 (1.69, 3.43) 4.89 (3.20, 7.47) Reference Reference Reference 2.56 (1.69, 3.43) 4.89 (3.20, 7.47) Reference Referen			

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Association of antibiotics use in preschool age with atopic and allergic skin diseases in young adulthood: A populationbased retrospective cohort study.

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Association of antibiotics use in preschool age with atopic and allergic skin diseases in young adulthood: A population-based retrospective cohort study. Yajia Li, M.A student¹, Danrong Jing, Ph.D. student¹, Yuzhou Huang, Ph.D. student¹, Juan Su, Ph.D.¹, Ji Li, Ph.D.¹, Juan Tao, Ph.D.², Shijun Shan, Ph.D.³, Xiaohui Wang, Ph.D.⁴, Xiaojing Kang, Ph.D.⁵, Bin Wu, Ph.D.⁶, Yi Xiao, Ph.D.^{1*}, Xiang Chen, Ph.D.^{1*}, Minxue Shen, Ph.D.^{1,7*} ¹Department of Dermatology; Hunan Engineering Research Center of Skin Health and Disease; Hunan Key Laboratory of Skin Cancer and Psoriasis, Xiangya Hospital, Central South University, Changsha, China ²Department of Dermatology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China ³Department of Dermatology, Xiang'an Hospital, Xiamen University, Xiamen, China ⁴Department of Dermatology, Zhongshan Hospital, Xiamen University, Xiamen, China ⁵Department of Dermatology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumchi, Xinjiang, China ⁶Department of Dermatology, People's Hospital, Inner Mongolia Medical University, Hohhot, China ⁷Department of Social Medicine and Health Management, Xiangya School of Public Health, Central South University, Changsha, China *Correspondence: Minxue Shen, Xiang Chen and Yi Xiao Address: Xiangya Hospital, 87 Xiangya Road, Changsha, Hunan, China 410008 Email: shenmx1988@csu.edu.cn (M.S.), chenxiangck@126.com (X.C.) and xiaoyixy@csu.edu.cn (Y.X.)Keywords: antibiotics, atopic and allergic skin diseases, preschool and young adulthood.

Background: Overuse and misuse of antibiotics is a public health problem in low- and middle-income

countries. Although the association of antibiotics with atopic and allergic diseases has been established,
 most studies focused on prenatal exposure and the occurrence of disease in infants or young children.

- 30 Objective: To investigate the association of preschool use of antibiotics with atopic and allergic skin diseases in young adulthood for the association of antibiotics use with eczema.
- 13 32 Design: Population-based retrospective cohort.

Setting and participants: The first-year college students (n=20123) from five universities were investigated. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively.

36 Methods: We conducted a dermatological field examination and a questionnaire survey inquiring the
 37 participants about the frequency of upper respiratory tract infection (URTI) and the preschool
 38 antibiotics use (before 7 years old). The two-level Probit model was used to estimate the associations,
 39 and adjusted risk ratio (aRR) and 95% confidence interval (CI) were presented as the effect size.

Results: A total of 20123 participants with complete information was included in the final analysis. The frequent antibiotics use intravenously (aRR 1.36, 95% CI 1.14–1.62) and orally (aRR 1.18, 95% CI 1.01–1.39) before 7 years old was significantly associated with atopic dermatitis in young adulthood. Similar trends could be observed in allergic skin diseases among those who use antibiotics orally and intravenously, with RRs of 1.16 (1.01, 1.34) and 1.33 (1.13, 1.57), respectively.

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- ³⁸ 47 Strengths and limitations of this study
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 - The main outcomes were diagnosed by specialists instead of self-report.
 - This study provides a relatively large and representative sample, and sufficient variations in geographic regions and sociodemographic subgroups, as well as the random effect at the university level, was fitted by the 2-level models, resulting in an unbiased estimation of associations.
 - Recall bias in the measurement of exposure to antibiotics might have been introduced, which could not be ignored in most retrospective studies.
 - We lacked the information about the type and dose of antibiotics, and there might be a reversed causal relationship because antibiotics could be used in the treatment of AD and other conditions accompanied by a bacterial infection.

59 1 Introduction

The incidence and prevalence of atopic and allergic conditions such as asthma, allergic rhinitis, food allergies, and atopic dermatitis (AD) among the worldwide population have significantly increased during the past several decades.[1-3] An area of environmental change that may be responsible for the increase of allergic and atopic diseases is the growing use of medications that may alter the development of the human microbiome.[4] It also seems that the use of some antibiotics, which can directly cause intestinal dysbiosis and affect the human microbiome and increase the risk for allergy development, is of particular concern in light of accumulating evidence.[5-7]

Furthermore, overuse and misuse of antibiotics is a severe public health problem worldwide, especially in low- and middle-income countries. In the last decade, prescriptions of broad-spectrum antibiotics increased by 49% in children under five years and doubled in children aged 5-17 years, concomitant with the increasing prevalence of allergic diseases.[8, 9] In China, 70% of outpatients attending primary care facilities with colds were inappropriately treated with antibiotics, often by intravenous infusion. The situation is even worse in children because many parents demand treatment with antibiotics[10]. However, most upper respiratory tract infections (URTI) in children are viral, for which antibiotics are unnecessary.[11-13]

The association between the use of antibiotics and atopic and allergic diseases has been observed in longitudinal studies. But most studies focused on antibiotics use during pregnancy or infancy when early colonization is initiated by maternal microbes.[14-17] With the childhood microbiome transition owing to alterations in food and exposure to more diverse microbes in external environments, children in preschool age (<7 yrs) are at higher risks of URTI infection and antibiotics treatment. However, the effect of antibiotics used during this period on atopic and allergic skin diseases that occurred in their young adulthood is not clear. The objective of this study was to evaluate the hypothesis that exposure to antibiotics in preschool age is associated with an increased risk of allergic and atopic skin diseases in young adulthood. We tested this hypothesis by conducting a retrospective study on college students.

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42852Materials and Methods

86 2.1 Study setting and design

This was a retrospective cohort study based on the data from the China College Student Skin Health Study (CCSSHS)[18]. The first-year college students from five universities were investigated. They underwent a health examination and completed a questionnaire survey. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively. The medical ethics committee of Xiangya Hospital, Central South University, approved the study (#201709993).

92 2.2 Exposure assessment

Two semi-quantitative questions served as the proxy measures of the frequency of antibiotics exposure
 in preschool age, with detailed explanations for the definitions of URTI and antibiotics. In our study,

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the definition of URTI refers to a series of acute illnesses that have an effect on the upper respiratory system including the common cold, acute otitis media, tonsillitis/tonsillopharyngitis, sinusitis, and recurrent sinusitis.[19] The first question was "How often did you have URTI in your preschool-age or before 7 years old", with three potential responses: ≤1 time/year, 2-3 times/year", and "4 or more times/year". The second question was "How often did you receive antibiotics treatment when you had

- a URTI", with four responses: "rare", "occasional", "often, orally; and "often, intravenously".
- 11 101 **2.3 Outcome assessment**

Diagnosis of skin diseases and inquiry of disease history were performed by dermatologists during the field survey. All subjects underwent skin examination by resident doctors in dermatology, and the diagnoses were further validated by senior dermatologists. Clinical manifestation, disease history, and family history were inquired about, and inspections were conducted to diagnose skin diseases. For recurrent skin diseases, only those with current symptoms and cutaneous lesions were diagnosed as cases. AD was diagnosed according to the Williams criteria.[20] Hand eczema was diagnosed according to eczema (rash) on the fingers, finger webs, palms, or back of hands, which had appeared once and continued for at least two weeks or had appeared several times or had been persistent. Allergies and urticaria were diagnosed by clinical manifestations, potential triggers, and histories. Asthma, allergic rhinitis, and allergic conjunctivitis were self-reported according to doctors' diagnoses. We also combined some of the outcomes. Atopic march is an apparent progression of allergic diseases from AD, to allergic asthma (AA) to allergic rhinitis (AR) and allergic conjunctivitis. [21, 22] We include the conditions of AD, AA, AR, and allergic conjunctivitis for the outcome of the atopic march. Allergic skin disease includes allergic reactions to food/drug/light, contact dermatitis, and urticaria. Participants with a history of atopic/allergic conditions but without the current disease are excluded.

117 2.4 Covariates

³⁶ 118 Demographic characteristics, socioeconomic status (annual family income and parental highest
 ³⁷ 119 educational level), family history, behavioral factors (dietary, passive smoking, and bathing habits)
 ³⁹ 120 were enquired by the questionnaire.

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 2.5 Statistical analysis

Categorical data were presented as number (%), and the between-group difference was tested using the chi-square test. Two-level Probit regression models (individual as level 1 and university as level 2) were used to estimate the associations of preschool exposure to antibiotics with atopic skin diseases in young adulthood, adjusting for level-1 covariates (gender, ethnicity, annual household income, and parental education) and level-2 random effects. The effect size was presented as relative risk (RR) and 95% confidence interval (CI). P< 0.05 was considered statistically significant for all tests. Statistical analysis was performed in SAS 9.4 (SAS Institute Inc., Cary, USA).

⁵³ ₅₄ 129 **3 Results**

A total of 27144 registries for new enrolment was identified; among them, 21086 (77.7%) consented
to participate, and 20123 (74.1%) who underwent the health examination and completed the online

questionnaire survey were included in the final analyses. The mean age was 18.3 ± 0.8 years and 10283(51.1%) were men. The characteristics of participants in the study are shown in Table 1. The prevalence rates of chronic urticaria, allergic reactions to food/drug/light, hand eczema, and AD were 1.89%, 2.27%, 3.35%, and 3.86%, respectively. The prevalence rates of AD and allergic skin disease were 3.86 % and 4.14%, respectively (Figure 1 and Table S1).

In general, URTI and the use of antibiotics were significantly associated with atopic and allergic diseases (Figure 1 and Table S1). For example, the prevalence of AD increased from 3.39% to 4.11% and 4.79% in participants who reported rare or occasional use, frequent oral use, and frequent intravenous use of antibiotics, respectively. Consistent trends could be observed in all atopic and allergic diseases and their combinations.

- After adjustments for sociodemographic factors (Figure 2 and Table S2), URTI and the use of antibiotics were significantly associated with atopic/allergic skin diseases. For instance, compared to those reporting rare or occasional use of antibiotics, the RRs for AD in participants who reported frequent oral administration and intravenous injection of antibiotics were 1.18 (95% CI: 1.01, 1.39) and 1.36 (95% CI: 1.14, 1.62), respectively. For other allergies or atopic diseases of skin or beyond the skin, the correlations were highly consistent despite some variations in the magnitude of the association.
- Because our study was not a prospective cohort, it was difficult to know if antibiotic use was ahead of suffering from AD. We further evaluated the joint effect of URTI and antibiotics on AD by including an interaction term in the model. As shown in Figure 3, in each category of antibiotic use, the frequency of URTI was positively associated with the risk of AD. Vice versa, in each category of URTI, antibiotic use was positively associated with AD according to the effect size, despite some insignificant results in categories with small sample size.

³⁶₃₇ 155 **4 Discussion**

This retrospective cohort study demonstrated that preschool exposure to antibiotics, either through oral administration or intravenous infusion, was associated with increased risks of having allergic and atopic skin diseases in young adulthood. Participants who reported frequent URTI in preschool-age also had higher risks of allergies and atopy.

Similar trends were identified in previous observational studies that early-life antibiotic use was associated with an increased risk of eczema, but there were still some inconsistent results.[23, 24] Meta-analysis including 22 studies with 394,517 patients concluded that children with antibiotics exposure in the first two years had increased odds of atopic eczema with an OR of 1.26 (95% CI: 1.15-1.37). Notably, the onset age of the outcomes in the included studies was the period of childhood (<12 years old). [7] A large population-based retrospective cohort study in twins showed that antibiotic use was also associated with an increased risk of eczema; however, it is likely that the relationship between early-life antibiotic use and eczema was confounded by shared familial environment and genetic factors.[25] However, current data lacked the information regarding the atopic and allergic skin diseases occurred in late adolescence to early adulthood, while we firstly investigated the effects of

preschool antibiotic in a retrospective study and revealed a positive association. Furthermore, we have

provided the data on the health seeking behavior dealing with a cold or fever in preschool age (shown

in Table S3), and we found there were 66.2% in participants with the atopic march and 64.7% in

participants allergic skin disease showed that they/their parents would like to receive antibiotics

treatment when the participants had a cold/fever in their preschool age. In those without atopic/allergic

diseases, this proportion ratio was 61.5%. We did not observe a significant difference in health seeking

behavior in our study, as most of the Chinese parents could pay close attention to the preschool health

of children, and keep a non-exclusion attitude to antibiotics use. Keeping antibiotics at home for

children was pervasive in China, as well as the parents sought medical care and use antibiotics in

dealing with respiratory tract infections.

Evidence showed that AD was the first manifestation of an atopic phenotype which begins in early childhood and the progression from AD to the diseases such as food allergy, asthma, and allergic rhinitis were more likely to be shown in adolescence. [22, 26, 27] The mechanisms behind the march from AD to allergic airway diseases and allergic conjunctivitis likely arise from initial epicutaneous allergen sensitization inducing robust local and systemic type 2 immune responses with increased production of type 2 cytokines including interleukin (IL)-4, IL-13, IL-31, and thymic stromal lymphopoietin.[28, 29] Most studies were prone to make these responses responsible for the commonly shared pathogenesis of cutaneous, airway, and conjunctiva inflammation, supporting the view that AD is not merely a disease confined to the skin, but is in fact, a systemic disease.[30, 31] Therefore, it could be explained that the increased risks beyond skin manifestations in young adulthood were consistent with those of skin diseases and some with even greater effect sizes. While not fully understood, the underlying mechanism of the association between antibiotics and atopic and allergic diseases can be elucidated by microbial diversity. The gut microbial community is dynamic and variable during the first 3 years of life, before stabilizing to an adult-like state.[32] Studies have demonstrated continued development through childhood into the teenage years.[33, 34] Dietary intake plays a key role in the development period of the gut microbiome. Breast-fed infants have microbiota enriched in *Lactobacillus*, *Staphylococcus*, and *Bifidobacterium*. Studies have shown that human milk symbiotic and potentially probiotic isolates contain microbes. and supplementation of *Bifidobacteria* was found to be effective in primary preventing allergic diseases.[35-37] But among children of preschool age, the dominance of *Bifidobacterium* diminishes with the alteration in dietary intake.[15] On the other hand, the high prevalence of antibiotic use may also lead to a concurrent increase in antibiotic-resistant bacteria.[38, 39] Antibiotic-treated children have a less diverse gut microbiota and less stable communities. Antibiotic therapy affects microbiome variety and thus may increase the risk of atopic diseases.[40, 41]

In our study, increased risks of atopic march or allergic diseases were observed in students who reported frequent URTI. Another potential explanation was related to the infections which could also affect microbial conditions. Except for the change in diet, children of preschool age tend to be exposed to more diverse microbes and infectious diseases including URTI in kindergarten or external environments. Respiratory viral infections, in particular, have been shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut, [42] which could further shape atopic microenvironments.

Several limitations should be noted, and the results should be interpreted with caution. First, recall bias in the measurement of exposure to antibiotics might have been introduced. While recall bias on the frequency of antibiotics use and URTIs should not be ignored, this is a limitation in most retrospective studies. We are not able to validate the medical records because China does not have a registry system for primary care, and a large number of patients with mild conditions also visit doctors in secondary and tertiary hospitals. While participants could obtain the information from their parents, but unfortunately, we could not evaluate the extent of recall bias. This will be in our further consideration in future studies.

Second, there was a lack of information about the type and dose of antibiotics, and we could not attribute the association to specific antibiotics. Third, there might be a reversed causal relationship, because antibiotics could be used in the treatment of AD and other conditions accompanied by bacterial infection. Last but not least, we assessed the role of URTI and antibiotics separately, because the two variables were significantly correlated (contingency coefficient=0.4, P<0.001) and were therefore not included in the same model to avoid collinearity and biased estimation of parameters. The association of URTI with AD and allergies may be confounded by antibiotics, and vice versa.

However, both infection and antibiotics may be correlated with allergies/atopies, with different mechanisms. Although under the hygiene hypothesis, exposure to pathogens during infancy and early childhood has been proposed to explain the lower prevalence of asthma and other atopic diseases among children in developing countries, [43, 44] some studies showed that early respiratory infections could not protect against atopic eczema or recurrent wheezing, but could drive the development of atopic disease. [45-49] Atopic sensitization, a process of generation of specific immunoglobulin E (sIgE) when exposed to an innocuous antigen, was common to all allergic diseases. As preschool URTI most probably represent viral infections in the majority of cases, some studies investigated a potential mechanistic explanation for how a respiratory viral infection could drive the development of atopic sensitization and disease. Martorano et al. used a Sendai virus to establish the mouse model mimicking a human limited respiratory syncytial virus infection and found that Sendai virus infection could promote the crosslinking of high-affinity IgE receptor (FceRI) on the lung conventional dendritic cells (cDC), which led to the production of the chemokine CCL28, recruiting IL-13 and driving the development of mucous cell metaplasia and airway hyperreactivity.[50] Another animal study found that except for the increase of sIgE against Sendai virus in mice, there was also a large increase in total IgE and it remained elevated long after the viral infection being resolved.[51] This notion has further been fuelled by findings that mice infected with the flu virus developed virus-specific mast cell degranulation in the skin, indicating a possible pathway of viral infections that could mediate allergic symptoms.[52] Besides, the respiratory viral infections were shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut.[42, 53] However, we cannot ignore that infections that do not require antibiotics are not captured in our design, such that it is difficult to assess whether the observed association is caused by a specific infection or antibiotics because they occur simultaneously in many cases.

Our study also has strengths. The primary strength is that the sample size for the retrospective cohort
 study was large. Second, the outcomes were diagnosed by specialists. In contrast, some previous

studies used self-reported diagnoses that might introduce misclassification bias. Third, the study had a relatively large and representative sample, and sufficient variations in geographic regions and sociodemographic subgroups. The random effect at the university level was fitted by the 2-level models, resulting in an unbiased estimation of associations.

To conclude, preschool children exposed to URTI or antibiotics may be at higher risks of atopic and allergic skin diseases in their young adulthood, especially among those who frequently had URTI or received antibiotics by intravenous infusion. Our study implies that unnecessary antibiotics treatment in children should be avoided to prevent the occurrence of atopic and allergic diseases in their later life. Prospective studies that consider the type and dose of antibiotics are warranted.

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5 Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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265 6 Ethics statement

This study was conducted according to the guidelines established in the Declaration of Helsinki. All procedures involving patients were approved by the institutional research ethics boards of Xiangya Hospital, Central South University (Changsha, China). Informed consent was obtained from all the students before the investigation.

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271 7 Patient and Public Involvement Statement

This is a retrospective cohort study based on the data from the China College Student Skin Health Study (CCSSHS). The first-year college students from five universities were recruited and investigated. They underwent a health examination and completed a questionnaire survey, and the results will be disseminated to study participants by a medical examination report. Participants were not involved in the design and implementation of the study.

277 8 Author contributions

Dr. Minxue Shen, Dr. Xiang Chen, and Dr. Yi Xiao are joint corresponding authors and have full
access to all the data in the study and take responsibility for the integrity of the data and the accuracy
of the data analysis.

- ³⁸₃₉ 281 Concept and design: Shen, Chen, and Xiao.
- ⁴⁰ 41 282 Acquisition, analysis, or interpretation of data: Y.J. Li, Jing, and Huang
- ⁴³ 283 Drafting of the manuscript: Y.J. Li
- $^{45}_{46}$ 284 Critical revision of the manuscript for important intellectual content: All authors.
- ⁴⁷ ₄₈ 285 Statistical analysis: Shen, Xiao, and Y.J. Li.
- ⁵⁰ 286 Administrative, technical, or material support: Su, J. Li, Tao, Shan, Wang, Kang, and
- ⁵² 287 Wu.
- 54 55 288 Supervision: Chen
- 56 57 289
- 58 59
- 60

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0 9 Conflict of interest

291 The authors declare no conflict of interest.

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- Figure 2. Association of early-life exposure to antibiotics with the risk of atopic/allergic diseases later
 in life. RR: risk ratio; CI: confidence interval.

Figure 3. The joint effect of URTI and antibiotics on AD after including an interaction term in the model. RR: risk ratio; CI: confidence interval.

15 464

¹⁷₁₈ 465 **Supplementary file captions**

- Table S1. The prevalence of atopic and allergic diseases in college students.
- 467 Table S2. Association of antibiotic and URTI exposure with atopic and allergic diseases in college
 468 students.

Liezoni

- Table S3. Health seeking behavior when dealing with a cold or fever in the preschool age.
- 470 Material S1. Chinese college students health survey questionaire (Translation version in English).

Characteristics	Ν	%
Gender		
Male	10283	51.1
Female	9840	48.9
Income (CNY)		
<10,000	2168	10.8
10,000–29,999	4376	21.7
30,000–49,999	3465	17.2
50,000–99,999	4417	22.0
100,000–199,999	4063	20.2
≥200,000	1634	8.1
Parental highest education		
Primary school	1320	6.6
Middle school	5316	26.4
High school	5021	24.9
College and above	8466	42.1
Ethnicity		
Han Chinese	16218	80.6
Other ethnicities	3905	19.4
Dassive smoke evpesure	3703	17.4
r assive smoke exposure	1,5002	70.0
Hardly	15883	78.9







338x170mm (300 x 300 DPI)

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 Supplementary file captions
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		BMJ Open		open-2020-04 by copyright		Page 22 of 3
atopic and allergic	diseases in colle	ge students		7768 on 21 Se including for	Antibiotics n (%)	
N, Prevalence (%) ^a	Rare	Occasional	Frequent	set Enseig Rateig	Often, or ally	Often, intravenously
				2021. ated t		
776 (3.86)	174 (2.99)	459 (3.99)	143 (5.1)		263 (4.11)	164 (4.79)
675 (3.35)	145 (2.49)	407 (3.54)	123 (4.38)	an erige (3.01)	243 (3.79)	122 (3.57)
456 (2.27)	121 (2.08)	255 (2.22)	80 (2.85)	d dur data n AB	152 (2.37)	92 (2.69)
381 (1.89)	96 (1.65)	207 (1.8)	78 (2.78)	ning (1.65)	133 (2.08)	78 (2.28)
833 (4.14)	217 (3.73)	460 (4)	156 (5.56)		285 (4.45)	167 (4.88)
				omjo		
3139 (15.6)	687 (11.79)	1825 (15.88)	627 (22.34)		1101 (17.19)	666 (19.47)
153 (0.76)	32 (0.55)	84 (0.73)	37 (1.32)	and 63.(0.61)	54 (0.84)	36 (1.05)
2273 (15.6)	486 (8.34)	1327 (11.55)	460 (16.39)	simi 984 (9.56)	809 (12.63)	480 (14.03)
303 (1.51)	46 (0.79)	171 (1.49)	86 (3.06)		117 (1.83)	75 (2.19)
allergic diseases in our s gic reactions to food/dri atitis, allergic asthma, a	study population. 1g/light, contact dern llergic rhinitis, and a	natitis, and urticaria. llergic conjunctivitis. 2		ne 11, 2025 at Agence Bibliographiq nnologies.		
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	Atopic and allergic N, Prevalence (%) ^a 776 (3.86) 675 (3.35) 456 (2.27) 381 (1.89) 833 (4.14) 3139 (15.6) 153 (0.76) 2273 (15.6) 303 (1.51) Illergic diseases in our strict reactions to food/drustitis, allergic asthma, a Atom strict asthma, a For peer rever	N, Prevalence Rare 776 (3.86) 174 (2.99) 675 (3.35) 145 (2.49) 456 (2.27) 121 (2.08) 381 (1.89) 96 (1.65) 833 (4.14) 217 (3.73) 3139 (15.6) 687 (11.79) 153 (0.76) 32 (0.55) 2273 (15.6) 486 (8.34) 303 (1.51) 46 (0.79) Ilergic diseases in our study population. fic reactions to food/drug/light, contact derm atitis, allergic asthma, allergic rhinitis, and a For peer review only - http://bm	BMJ Open topic and allergic diseases in college students N, Prevalence URTL, n (%) (%) ^a Rare Occasional 7776 (3.86) 174 (2.99) 459 (3.99) 675 (3.35) 145 (2.49) 407 (3.54) 456 (2.27) 121 (2.08) 255 (2.22) 381 (1.89) 96 (1.65) 207 (1.8) 833 (4.14) 217 (3.73) 460 (4) 3139 (15.6) 687 (11.79) 1825 (15.88) 153 (0.76) 32 (0.55) 84 (0.73) 2273 (15.6) 486 (8.34) 1327 (11.55) 303 (1.51) 46 (0.79) 171 (1.49) Itergic diseases in our study population. per reactions to food/drug/light, contact dermatitis, and urticaria. tits, allergic asthma, allergic rhinitis, and allergic conjunctivitis. and urticaria.	BMJ Open topic and allergic diseases in college students N Prevalence (%) ^a Race Occasional Frequent 776 (3.86) 174 (2.99) 459 (3.99) 143 (5.1) 675 (3.35) 145 (2.49) 407 (3.54) 123 (4.38) 456 (2.27) 121 (2.08) 255 (2.22) 80 (2.85) 381 (1.89) 96 (1.65) 207 (1.8) 78 (2.78) 333 (4.14) 217 (3.73) 460 (4) 156 (5.56) 153 (0.76) 32 (0.55) 84 (0.73) 37 (1.32) 2273 (15.6) 46 (8.34) 1327 (11.55) 460 (16.39) 303 (1.51) 46 (0.79) 171 (1.49) 86 (3.06) Itergie diseases in our study population. the reactions to food/drug/light, contact dermatitis, and urticaria. this, allergie asthma, allergie rhinitis, and allergie conjunctivitis.	BMJ Open Wo opprove on 21 Segment of the coll of t	BMJ Open oppose stopic and allergic diseases in college students or setting of the set of the

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2 3					17768 t, incl		
4	Table S2. Association of antibiotic	and URTI expos	ure with atopic and a	llergic diseases in co	ollege stadents		
6 7		<u> </u>	URTI, aRR (95%CI) ^a	8	for c A	antibiotics, aRR (95%C	I) ^a
8	Disease	Rare	Occasional	Frequent	Rare a consistent	Often, orally	Often, intravenously
9 10	Skin				er 20 relate		
11 12	Atopic dermatitis	Reference	1.32 (1.09, 1.54)	1.59 (1.27, 1.98)	Reference	1.18 (1.01, 1.39)	1.36 (1.14, 1.62)
13 14	Hand eczema	Reference	1.32 (1.08, 1.56)	1.60 (1.26, 2.02)	Reference	1.27 (1.08, 1.49)	1.17 (0.95, 1.44)
15	Allergic reactions to food/drug/light	Reference	1.10 (0.92, 1.28)	1.30 (1.04, 1.63)	an er lo Referance	1.15 (0.97, 1.37)	1.36 (1.12, 1.65)
16 17	Chronic urticaria	Reference	0.97 (0.76, 1.17)	1.58 (1.21, 2.05)	ar c Reference	1.13 (0.90, 1.40)	1.39 (1.09, 1.78)
18 19	Allergic skin disease ^b	Reference	1.04 (0.89, 1.20)	1.46 (1.22, 1.76)	Rest gnce	1.16 (1.01, 1.34)	1.33 (1.13, 1.57)
20	Beyond skin				g, Al		
21	Atopic march ^c	Reference	1.39 (1.26, 1.52)	2.08 (1.85, 2.34)	Reference	1.35 (1.24, 1.48)	1.55 (1.40, 1.71)
23 24	Allergic conjunctivitis	Reference	1.89 (1.13, 2.66)	3.49 (2.05, 5.96)	Interence	1.58 (1.08, 2.32)	2.72 (1.75, 4.23)
25 26	Allergic rhinitis	Reference	1.43 (1.27, 1.59)	2.13 (1.86, 2.43)	Reference	1.39 (1.26, 1.53)	1.56 (1.39, 1.74)
27	Asthma	Reference	2.56 (1.69, 3.43)	4.89 (3.20, 7.47)	Raference	1.92 (1.52, 2.43)	2.10 (1.64, 2.70)
28 29	^a Adjusted for the fixed effects of gender, in	come, education, pas	sive smoking, and ethnicity	and the random effect of	f the universite		
30	^b Allergic skin disease includes allergic reac	tions to food/drug/lig	ght, contact dermatitis, and	urticaria.	ne 1 hno		
31 32	^c Atopic march refers to atopic dermatitis, a	llergic asthma, allerg	ic rhinitis, and allergic conj	unctivitis.	1, 20 logie		
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			Health se	eeking behavior,	n(%) ^b	Septeml Ens for uses
Disease condition	Total	Ignore them	Drink water or have a rest	Receive antibiotics orally or intravenously	Receive Chinese traditional medicine orally	ber 2021. Bownload eignement Superie related to text and
Skin		\mathcal{O}				ded t our (/ data
Atopic dermatitis	776	20 (2.6)	370 (47.6)	512 (65.9)	194 (25.0)	
Hand eczema Allergic reactions to food/drug/light	675 456	32 (4.7) 9 (2.0)	343 (50.8) 227 (49.7)	430 (63.7) 286 (62.7)	149 (22.0) 95 (20.8)	ning, \cdot (0.2)
Chronic urticaria Allergic skin disease °	381 833	8 (2.1) 17 (2.0)	158 (41.4) 384 (46.0)	257 (67.4) 539 (64.7)	100 (26.2) 194 (23.2)	l traini 2 (0.2)
Beyond skin						ng,
Atopic march ^d	3139	66 (2.1)	1542 (49.1)	2081 (66.2)	728 (23.1)	and 😫 (0.3
Allergic conjunctivitis	153	4 (2.6)	83 (54.2)	107 (69.9)	36 (23.5)	sin 🗳 (0)
Allergic rhinitis	2273	42 (1.8)	1135 (49.9)	1515 (66.6)	532 (23.4)	$\frac{1}{8}$ $\frac{1}{8}$ (0.4)
Asthma	303	7 (2.3)	154 (50.8)	206 (67.9)	70 (23.1)	ec 2(0.6)
Without atopic/allergic diseases	16343	597 (3.7)	7761 (47.4)	10057 (61.5)	3058 (18.7)	ne 76 (0.4
ultiple selections are allower oportion ratios in population lergic skin disease includes topic march refers to atopic o	d in the ques ns. allergic react dermatitis, al	tionnaire. ions to food/drug/ligh lergic asthma, allergic	nt, contact dermatitis, c rhinitis, and allergic	and urticaria conjunctivitis		025 at Agence E es.

Material S1. Chinese college students health survey questionnaire (English version)

Chinese college students health survey questionnaire

Informed consent

Welcome to participate in the Chinese University Student Health Survey. In order to promte a better health management for Chinese college freshmen, you are invited to fill out a questionnaire including several parts: (A) General information; (B) Medical history, (C) Lifestyle habits, (D) Skin health, which take about 15 minutes to answer. We will provide you with reasonable health education and health management based on this information, combined with the results of the health checkup. All the information you fill in will be kept strictly confidential. Continue to fill in the following content, indicating that you and your guardian have understood and are willing to continue to cooperate with our work. Thanks you!

A. General information

A01. Before you went to university, please provide your address.								
(Specific to districts and counties)								
A02. Have you moved to other places (cross-city) in the past 10 years								
(Single selection, if "No" jump to A04)								
O Never O Ever								
A03. If so, the previous address is? (Specific to districts and counties)								
A04. Sex (Single selection)								
O Male O Female								
A05. Your Ethnicity:								
A06. Annual household income. (Single selection)								
A06. Annual household income. (Single selection)								
A06. Annual household income. (Single selection) • <10,000								
A06. Annual household income. (Single selection) \circ <10,000								
A06. Annual household income. (Single selection) \circ <10,000								

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0	blow College	0	Postgraduate or	0	Unclear				
			above						
A08. Yo	A08. Your mother's highest education (Single selection)								
0	Primary school or	0	Middle school	0	High school				
	blow								
0	College	0	Postgraduate or	0	Unclear				
			above						

B. Medical History										
B01. Ha	B01. Have you ever been specifically diagnosed with any of the following									
cardiova	ascular or metabolic dis	ease	s? (Multiple selection.	s are	allowed)					
	Hypertension		Coronary heart		Hyperlipidemia					
			disease							
	Obesity		Fatty liver		Gout					
	Psoriasis		None of above							
В02. На	ave you ever been diagr	osec	l with any of the follo	wing	allergic diseases?					
(Multipl	le selections are allowe	d)								
	Asthma		Allergic Rhinitis		Allergic					
					conjunctivitis					
	Eczema		Urticaria		None of above					
В03. На	ave you ever been diagr	iosec	l with any of the follo	wing	infectious diseases?					
(Multipl	le selections are allowe	d)								
	Tuberculosis or other		Hepatitis B		Hepatitis C					
forms o	f tuberculosis									
	Helicobacter pylori		HIV infection		None of above					
infection	n									
B04. Ha	ave you ever been diagr	osec	l with any of the follo	wing	endocrine diseases?					
(Multip	le selections are allowe	d)								

	Type 1 diabetes	I	□ Type 2 diab	oetes		Polycystic ovarian syndrome				
	Hypertrichosis	l	□ Hypothyroi	dism		Hyperthyroidism				
	Graves disease	I	☐ Hashimoto			None of above				
			thyroiditis							
B05.Ha	ve you ever been di	agnos	ed with any of	the fol	lowing	immune diseases?				
(Multiple selections are allowed)										
	SLE		Scleroderma			Sjogren syndrome				
	Uveitis		Rheumatoid	arthrit	is 🗆	Dermatomyositis				
	None of above									
B06. Have you ever been diagnosed with any of the following hematologic										
diseases	s? (Multiple selectio	ns ar	e allowed)							
	Iron-deficiency		Megaloblasti	c		Thalassemia				
anemia			anemia							
	Anemia		Hemophilia			leucocythemia				
	Lymphadenoma		None of abov	/e						
B07. Ha	ave you ever been di	agno	sed with any of	the fo	llowing	mental or				
neurolo	gical disorders? (Mi	ıltiple	e selections are	allowe	ed)					
	ADHD and attention	on de	ficit 🛛 Dep	ressive	e disord	er 🛛 Anxiety				
disorde	r									
	Schizophrenia		□ Nor	e of al	oove					
B08. Ha	ave you ever had any	y of t	ne following fo	od alle	rgies?	Multiple selections				
are allo	wed)									
	None		Milk		Egg					
	Wheat		Soybean		Fish					
	Nuts		Fruit		Crusta	ceans (e.g., shrimp,				
					crab, e	tc.)				
п	Others	П	Unclear							

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selections are allowed)										
	None		Antibiotics		Non-	steroidal anti-				
	Contrast medium		Anesthetic		infla	mmatory drugs				
					analg	gesics (e.g., aspirin)				
	Anticonvulsant		Chemotherapy		Othe	rs				
			drugs							
	Unclear									
B10. Have you ever been allergic to any of the following environmental substances?										
(Multiple selections are allowed)										
	None		Dust mite		Myc	ete				
	Animal skins		Pollen		Hous	se dust				
	Cockroach		Others		Uncl	ear				
B11. Do you have an excessive bug bite response? (Single selection)										
O No O Yes										
B12. In	the past year, have	you ł	nad a dog, cat or o	ther	small	stuffed animal such as				
rabbit, g	guinea pig, hamster,	etc.?	(Multiple selection	ons a	ire allo	owed)				
	No		Dog			Cat				
	Other stuffed		Unclear							
animals	5									
B13. D	o you have a long hi	story	of close exposure	e to c	chemic	cals? (Multiple				
selectio	ns are allowed)									
	None		Formaldehyde			Gasoline				
	Oil varnish		Others			Unclear				
B14. H	ave you used or take	n an	y medication almo	ost ev	very d	ay for the last 2 weeks?				
(Multip	le selections are allo	wed)							
	None		Antibiotics			Nonsteroidal anti-				
	Hormone		Antituberculosis	5		inflammatory drugs				
			drugs			and analgesics				
						8				

0	No	O Yes	\$	0	Unclear
B16. H	ow often do you	have "colds	and fevers" in	your e	arly school years
(before	age of 7 years o	ld)? (Single	selection)		
0	Rare O	Occasional	(Several	O 0	ften (almost every
		times a yea	r)	m	onth)
B17. W	hich way did yo	ou (or your p	arents) usually	deal w	ith your "cold or
fever"	in the early scho	ool age years	? (Multiple selec	ctions d	are allowed)
	Ignore them	Drin	k more water or		Receive antibiotic
		have	e a rest		orally
	Oral Chinese		eive antibiotics		Others
Traditio	onal medicine	intra	venously		
B18. W	hich of the follo	wing metho	ds can improve	or cur	e your "Cold or fe
in the e	early school age	years? (Sing	le selection)		
0	It usually cured without		• By oral antibiotics occasionally		
0	Often by antibiotics orally		• Often by a	ntibiot	tics intravenously
			0		

C. Lifestyle Habits

C01. Do you smoke (refers to smoking at least one cigarette a day for more than six					
months) (Single selection, jump to C3 if you choose "hardly")					
O Hard	$lly \qquad \mathbf{O} < 1 pac$	ket O 1	-2 packets	• > 2 packs/day	
	/day	/	day		
(about 20					
cigarettes in a					
packect)					
C02. If you smoke, how many years have you smoked in total so far? (Single					
selection)					
o < 1 y	vear O	1-3 years	0	> 3 years	

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D. Skin Health

D01.Ho	ow many showers do	you	take per week in the sp	ring	and fall? (Single
selectio	on)				
0	≤ 1 time per week	0	2~4 times per week	0	5~7 times per week
0	8~10 times per	0	>10 times per week		
week					
D02. H	ow long do you take	a sho	ower in spring and fall?	o (Sin	gle selection)

Page 31 of 30

\mathbf{O} < 5 minute	es O d	5-10 minutes	ο	11-20 minu	ites
O 21-30 min	utes O >	> 30 minutes			
D03. What kin	D03. What kind of toiletries do you use most? (Single selection)				
O None	O Soap	o s	Shower gel	O O1	thers
D04. In spring	and fall, the temper	ature of your ba	th is (Sing	le selection)	
• Low temp	erature(<35 O	Close to the body	y	• High te	mperature(>
centigrade) t	emperature(35-4	40	40 centi	grade)
		centigrade)			
D05. Do you u	se moisturizers all o	over your body a	ılmost dail	y in fall and	winter?
(Single selection	on)				
O No		0	Yes		
D06. How ofte	n do you use facial	cleansing produ	cts (e.g. cl	eanser, soap)? (Single
selection)					
• Hardl	y O Usually	y O (Once per d	ay O $\geq t$	wice per
				da	У
D07. How ofte	n have you washed	your hair in the	past two y	ears? (Singl	le selection)
$\mathbf{O} \geq Twie$	ce per day O	Once per day		0	Once on
					alternate
					days
O Once	every 2-6 days O	Once a week	or more	5	
D08. In the pas	at two years, what k	ind of toiletries	you use is?	? (Single sel	ection)
O None	O Shampoo	• Shampo	00 +	0	Others
		conditio	oner		
D09. Have you used hair care/hair products in the past two years? (multiple					
selections)					
□ None		□ Ess	ential oil,	elastin and o	other hair
		care	e products		
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Association of antibiotics use in preschool age with atopic and allergic skin diseases in young adulthood: A populationbased retrospective cohort study.

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Association of antibiotics use in preschool age with atopic and allergic skin diseases in young adulthood: A population-based retrospective cohort study.

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 41 20 (Y.X.)
- Keywords: antibiotics, atopic and allergic skin diseases, preschool and young adulthood.
- 45 46

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23 Abstract

Background: Overuse and misuse of antibiotics is a public health problem in low- and middle-income

countries. Although the association of antibiotics with atopic and allergic diseases has been established,
 most studies focused on prenatal exposure and the occurrence of disease in infants or young children.

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 27 Objective: To investigate the association of preschool use of antibiotics with atopic and allergic skin diseases in young adulthood.
- 13 29 Design: Population-based retrospective cohort.

Setting and participants: The first-year college students (n=20123) from five universities were investigated. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively.

33 Methods: We conducted a dermatological field examination and a questionnaire survey inquiring the
 34 participants about frequency of upper respiratory tract infection (URTI) and the preschool antibiotics
 35 use (prior to 7 years old). The two-level Probit model was used to estimate the associations, and
 36 adjusted risk ratio (aRR) and 95% confidence interval (CI) were presented as the effect size.

Results: A total of 20123 participants with complete information was included in the final analysis. The frequent antibiotics use intravenously (aRR 1.36, 95% CI 1.14–1.62) and orally (aRR 1.18, 95% CI 1.01–1.38) prior to 7 years old was significantly associated with atopic dermatitis in young adulthood. Similar trends could be observed in allergic skin diseases among those who use antibiotics orally and intravenously, with RRs of 1.16 (1.01, 1.34) and 1.33 (1.13, 1.57), respectively.

- 42 Conclusions: Preschool URTI and antibiotics use significantly increases the risk of atopic and allergic
 43 skin diseases in young adulthood.
- 38 44 Strengths and limitations of this study
 39
 - The main outcomes were diagnosed by specialists instead of self-report.
 - This study provides a relatively large and representative sample, and sufficient variations in geographic regions and sociodemographic subgroups, as well as the random effect at the university level was fitted by the 2-level models, resulting in an unbiased estimation of associations.
 - Recall bias in the measurement of exposure to antibiotics might have been introduced, which
 could not be ignored in most retrospective studies.
 - We lacked the information about the type and dose of antibiotics, and there might be a reversed causal relationship because antibiotics could be used in the treatment of AD and other conditions accompanied by a bacterial infection.

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Introduction

The incidence and prevalence of atopic and allergic conditions such as asthma, allergic rhinitis, food allergies, and atopic dermatitis (AD) among the worldwide population have significantly increased during the past several decades.[1-3] An area of environmental change that may be responsible for the increase of allergic and atopic diseases is the growing use of medications which may alter the development of human microbiome.[4] It also seems that use of some antibiotics, which can directly cause intestinal dysbiosis and affect human microbiome and increase the risk for allergy development, is of particular concern in light of accumulating evidence.[5-7]

Furthermore, overuse and misuse of antibiotics is a severe public health problem worldwide, especially in low- and middle-income countries. In the last decade, prescriptions of broad-spectrum antibiotics increased by 49% in children under five years and doubled in children aged 5-17 years, concomitant with the increasing prevalence of allergic diseases.[8, 9] In China, 70% of outpatients attending primary care facilities with colds were inappropriately treated with antibiotics, often by intravenous infusion. The situation is even worse in children because many parents demand treatment with antibiotics[10]. However, most upper respiratory tract infections (URTI) in children are viral, for which antibiotics are unnecessary.[11-13]

The association between the use of antibiotics and atopic and allergic diseases has been observed in longitudinal studies. But most studies focused on antibiotics use during pregnancy or infancy when early colonization is initiated by maternal microbes.[14-17] With the childhood microbiome transition owing to alterations in food and exposure to more diverse microbes in external environments, children in preschool age (<7 yrs) are at higher risks of URTI infection and antibiotics treatment. However, the effect of antibiotics used during this period on atopic and allergic skin diseases that occurred in their young adulthood is not clear. The objective of this study was to evaluate the hypothesis that exposure to antibiotics in preschool age is associated with an increased risk of allergic and atopic skin diseases in young adulthood. We tested this hypothesis by conducting a retrospective study in college students.

Materials and Methods

2.1 Study setting and design

This was a retrospective cohort study based on the data from the China College Student Skin Health Study (CCSSHS)[18]. The first-year college students from five universities were investigated. They underwent a health examination and completed a questionnaire survey. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively. The medical ethics committee of Xiangya Hospital, Central South University, approved the study (#201709993).

2.2 **Exposure** assessment

Two semi-quantitative questions served as the proxy measures of the frequency of antibiotics exposure in preschool age, with detailed explanations for the definitions of URTI and antibiotics. In our study,

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the definition of URTI refers to a series of acute illnesses that have an effect on the upper respiratory system including the common cold, acute otitis media, tonsillitis/tonsillopharyngitis, sinusitis and recurrent sinusitis.[19] The first question was "How often did you have URTI in your preschool age or before 7 years old", with three potential responses: ≤ 1 time/year, 2-3 times/year", and "4 or more times/year". The second question was "How often did you receive antibiotics treatment when you had a URTI", with four responses: "rare", "occasional", "often, orally; and "often, intravenously".

2.3 **Outcome assessment**

Diagnosis of skin diseases and inquiry of disease history were performed by dermatologists during the field survey. All subjects underwent skin examination by resident doctors in dermatology, and the diagnoses were further validated by senior dermatologists. Clinical manifestation, disease history, and family history were inquired about, and inspections were conducted to diagnose skin diseases. For recurrent skin diseases, only those with current symptoms and cutaneous lesions were diagnosed as cases. AD was diagnosed according to the Williams criteria.[20] Hand eczema was diagnosed according to eczema (rash) on the fingers, finger webs, palms, or back of hands, which had appeared once and continued for at least two weeks or had appeared several times or had been persistent. Allergies and urticaria were diagnosed by clinical manifestations, potential triggers, and histories. Asthma, allergic rhinitis, and allergic conjunctivitis were self-reported according to doctors' diagnoses. We also combined some of the outcomes. Atopic march is an apparent progression of allergic diseases from AD, to allergic asthma (AA) to allergic rhinitis (AR) and allergic conjunctivitis. [21, 22] We include the conditions of AD, AA, AR, and allergic conjunctivitis for the outcome of the atopic march. Allergic skin disease includes allergic reactions to food/drug/light, contact dermatitis, and urticaria. Participants with a history of atopic/allergic conditions but without the current disease are excluded.

Covariates 2.4

Demographic characteristics, socioeconomic status (annual family income and parental highest educational level), family history, behavioral factors (dietary, passive smoking, and bathing habits) were inquired by the questionnaire. The questionnaire used in the study was shown in Material S1.

2.5 Statistical analysis

Categorical data were presented as number (%), and the between-group difference was tested using the chi-square test. Two-level Probit regression models (individual as level 1 and university as level 2) were used to estimate the associations of preschool exposure to antibiotics with atopic skin diseases in young adulthood, adjusting for level-1 covariates (gender, ethnicity, annual household income and parental education) and level-2 random effects. The effect size was presented as relative risk (RR) and 95% confidence interval (CI). P< 0.05 was considered statistically significant for all tests. Statistical analysis was performed in SAS 9.4 (SAS Institute Inc., Cary, USA).

Results

> A total of 27144 registries for new enrolment was identified; among them, 21086 (77.7%) consented to participate, and 20123 (74.1%) who underwent the health examination and completed the online

questionnaire survey were included in the final analyses. The mean age was 18.3 ± 0.8 years and 10283(51.1%) were men. The characteristics of participants in the study are shown in the Table 1. The prevalence rates of chronic urticaria, allergic reactions to food/drug/light, hand eczema, and AD were 1.89%, 2.27%, 3.35%, and 3.86%, respectively. The prevalence rates of AD and allergic skin disease were 3.86 % and 4.14%, respectively (Figure 1 and Table S1).

In general, URTI and the use of antibiotics were significantly associated with atopic and allergic diseases dose-dependently (Figure 1 and Table S1). For example, the prevalence of AD increased from 3.39% to 4.11% and 4.79% in participants who reported rare or occasional use, frequent oral use, and frequent intravenous use of antibiotics, respectively. Consistent trends could be observed in all atopic and allergic diseases and their combinations.

After adjustments for sociodemographic factors (Figure 2 and Table S2), URTI and the use of antibiotics were significantly associated with atopic/allergic skin diseases in dose-response manners. For instance, compared to those reporting rare or occasional use of antibiotics, the RRs for AD in participants who reported frequent oral administration and intravenous injection of antibiotics was 1.18 (95% CI: 1.01, 1.39) and 1.36 (95% CI: 1.14, 1.62), respectively. For other allergies or atopic disease of skin or beyond skin, the correlations were highly consistent despite some variations in the magnitude of the association.

Furthermore, we have provided the data on the health seeking behavior dealing with a cold or fever in preschool age (shown in the Table 2), and we found there were 66.2% among participants with the atopic march and 64.7% among participants with allergic skin disease showed that they/their parents would like to seek antibiotics treatment when they had a cold/fever in their preschool age. In those without atopic/allergic diseases, this proportion ratio was 61.5%. Indeed, we found a moderate but significant difference in the seeking behavior of antibiotic treatment between those with allergic skin disease/atopic march and healthy participants (P=0.001). Similar trends could be seen in AD patients and non-patients (P=0.034).

Besides, because our study was not a prospective cohort, it was difficult to know if antibiotic use was ahead of suffering from AD. We further evaluated the joint effect of URTI and antibiotics on AD by including an interaction term in the model. As shown in Figure 3, in each category of antibiotic use, the frequency of URTI was positively associated with the risk of AD. Vice versa, in each category of URTI, antibiotic use was positively associated with AD according to the effect size, despite some insignificant results in categories with small sample size.

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161 4 Discussion

This retrospective cohort study demonstrated that preschool exposure to antibiotics, either through oral
 administration or intravenous infusion, was associated with increased risks of having allergic and
 atopic skin diseases in young adulthood. Participants who reported frequent URTI in preschool-age
 also had higher risks of allergies and atopy.

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Similar trends were identified in previous observational studies that early-life antibiotic use was associated with an increased risk of eczema, but there were still some inconsistent results.[23, 24] Meta-analysis including 22 studies with 394,517 patients concluded that children with antibiotics exposure in the first two years had increased odds of atopic eczema with an OR of 1.26 (95%CI: 1.15-1.37). Notably, the onset age of the outcomes in the included studies was the period of childhood (<12years old). [7] A large population-based retrospective cohort study in twins showed that antibiotic use was also associated with an increased risk of eczema; however, it is likely that the relationship between early-life antibiotic use and eczema was confounded by shared familial environment and genetic factors.[25] However, current data lacked the information regarding the atopic and allergic skin diseases occurred in late adolescence to early adulthood, while we firstly investigated the effects of preschool antibiotic in a retrospective study and revealed a positive association. We did not observe significant difference in health seeking behavior in our study, as most of the Chinese parents could pay a close attention to prschool health of children, and keep a non-exclusion attitude to antibiotics use. Using antibiotics at home, seeking medical care, and use antibiotics in the hospital for children was pervasive in China when parents dealing with children's respiratory tract infections. However, the results should be discussed with caution as doctor seeking behavior varies a lot in populations. In this setting, children with AD will seek a doctor frequently and more likely get a URTI diagnosis if they also have a cold. Equally, children with asthma and wheezing will more frequently get a URTI diagnosis and are more likely to get an antibiotic.

Evidence showed that AD was the first manifestation of an atopic phenotype which begins in early childhood and the progression from AD to the diseases such as food allergy, asthma, and allergic rhinitis were more likely to be shown in adolescence. [22, 26, 27] The mechanisms behind the march from AD to allergic airway diseases and allergic conjunctivitis likely arise from initial epicutaneous allergen sensitization inducing robust local and systemic type 2 immune responses with increased production of type 2 cytokines including interleukin (IL)-4, IL-13, IL-31, and thymic stromal lymphopoietin. [28, 29] Most studies were prone to make these responses responsible for the commonly shared pathogenesis of cutaneous, airway, and conjunctiva inflammation, supporting the view that AD is not merely a disease confined to the skin, but is in fact, a systemic disease.[30, 31] Therefore, it could be explained that the increased risks beyond skin manifestations in young adulthood were consistent with those of skin diseases and some with even greater effect sizes. While not fully understood, the underlying mechanism of the association between antibiotics and atopic and allergic diseases can be elucidated by microbial diversity. The gut microbial community is dynamic and variable during the first 3 years of life, before stabilizing to an adult-like state.[32] Studies have demonstrated continued development through childhood into the teenage years.[33, 34] Dietary intake plays a key role in the development period of the gut microbiome. Breast-fed infants have microbiota enriched in Lactobacillus, Staphylococcus, and Bifidobacterium. Studies have shown that human milk contain symbiotic and potentially probiotic microbes. and supplementation isolates of Bifidobacteria was found to be effective in primary preventing allergic diseases.[35-37] But among children of preschool age, the dominance of *Bifidobacterium* diminishes with the alteration in dietary intake.[15] On the other hand, the high prevalence of antibiotic use may also lead to a concurrent increase in antibiotic-resistant bacteria.[38, 39] Antibiotic-treated children have a less diverse gut

microbiota and less stable communities. Antibiotic therapy affects microbiome variety and thus may
 increase the risk of atopic diseases.[40, 41]

In our study, increased risks of atopic march or allergic diseases were observed in students who reported frequent URTI. Another potential explanation was related to the infections which could also affect microbial conditions. Except for the change in diet, children of preschool age tend to be exposed to more diverse microbes and infectious diseases including URTI in kindergarten or external environments. Respiratory viral infections, in particular, have been shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut, [42] which could further shape atopic microenvironments.

Several limitations should be noted, and the results should be interpreted with caution. First, recall bias in the measurement of exposure to antibiotics might have been introduced. While recall bias on the frequency of antibiotics use and URTIs should not be ignored, this is a limitation in most retrospective studies. Besides, selection bias might also be introduced as students with skin conditions might be more interested to participate and recall carefully. We are not able to validate the medical records because China does not have a registry system for primary care, and a large number of patients with mild conditions also visit doctors in secondary and tertiary hospitals. While participants could obtain the information from their parents, but unfortunately, we could not evaluate the extent of recall bias. Similarly, for the conditions of the disease including asthma, allergic rhinitis and allergic conjunctivitis, which we collected based on both clinical diagnosis and questionnaire data, we could not ignore the atopic conditions in the past that might not be existing anymore, though in previous studies, the 'atopic march' referred to the sequential development of symptoms and was considered to be not strictly limited by the occurring time. [43,44] Those will be in our further consideration in future studies.

Second, there was a lack of information about the type and dose of antibiotics, as well as some antibiotic use for the treatment of low respiratory tract infection, skin infections, and other infections, which was not collected while could also affect the microbiome. So we could not attribute the associations to specific antibiotics use. Third, we noticed that some factors related to the allergic/atopic conditions in preschool age could be ignored, such as prematurity, the doctor seeking behavior, etc., and we had difficulty in fully collecting of related information and need to explain the results with caution. Last but not least, there might be a reversed causal relationship because antibiotics could be used in the treatment of AD and other conditions accompanied by bacterial infection. We assessed the role of URTI and antibiotics separately, because the two variables were significantly correlated (contingency coefficient=0.4, P<0.001) and were therefore not included in the same model to avoid collinearity and biased estimation of parameters. It is possible that the association of URTI with AD and allergies is confounded by antibiotics, and vice versa.

However, both infection and antibiotics may be correlated with allergies/atopies, with different
 the mechanisms. Although under the hygiene hypothesis, exposure to pathogens during infancy and early
 childhood has been proposed to explain the lower prevalence of asthma and other atopic diseases
 among children in developing countries, [45, 46] some studies showed that early respiratory infections

could not protect against atopic eczema or recurrent wheezing, but could drive the development of atopic disease. [47-51] Atopic sensitization, a process of generation of specific immunoglobulin E (sIgE) when exposed to an innocuous antigen, was common to all allergic diseases. As preschool URTI most probably represent viral infections in the majority of cases, some studies investigated a potential mechanistic explanation for how a respiratory viral infection could drive the development of atopic sensitization and disease. Martorano et al. used a Sendai virus to establish the mouse model mimicking a human limited respiratory syncytial virus infection and found that Sendai virus infection could promote the crosslinking of high-affinity IgE receptor (FceRI) on the lung conventional dendritic cells (cDC), which led to the production of the chemokine CCL28, recruiting IL-13 and driving the development of mucous cell metaplasia and airway hyperreactivity.[52] Another animal study found that except for the increase of sIgE against Sendai virus in mice, there was also a large increase in total IgE and it remained elevated long after the viral infection being resolved.[53] This notion has further been fuelled by findings that mice infected with flu virus developed virus-specific mast cell degranulation in the skin, indicating a possible pathway of viral infections that could mediate allergic symptoms.[54] Besides, the respiratory viral infections were shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut.[42, 55] However, we cannot ignore that infections that do not require antibiotics are not captured in our design, such that it is difficult to assess whether the observed association is caused by a specific infection or antibiotics because they occur simultaneously in many cases.

Our study also has strengths. The primary strength is that the sample size for the retrospective cohort study was large. Second, the outcomes were diagnosed by specialists. In contrast, some previous studies used self-reported diagnoses that might introduce misclassification bias. Third, the study had a relatively large and representative sample, and sufficient variations in geographic regions and sociodemographic subgroups. The random effect at the university level was fitted by the 2-level models, resulting in an unbiased estimation of associations.

To conclude, preschool children exposed to URTI or antibiotics may be at higher risks of atopic and allergic skin diseases in their young adulthood, especially among those who frequently had URTI or received antibiotics by intravenous infusion. Our study implies that unnecessary antibiotics treatment in children should be avoided to prevent the occurrence of atopic and allergic diseases in their later life. Prospective studies that consider the type and dose of antibiotics are warranted.

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5 Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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280 6 Ethics statement

This study was conducted according to the guidelines established in the Declaration of Helsinki. All
procedures involving patients were approved by the institutional research ethics boards of Xiangya
Hospital, Central South University (Changsha, China). Informed consent was obtained from all the
students before the investigation.

18 19 285

21 286 7 Patient and Public Involvement Statement

23 287 This is a retrospective cohort study based on the data from the China College Student Skin Health 24 Study (CCSSHS). The first-year college students from five universities were recuited and investigated. 288 25 26 289 They underwent a health examination and completed a questionnaire survey, and the results will be 27 290 disseminated to study participants by a medical examination report. Participants were not involved in 28 291 the design and implementation of the study. 29

292 8 Author contributions

Dr. Minxue Shen, Dr. Xiang Chen, and Dr. Yi Xiao are joint corresponding authors and have full
access to all the data in the study and takes responsibility for the integrity of the data and the accuracy
of the data analysis.

- ³⁸₃₉ 296 Concept and design: Shen, Chen, and Xiao.
- 40 41 297 Acquisition, analysis, or interpretation of data: Y.J. Li, Jing, and Huang
- ⁴³ 298 Drafting of the manuscript: Y.J. Li
- $^{45}_{46}$ 299 Critical revision of the manuscript for important intellectual content: All authors.
- ⁴⁷ ₄₈ 300 Statistical analysis: Shen, Xiao, and Y.J. Li.
- ⁵⁰ 301 Administrative, technical, or material support: Su, J. Li, Tao, Shan, Wang, Kang, and
- ⁵² 302 Wu.
- 54 55 303 Supervision: Chen
- 56 57 304
- 58 59
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305 9 Conflict of interest

306 The authors declare no conflict of interest.

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Figure legends

- Figure 1. The prevalence of atopic and allergic diseases in exposure vs. non-exposure group of antibiotics and URTI.
- Figure 2. Association of early-life exposure to antibiotics with the risk of atopic/allergic diseases later in life. RR: risk ratio; CI: confidence interval.

Figure 3. The joint effect of URTI and antibiotics on AD after including an interaction term in the model. RR: risk ratio; CI: confidence interval.

Supplementary file captions

- Material S1. Chinese college students health survey questionaire (Translation version in English).
- Table S1. The prevalence of atopic and allergic diseases in college students.
- Table S2. Association of antibiotic and URTI exposure with atopic and allergic diseases in college students.
| Characteristics | Ν | % |
|-------------------------------|-------|------|
| Gender | | |
| Male | 10283 | 51.1 |
| Female | 9840 | 48.9 |
| Income (CNY) | | |
| <10,000 | 2168 | 10.8 |
| 10,000–29,999 | 4376 | 21.7 |
| 30,000–49,999 | 3465 | 17.2 |
| 50,000–99,999 | 4417 | 22.0 |
| 100,000–199,999 | 4063 | 20.2 |
| ≥200,000 | 1634 | 8.1 |
| Parental highest
education | | |
| Primary school | 1320 | 6.6 |
| Middle school | 5316 | 26.4 |
| High school | 5021 | 24.9 |
| College and above | 8466 | 42.1 |
| Ethnicity | | |
| Han Chinese | 16218 | 80.6 |
| Other ethnicities | 3905 | 19.4 |
| | | - |
| | | |
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			Health	seeking behavior, n	(%) ^b for a Set	
Disease condition	Total	Ignore them	Drink water or have a rest	Receive antibiotics orally or intravenously	Receive Chineseignemer traditional definement Su medicine orally to tex	Unknov
Skin					uperio ttanc	
Atopic dermatitis	776	20 (2.6)	370 (47.6)	512 (65.9)	194 (25.0) dat et de	3(0.3)
Allergic reactions to	0/5	32 (4.7)	343 (30.8)	430 (63.7)		4 (0.3
food/drug/light	456	9 (2.0)	227 (49.7)	280 (62.7)	93 (20.8) ning	1 (0.2
Chronic urticaria Allergic skin disease ° Beyond skin	833	8 (2.1) 17 (2.0)	158 (41.4) 384 (46.0)	257 (67.4) 539 (64.7)	100 (26.2) F 194 (23.2) A trai	1 (0.3 2 (0.2
Atopic march ^d	3139	66 (2.1)	1542 (49.1)	2081 (66.2)	728 (23.1) ni ng	12 (0.3
Allergic conjunctivitis	153	4 (2.6)	83 (54.2)	107 (69.9)	36 (23.5) a	0 (0)
Allergic rhinitis	2273	42 (1.8)	1135 (49.9)	1515 (66.6)	532 (23.4) s	8 (0.4
Asthma	303	7 (2.3)	154 (50.8)	206 (67.9)	70 (23.1) The P	2 (0.6
Without atopic/allergic diseases	16343	597 (3.7)	7761 (47.4)	10057 (61.5)	3058 (18.7) rtechn une	76 (0.4
^a Multiple selections are allowed	in the questionna	aire.			ologi	
^b Proportion ratios in populations	l.				025 at es.	
^c Allergic skin disease includes a	llergic reactions	to food/drug/light. co	ontact dermatitis. and	urticaria.	Age	
5	0		,		nce	



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Supplementary file captions

Material S1. Chinese college students health survey questionaire (Translation version in English)

Table S1. The prevalence of atopic and allergic diseases in college students.

Table S2. Association of antibiotic and URTI exposure with atopic and allergic diseases in college students.

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Material S1. Chinese college students health survey questionaire (English version)

Chinese college students health survey questionaire

Informed consent

Welcome to participate in the Chinese University Student Health Survey. In order to promte a better health management for Chinese college freshmen, you are invited to fill out a questionnaire including several parts: (A) General information; (B) Medical history, (C) Lifestyle habits, (D) Skin health, which take about 15 minutes to answer. We will provide you with reasonable health education and health management based on this information, combined with the results of the health checkup. All the information you fill in will be kept strictly confidential. Continue to fill in the following content, indicating that you and your guardian have understood and are willing to continue to cooperate with our work. Thanks you!

A. General information

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years
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0,000 - 49,999
0,000 - 49,999 ≥200,000
0,000 - 49,999 ≥200,000

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	blow				
ο	College	С	Postgraduate or	0	Unclear
	C		above		
A08. Yo	our mother's highest ea	duca	ation (Single selection)		
0	Primary school or	С	Middle school	0	High school
	blow				
ο	College	С	Postgraduate or	0	Unclear
			above		
	0				
	lical History				
B. Mee	lical History				
B01. H	ave you ever been	spo	ecifically diagnosed v	vith	any of the following
cardiova	ascular or metabolic d	isea	ses? (Multiple selection	is ar	e allowed)
	Hypertension	C	Coronary heart		Hyperlipidaemia
			disease		
	Obesity	Ľ	☐ Fatty liver		Gout
	Psoriasis	C	None of above		
В02. На	ave you ever been di	agn	osed with any of the	follo	wing allergic diseases?
(Multipl	e selections are allow	ed)			
	Asthma	C	Allergic Rhinitis		Allergic
					conjunctivitis
	Eczema	C	Urticaria		None of above
В03. На	ave you ever been dia	igno	osed with any of the fo	llow	ing infectious diseases?
(Multipl	le selections are allow	ed)			
	Tuberculosis or other	r C	Hepatitis B		Hepatitis C
forms of	f tuberculosis				
	Helicobacter pylori	C	HIV infection		None of above
infection	n				
B04. Ha	ave you ever been dia	igno	osed with any of the fo	llow	ing endocrine diseases?
(Multipl	e selections are allow	ed)			

	Type 1 diabetes		Type 2 diabetes		Polycystic ovarian
	Hypertrichosis	п	Hypothyroidism		Hyperthyroidism
	Graves disease		Hashimoto		None of above
	Graves disease		thyroiditis		None of above
B05.Ha	we you ever been d	liagnos	ed with any of the	he follow	ing immune diseases?
(Multip	le selections are allo	wed)			
	SLE		Scleroderma		Sjogren syndrome
	Uveitis		Rheumatoid arthr	ritis 🛛	Dermatomyositis
	None of above				
B06. H	Iave you ever been	n diag	mosed with any	of the f	following hematologic
diseases	s? (Multiple selection	ns are	allowed)		
	Iron-deficiency		Megaloblastic		Thalassemia
anemia			anemia		
	Anemia		Hemophilia		leucocythemia
	Lymphadenoma		None of above		
B07. H	lave you ever bee	n dia	gnosed with any	of the	following mental or
neurolo	gical disorders? (Mu	ltiple s	elections are allow	wed)	
	ADHD and attenti	on def	icit 🛛 Depressi	ve disord	er 🛛 Anxiety
disorde	r				
	Schizophrenia		\Box None of	above	
B08. H	ave you ever had ar	ny of t	he following food	allergies	? (Multiple selections
are allo	wed)				
	None		/lilk 🛛	Egg	
	Wheat	□ S	oybean E	F ish	
	Nuts	🗆 F	ruit C	Crusta	ceans (e.g., shrimp,
				crab, e	etc.)

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selectio	ns are allowed)				
	None		Antibiotics		Non-steroidal
	Contrast medium		Anesthetic		anti-inflammatory drugs
					analgesics (e.g., aspirin)
	Anticonvulsant		Chemotherapy		Others
			drugs		
	Unclear				
B10. Ha	ave you ever been al	lergi	ic to any of the f	ollow	ing environmental substances?
(Multip	le selections are allo	wed	')		
	None		Dust mite		Mycete
	Animal skins		Pollen		House dust
	Cockroach		Others		Unclear
B11. Do	o you have an excess	sive	bug bite response	e? (Sir	ngle selection)
0	No		0	Yes	
B12. In	the past year, have	you	had a dog, cat o	or othe	r small stuffed animal such as
rabbit, g	guinea pig, hamster,	etc.?	o (Multiple select	tions a	re allowed are allowed)
	No		Dog		□ Cat
	Other stuffed		Unclear		
animals	3				
B13. D	Do you have a lon	g h	istory of close	expos	sure to chemicals? (Multiple
selectio	ns are allowed)				
	None		Formaldehyde		□ Gasoline
	Oil varnish		Others		□ Unclear
B14. Ha	ave you used or take	en an	y medication all	nost e	very day for the last 2 weeks?
(Multip	le selections are allo	wed)		
	None		Antibiotics		□ Nonsteroidal
	Hormone		Antituberculos	is	anti-inflammatory
			drugs		drugs and analgesics
	Others		Clear		(NASIDS)



C. Lifestyle Habits

C01.Do you smoke (refers to smoking at least one cigarette a day for more than six months) (*Single selection, jump to C3 if you choose "hardly"*) O Hardly O < 1 packet O 1-2 packets O > 2 packs/day /day /day (about 20 cigarettes in a packect)

C02. If you smoke, how many years have you smoked in total so far? (Single selection)

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2			
3 4	O < 1 year O	1-3 years O	> 3 years
5	CO3 In the last month your	frequency of passive smol	zing is (the involuntary
6 7	Cos. In the last month, your	frequency of passive shiol	ang is (the involuntary
8	inhalation of smoke caused by	other people's smoking in	your living or working
9 10	environment) (Single selection,	jump to C5 if you choose "he	ardly")
11	O Hardly O	< 1 dav/week O	1-2 days/week
12			
14	O 3-5 days/week O	6-/ days/week	
15	C04. How many years have you	been second hand smoking	? (Single selection)
17 18	\circ < 2 years \circ	2-3 years O 4-6 years	\bullet > 6 years
19	C05 How often do you drink	alcohol? (refering to once	a week for at least six
20 21			a week for at reast six
22	months) (<i>Single selection, jump</i>	to C9 if you choose "hardly"	')
23 24	O Hardly O	Once a week O	2-4 times/week
25	O 5-7 times/week O	8-10 times/week O	> 10 times/week
26 27	CO6 How money years have ye	been drintring? (Single gale	ation)
28	Coo. now many years have you	i been drinking? (Single seled	
29 30	\mathbf{O} < 1 year \mathbf{O}	1-3years O 4-5years	$\mathbf{O} > 5$ years
31	C07. What's your main drink? (Single selection)	
32 33	O Beer O Liqueu		weet O Chinese
34			
35 36		V	vine rice wine
37	C08. How much do you drink o	n average each time? (Single	e selection)
38 39	O Less (1 bottle of beer of	or 50-100g other types of alc	hohol)
40		si 50 100g other types of the	nonory
41	• Medium (2 bottles of b	eer, or 100g other types of al	chohol)
42 43	• Much (three bottles of	beer, or 150g other types of a	alchohol)
44			
45	• A lot (more than 3 b	ottles of beer, or more th	an 150g other types of
46 47	alchohol)		
47			
49			
50			
51	D Skin Health		
52 53	- Shin Health		
54	D01 How many showers do y	you take per week in the	spring and fall? (Single
55		se sure per neek in the	and min with (Stright
56	selection)		
57			

1

58 59 60

 ≤ 1 time per week 2~4 times per week 5~7 times per week Ο 0 Ο

D02. H	low long do yo	ou take a	show	er in spring	g and fall? (Single	e selectio	on)
0 <5	5 minutes	C	D 5	-10 minute	s	O 11	l-20 min	nutes
O 21-	-30 minutes	(C >	· 30 minute	S			
D03. W	Vhat kind of to	oiletries do	o you	i use most?	(Single sel	ection	2)	
O No	one	O Soa	ap		O Shower	gel	0 (Others
D04. Ir	n spring and fa	ll, the ter	npera	ature of you	ur bath is (S	ingle	selection	1)
O Lo	w temperatur	re(<35 C) C	Close to	the body	νο	High t	emperature(
cer	ntigrade)		te	emperature	(35-40		40 cen	tigrade)
			C	entigrade)				
D05. E	Do you use m	oisturizer	all	over your	body almos	st dail	ly in fal	1 and winte
(Single	selection)							
	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,							
ο	No				O Yes			
O	No Iow often do	vou use f	facial	cleansing	• Yes	.g. cl	eanser. s	soap)? (Sino
O D06. H	No Iow often do y	you use f	facial	cleansing	O Yes products (e	.g. cl	eanser, s	soap)? (Sing
O D06. H selectic	No Iow often do y on) Hardly	you use f	facial	cleansing	O Yes products (e	.g. clo	eanser, s	soap)? (Sing
O D06. H selectic O	No Iow often do y on) Hardly	you use f O Us	Facial sually	cleansing	O Yes products (e O Once pe	e.g. clo er day	eanser, s O ≥	soap)? (<i>Sing</i> etwice per
O D06. H selectic O	No How often do y on) Hardly	you use f O Us	facial sually	cleansing	• Yes products (e	e.g. clo er day	eanser, s $\mathbf{O} \geq d$ d	soap)? (<i>Sing</i> etwice per lay
O D06. H selectic O D07. H	No How often do y on) Hardly	you use f O Us e you was	facial mually	cleansing your hair ir	• Yes products (e • Once pe	e.g. cle er day ro yea	eanser, s O ≥ d rs? (Sing	soap)? (Sing etwice per lay gle selection
O D06. H selectic O D07. H	No How often do (200) Hardly Hardly Low often have \geq Twice per	you use f O Us e you was day	facial sually shed y	cleansing your hair ir Once per	• Yes products (e • Once pe • the past tw day	e.g. cle er day	eanser, s O ≥ d rs? (Sing O	soap)? (Sing etwice per lay gle selection Once on
O D06. H selectic O D07. H	No How often do $(2n)$ Hardly Hardly Low often have \geq Twice per	you use f O Us e you was day	facial sually shed y	cleansing your hair ir Once per	 Yes products (e Once pe the past two day 	e.g. cle er day ro yea	eanser, s O ≥ d rs? <i>(Sing</i> O	soap)? (Sing etwice per lay gle selection Once on alternate
O D06. H selectic O D07. H	No How often do $(2n)$ Hardly Hardly Low often have \geq Twice per	you use f O Us e you was day	facial sually shed y	cleansing your hair ir Once per	 Yes products (e Once pe the past two day 	e.g. cle er day ro yea	eanser, s O ≥ d rs? <i>(Sing</i> O	soap)? (Sing etwice per lay gle selection Once on alternate days
O D06. H selectic O D07. H O	No Iow often do (200) Hardly Iow often have \geq Twice per Once every (200)	you use f O Us e you was day 2-6 days	facial sually shed y O	cleansing your hair ir Once per Once a w	 Yes products (e Once pe once pe the past two day 	e.g. cle er day ro yea	eanser, s O ≥ d rs? <i>(Sing</i>	soap)? (Sing etwice per lay gle selection Once on alternate days
O D06. H selectic O D07. H O D07. H	No Iow often do (200) Hardly Iow often have \geq Twice per Once every (200) in the past two	you use f O Us e you was day 2-6 days years, wh	Facial sually shed y O O nat kin	cleansing your hair ir Once per Once a w	 Yes products (e Once pe Once pe the past two day 	e.g. cle er day ro yea	eanser, s	soap)? (Sing etwice per lay gle selection Once on alternate days
O D06. H selectic O D07. H O D08. Ir O	No Iow often do (200) Hardly Iow often have \geq Twice per Once every (200) in the past two None O	you use f O Us e you was day 2-6 days years, wh Shamp	Facial sually shed y O o at kin	cleansing your hair ir Once per Once a w nd of toilet O Sha	 Yes products (e Once pe Once pe the past two day 	e.g. cle er day ro yea	eanser, s O ≥ d rs? (Sing O Single se + O	soap)? (Sing etwice per lay gle selection Once on alternate days election) Others
O D06. H selectic O D07. H O D08. Ir O	No Iow often do (200) Hardly Iow often have \geq Twice per Once every (200) in the past two None O	you use f O Us e you was day 2-6 days years, wh Shamp	Facial sually shed y o o nat kin ooo	cleansing your hair ir Once per Once a w nd of toilet O Sha cor	 Yes products (e Once pe Once pe the past two day 	e.g. cle er day ro yea	eanser, s O ≥ d rs? (Sing O Single se + O	soap)? (Sing etwice per lay gle selection Once on alternate days election) Others

I				
		care p	roducts	
	Hair gel	□ Others	5	
D10. In	the last two years, how ofte	en have you dyed	your hair? (S	Single selection)
0	Never O	Less than once a	year O	Once every 2 to 6
				months
0	Once every 7 to 11 O	More than once a	a	
months		month		
D11. In	the past two years, your pe	rm frequency is (S	ingle selecti	ion)
0	Never O	Less than once a	year O	Once every 2 to 6
				months
0	Once every 7 to 11 O	More than once a	a	
months		month		
D12. D	o you have frequent itchy sl	tin, and to what ex	tent (0 is no	ot itchy at all and 10
is extre	mely itchy)?			
0	- 1 - 2 - 3 - 4	- 5 - 6 -	- 7 - 8	- 9 - 10
D13. D	o you have regular skin pai	n, and to what exte	ent (0 is no	pain at all and 10 is
extreme	e pain)?			
0	- 1 - 2 - 3 - 4	- 5 - 6 -	- 7 – 8	- 9 - 10

Occasional 459(3.99) 407(3.54) 255(2.22) 207(1.8) 460(4)	Frequent R 143(5.1) 123(4.38) 80(2.85) 78(2.78) 156(5.56)	es related to text and data mining, Al	Often,orally 263(4.11) 243(3.79) 152(2.37) 133(2.08)	Often, intravenous 164(4.79) 122(3.57) 92(2.69) 78(2.28)
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able S2. Association of antibioti	c and URTI exp	BMJ (osure with atopic an	Open Ind allergic diseases	iopen-2020-047768 on ts 1 by copyright, including to the state in college s		Page 3
Disease	URTI, aRR (95%CI) ^a			of S Antibiotics, aRR (95%CI) a		
	Rare	Occasional	Frequent	Rare / occave i ognati Rare / occave i ognati	Often, orally	Often, intravenously
Skin				er 202 elatec		
Atopic dermatitis	Reference	1.32 (1.09, 1.54)	1.59 (1.27, 1.98)	Reference D	1.18 (1.01, 1.39)	1.36 (1.14, 1.62)
Hand eczema	Reference	1.32 (1.08, 1.56)	1.60 (1.26, 2.02)	Reference of the second	1.27 (1.08, 1.49)	1.17 (0.95, 1.44)
Allergic reactions to food/drug/light	Reference	1.10 (0.92, 1.28)	1.30 (1.04, 1.63)	nd Gade Referencia	1.15 (0.97, 1.37)	1.36 (1.12, 1.65)
Chronic urticaria	Reference	0.97 (0.76, 1.17)	1.58 (1.21, 2.05)	Reference d To	1.13 (0.90, 1.40)	1.39 (1.09, 1.78)
Allergic skin disease ^b	Reference	1.04 (0.89, 1.20)	1.46 (1.22, 1.76)	Reference .	1.16 (1.01, 1.34)	1.33 (1.13, 1.57)
Beyond skin				p://br j, Al t		
Atopic march ^c	Reference	1.39 (1.26, 1.52)	2.08 (1.85, 2.34)	Referentie	1.35 (1.24, 1.48)	1.55 (1.40, 1.71)
Allergic conjunctivitis	Reference	1.89 (1.13, 2.66)	3.49 (2.05, 5.96)	Reference b	1.58 (1.08, 2.32)	2.72 (1.75, 4.23)
Allergic rhinitis	Reference	1.43 (1.27, 1.59)	2.13 (1.86, 2.43)	Reference 8	1.39 (1.26, 1.53)	1.56 (1.39, 1.74)
Asthma	Reference	2.56 (1.69, 3.43)	4.89 (3.20, 7.47)	Reference o	1.92 (1.52, 2.43)	2.10 (1.64, 2.70)

^a Adjusted for the fixed effects of gender, income, education, passive smoking, and ethnicity and the random effect of university.
 ^b Allergic skin disease includes allergic reactions to food/drug/light, contact dermatitis, and urticaria.
 ^c Atopic march refers to atopic dermatitis, allergic asthma, allergic rhinitis, and allergic conjunctivitis.

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Association of antibiotics use in preschool age with atopic and allergic skin diseases in young adulthood: A population-based retrospective cohort study.

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²₃ 23 Abstract

Background: Overuse and misuse of antibiotics is a public health problem in low- and middle-income countries. Although the association of antibiotics with atopic and allergic diseases has been established, most studies focused on prenatal exposure and the occurrence of disease in infants or young children.

- 8
 9 27 Objective: To investigate the association of preschool use of antibiotics with atopic and allergic skin
 10 28 diseases in young adulthood.
- 12 29 Design: Population-based retrospective cohort.

Setting and participants: The first-year college students (n=20123) from five universities were investigated. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively.

Methods: We conducted a dermatological field examination and a questionnaire survey inquiring the
 participants about the frequency of upper respiratory tract infection (URTI) and the preschool
 antibiotics use (prior to 7 years old). The two-level Probit model was used to estimate the associations,
 and adjusted risk ratio (aRR) and 95% confidence interval (CI) were presented as the effect size.

Results: A total of 20123 participants with complete information was included in the final analysis. The frequent antibiotics use intravenously (aRR 1.36, 95% CI 1.14–1.62) and orally (aRR 1.18, 95% CI 1.01–1.38) prior to 7 years old was significantly associated with atopic dermatitis in young adulthood. Similar trends could be observed in allergic skin diseases among those who use antibiotics orally and intravenously, with RRs of 1.16 (1.01, 1.34) and 1.33 (1.13, 1.57), respectively.

42 Conclusions: Preschool URTI and antibiotics use significantly increases the risk of atopic and allergic
 43 skin diseases in young adulthood.

- 35
 44 Strengths and limitations of this study
 - The main outcomes were diagnosed by specialists instead of self-report.
 - This study provides a relatively large and representative sample, and sufficient variations in geographic regions and sociodemographic subgroups, as well as the random effect at the university level, was fitted by the 2-level models, resulting in an unbiased estimation of associations.
 - Recall bias in the measurement of exposure to antibiotics might have been introduced, which could not be ignored in most retrospective studies.
 - We lacked the information about the type and dose of antibiotics, and there might be a reversed causal relationship because antibiotics could be used in the treatment of AD and other conditions accompanied by a bacterial infection.

Introduction

The incidence and prevalence of atopic and allergic conditions such as asthma, allergic rhinitis, food allergies, and atopic dermatitis (AD) among the worldwide population have significantly increased during the past several decades.[1-3] An area of environmental change that may be responsible for the increase of allergic and atopic diseases is the growing use of medications that may alter the development of the human microbiome.[4] It also seems that the use of some antibiotics, which can directly cause intestinal dysbiosis and affect the human microbiome and increase the risk for allergy development, is of particular concern in light of accumulating evidence.[5-7]

Furthermore, overuse and misuse of antibiotics is a severe public health problem worldwide, especially in low- and middle-income countries. In the last decade, prescriptions of broad-spectrum antibiotics increased by 49% in children under five years and doubled in children aged 5–17 years, concomitant with the increasing prevalence of allergic diseases.[8, 9] In China, 70% of outpatients attending primary care facilities with colds were inappropriately treated with antibiotics, often by intravenous infusion. The situation is even worse in children because many parents demand treatment with antibiotics[10]. However, most upper respiratory tract infections (URTI) in children are viral, for which antibiotics are unnecessary.[11-13]

The association between the use of antibiotics and atopic and allergic diseases has been observed in longitudinal studies. But most studies focused on antibiotics use during pregnancy or infancy when early colonization is initiated by maternal microbes.[14-17] With the childhood microbiome transition owing to alterations in food and exposure to more diverse microbes in external environments, children in preschool age (<7 yrs) are at higher risks of URTI infection and antibiotics treatment. However, the effect of antibiotics used during this period on atopic and allergic skin diseases that occurred in their young adulthood is not clear. The objective of this study was to evaluate the hypothesis that exposure to antibiotics in preschool age is associated with an increased risk of allergic and atopic skin diseases in young adulthood. We tested this hypothesis by conducting a retrospective study in college students.

- **Materials and Methods**
- Study setting and design 2.1

This was a retrospective cohort study based on the data from the China College Student Skin Health Study (CCSSHS)[18]. The first-year college students from five universities were investigated. They underwent a health examination and completed a questionnaire survey. The sampled universities are located in Changsha, Wuhan, Xiamen, Urumqi, and Hohhot, respectively. The medical ethics committee of Xiangya Hospital, Central South University, approved the study (#201709993).

2.2 **Exposure** assessment

Two semi-quantitative questions served as the proxy measures of the frequency of antibiotics exposure in preschool age, with detailed explanations for the definitions of URTI and antibiotics. In our study, the definition of URTI refers to a series of acute illnesses that have an effect on the upper respiratory system including the common cold, acute otitis media, tonsillitis/tonsillopharyngitis, sinusitis, and recurrent sinusitis.[19] The first question was "How often did you have URTI in your preschool-age or before 7 years old", with three potential responses: ≤ 1 time/year, 2-3 times/year", and "4 or more

- 96 times/year". The second question was "How often did you receive antibiotics treatment when you had
- a URTI", with four responses: "rare", "occasional", "often, orally; and "often, intravenously".

2.3 Outcome assessment

Diagnosis of skin diseases and inquiry of disease history were performed by dermatologists during the field survey. All subjects underwent skin examination by resident doctors in dermatology, and the diagnoses were further validated by senior dermatologists. Clinical manifestation, disease history, and family history were inquired about, and inspections were conducted to diagnose skin diseases. For recurrent skin diseases, only those with current symptoms and cutaneous lesions were diagnosed as cases. AD was diagnosed according to the Williams criteria.[20] Hand eczema was diagnosed according to eczema (rash) on the fingers, finger webs, palms, or back of hands, which had appeared once and continued for at least two weeks or had appeared several times or had been persistent. Allergies and urticaria were diagnosed by clinical manifestations, potential triggers, and histories. Asthma, allergic rhinitis, and allergic conjunctivitis were self-reported according to doctors' diagnoses. We also combined some of the outcomes. Atopic march is an apparent progression of allergic diseases from AD, to allergic asthma (AA) to allergic rhinitis (AR) and allergic conjunctivitis. [21, 22] We include the conditions of AD, AA, AR, and allergic conjunctivitis for the outcome of the atopic march. Allergic skin disease includes allergic reactions to food/drug/light, contact dermatitis, and urticaria. Participants with a history of atopic/allergic conditions but without the current disease are excluded.

²⁵₂₆ 114 **2.4 Covariates**

Demographic characteristics, socioeconomic status (annual family income and parental highest
 educational level), family history, behavioral factors (dietary, passive smoking, and bathing habits)
 were inquired by the questionnaire. The questionnaire used in the study was shown in Material S1.

3132 118 2.5 Statistical analysis

Categorical data were presented as number (%), and the between-group difference was tested using the chi-square test. Two-level Probit regression models (individual as level 1 and university as level 2) were used to estimate the associations of preschool exposure to antibiotics with atopic skin diseases in young adulthood, adjusting for level-1 covariates (gender, ethnicity, annual household income, and parental education) and level-2 random effects. The effect size was presented as relative risk (RR) and 95% confidence interval (CI). P< 0.05 was considered statistically significant for all tests. Statistical analysis was performed in SAS 9.4 (SAS Institute Inc., Cary, USA).

43 126 **3 Results**

A total of 27144 registries for new enrolment was identified; among them, 21086 (77.7%) consented to participate, and 20123 (74.1%) who underwent the health examination and completed the online questionnaire survey were included in the final analyses. The mean age was 18.3 ± 0.8 years and 10283(51.1%) were men. The characteristics of participants in the study are shown in Table 1. The prevalence rates of chronic urticaria, allergic reactions to food/drug/light, hand eczema, and AD were 1.89%, 2.27%, 3.35%, and 3.86%, respectively. The prevalence rates of AD and allergic skin disease were 3.86 % and 4.14%, respectively (Figure 1 and Table S1).

In general, URTI and the use of antibiotics were significantly associated with atopic and allergic
 diseases dose-dependently (Figure 1 and Table S1). For example, the prevalence of AD increased from
 3.39% to 4.11% and 4.79% in participants who reported rare or occasional use, frequent oral use, and

- frequent intravenous use of antibiotics, respectively. Consistent trends could be observed in all atopic
 and allergic diseases and their combinations
- ³ 138 and allergic diseases and their combinations.

After adjustments for sociodemographic factors (Figure 2 and Table S2), URTI and the use of antibiotics were significantly associated with atopic/allergic skin diseases in dose-response manners. For instance, compared to those reporting rare or occasional use of antibiotics, the RRs for AD in participants who reported frequent oral administration and intravenous injection of antibiotics was 1.18 (95% CI: 1.01, 1.39) and 1.36 (95% CI: 1.14, 1.62), respectively. For other allergies or atopic diseases of skin or beyond skin, the correlations were highly consistent despite some variations in the magnitude of the association.

- Furthermore, we have provided the data on the health seeking behavior dealing with a cold or fever in preschool age (shown in Table 2), and we found there were 66.2% among participants with the atopic march and 64.7% among participants with allergic skin disease showed that they/their parents would like to seek antibiotics treatment when they had a cold/fever in their preschool age. In those without atopic/allergic diseases, this proportion ratio was 61.5%. Indeed, we found a moderate but significant difference in the seeking behavior of antibiotic treatment between those with allergic skin disease/atopic march and healthy participants (P=0.001). Similar trends could be seen in AD patients and non-patients (P=0.034).
- Besides, because our study was not a prospective cohort, it was difficult to know if antibiotic use was ahead of suffering from AD. We further evaluated the joint effect of URTI and antibiotics on AD by including an interaction term in the model. As shown in Figure 3, in each category of antibiotic use, the frequency of URTI was positively associated with the risk of AD. Vice versa, in each category of URTI, antibiotic use was positively associated with AD according to the effect size, despite some insignificant results in categories with a small sample size.
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³⁴ ₃₅ 161 **4 Discussion**

This retrospective cohort study demonstrated that preschool exposure to antibiotics, either through oral administration or intravenous infusion, was associated with increased risks of having allergic and atopic skin diseases in young adulthood. Participants who reported frequent URTI in preschool-age also had higher risks of allergies and atopy.

Similar trends were identified in previous observational studies that early-life antibiotic use was associated with an increased risk of eczema, but there were still some inconsistent results. [23, 24] Meta-analysis including 22 studies with 394,517 patients concluded that children with antibiotics exposure in the first two years had increased odds of atopic eczema with an OR of 1.26 (95%CI: 1.15-1.37). Notably, the onset age of the outcomes in the included studies was the period of childhood (≤ 12 vears old). [7] A large population-based retrospective cohort study in twins showed that antibiotic use was also associated with an increased risk of eczema. However, the relationship between early-life antibiotic use and eczema was likely to be confounded by shared familial environment and genetic factors.[25] However, current data lacked the information regarding the atopic and allergic skin diseases occurred in late adolescence to early adulthood, while we firstly investigated the effects of preschool antibiotic in a retrospective study and revealed a positive association. Chinese parents were found to pay close attention to the preschool health of children and keep a non-exclusion attitude to antibiotics use. Using antibiotics at home, seeking medical care, and use antibiotics in the hospital for children was pervasive in China when parents dealing with children's respiratory tract infections.

However, the results should be discussed with caution as a doctor seeking behavior varies a lot in
 populations. In this setting, children with AD will seek a doctor frequently and more likely get a URTI

diagnosis if they also have a cold. Equally, children with asthma and wheezing will more frequently
 get a URTI diagnosis and are more likely to get an antibiotic.

Evidence showed that AD was the first manifestation of an atopic phenotype that begins in early childhood and the progression from AD to the diseases such as food allergy, asthma, and allergic rhinitis were more likely to be shown in adolescence. [22, 26, 27] The mechanisms behind the march from AD to allergic airway diseases and allergic conjunctivitis likely arise from initial epicutaneous allergen sensitization inducing robust local and systemic type 2 immune responses with increased production of type 2 cytokines including interleukin (IL)-4, IL-13, IL-31, and thymic stromal lymphopoietin.[28, 29] Most studies were prone to make these responses responsible for the commonly shared pathogenesis of cutaneous, airway, and conjunctiva inflammation, supporting the view that AD is not merely a disease confined to the skin, but is in fact, a systemic disease.[30, 31] Therefore, it could be explained that the increased risks beyond skin manifestations in young adulthood were consistent with those of skin diseases and some with even greater effect sizes. While not fully understood, the underlying mechanism of the association between antibiotics and atopic and allergic diseases can be elucidated by microbial diversity. The gut microbial community is dynamic and variable during the first 3 years of life, before stabilizing to an adult-like state.[32] Studies have demonstrated continued development through childhood into the teenage years.[33, 34] Dietary intake plays a key role in the development period of the gut microbiome. Breast-fed infants have microbiota enriched in *Lactobacillus*, *Staphylococcus*, and *Bifidobacterium*. Studies have shown that human milk contain symbiotic and potentially probiotic microbes, and isolates supplementation of Bifidobacteria was found to be effective in the primary prevention of allergic diseases.[35-37] But among children of preschool age, the dominance of *Bifidobacterium* diminishes with the alteration in dietary intake.[15] On the other hand, the high prevalence of antibiotic use may also lead to a concurrent increase in antibiotic-resistant bacteria.[38, 39] Antibiotic-treated children have a less diverse gut microbiota and less stable communities. Antibiotic therapy affects microbiome variety and thus may increase the risk of atopic diseases.[40, 41]

In our study, increased risks of atopic march or allergic diseases were observed in students who reported frequent URTI. Another potential explanation was related to the infections which could also affect microbial conditions. Except for the change in diet, children of preschool age tend to be exposed to more diverse microbes and infectious diseases including URTI in kindergarten or external environments. Respiratory viral infections, in particular, have been shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut, [42] which could further shape atopic microenvironments.

Several limitations should be noted, and the results should be interpreted with caution. First, recall bias in the measurement of exposure to antibiotics might have been introduced. While recall bias on the frequency of antibiotics use and URTIs should not be ignored, this is a limitation in most retrospective studies. Besides, selection bias might also be introduced as students with skin conditions might be more interested to participate and recall carefully. We are not able to validate the medical records because China does not have a registry system for primary care, and a large number of patients with mild conditions also visit doctors in secondary and tertiary hospitals. While participants could obtain the information from their parents, but unfortunately, we could not evaluate the extent of recall bias. Similarly, for the conditions of the disease including asthma, allergic rhinitis, and allergic conjunctivitis, which we collected based on both clinical diagnosis and questionnaire data, we could not ignore the atopic conditions in the past that might not be existing anymore, though in

previous studies, the 'atopic march' referred to the sequential development of symptoms and was
 227 considered to be not strictly limited by the occurring time. [43,44] Those will be in our further
 228 consideration in future studies.

Second, there was a lack of information about the type and dose of antibiotics, as well as some antibiotic use for the treatment of low respiratory tract infection, skin infections, and other infections, which was not collected while could also affect the microbiome. So we could not attribute the associations to specific antibiotics use. Third, we noticed that some factors related to the allergic/atopic conditions in preschool age could be ignored, such as prematurity, the doctor seeking behavior, etc., and we had difficulty in fully collecting of related information and need to explain the results with caution. Last but not least, there might be a reversed causal relationship because antibiotics could be used in the treatment of AD and other conditions accompanied by bacterial infection. We assessed the role of URTI and antibiotics separately, because the two variables were significantly correlated (contingency coefficient=0.4, P<0.001) and were therefore not included in the same model to avoid collinearity and biased estimation of parameters. It is possible that the association of URTI with AD and allergies is confounded by antibiotics, and vice versa.

However, both infection and antibiotics may be correlated with allergies/atopies, with different mechanisms. Although under the hygiene hypothesis, exposure to pathogens during infancy and early childhood has been proposed to explain the lower prevalence of asthma and other atopic diseases among children in developing countries, [45, 46] some studies showed that early respiratory infections could not protect against atopic eczema or recurrent wheezing, but could drive the development of atopic disease. [47-51] Atopic sensitization, a process of generation of specific immunoglobulin E (sIgE) when exposed to an innocuous antigen, was common to all allergic diseases. As preschool URTI most probably represents viral infections in the majority of cases, some studies investigated a potential mechanistic explanation for how a respiratory viral infection could drive the development of atopic sensitization and disease. Martorano et al. used a Sendai virus to establish the mouse model mimicking a human limited respiratory syncytial virus infection and found that Sendai virus infection could promote the crosslinking of high-affinity IgE receptor (FceRI) on the lung conventional dendritic cells (cDC), which led to the production of the chemokine CCL28, recruiting IL-13 and driving the development of mucous cell metaplasia and airway hyperreactivity.[52] Another animal study found that except for the increase of sIgE against Sendai virus in mice, there was also a large increase in total IgE and it remained elevated long after the viral infection being resolved.[53] This notion has further been fuelled by findings that mice infected with the flu virus developed virus-specific mast cell degranulation in the skin, indicating a possible pathway of viral infections that could mediate allergic symptoms.[54] Besides, the respiratory viral infections were shown to initiate a cascade of host immune responses altering microbial growth in the respiratory tract and gut. [42, 55] However, we cannot ignore that infections that do not require antibiotics are not captured in our design, such that it is difficult to assess whether the observed association is caused by a specific infection or antibiotics because they occur simultaneously in many cases.

Our study also has strengths. The primary strength is that the sample size for the retrospective cohort study was large. Second, the outcomes were diagnosed by specialists. In contrast, some previous studies used self-reported diagnoses that might introduce misclassification bias. Third, the study had a relatively large and representative sample, and sufficient variations in geographic regions and sociodemographic subgroups. The random effect at the university level was fitted by the 2-level models, resulting in an unbiased estimation of associations.

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To conclude, preschool children exposed to URTI or antibiotics may be at higher risks of atopic and

allergic skin diseases in their young adulthood, especially among those who frequently had URTI or

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275 5 Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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279 6 Ethics statement

This study was conducted according to the guidelines established in the Declaration of Helsinki. All procedures involving patients were approved by the institutional research ethics boards of Xiangya Hospital, Central South University (Changsha, China). Informed consent was obtained from all the students before the investigation.

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¹⁹285 7 Patient and Public Involvement Statement

21 286 This is a retrospective cohort study based on the data from the China College Student Skin Health 22 287 Study (CCSSHS). The first-year college students from five universities were recruited and 23 288 investigated. They underwent a health examination and completed a questionnaire survey, and the 24 25 289 results will be disseminated to study participants by a medical examination report. Participants were 26 290 not involved in the design and implementation of the study. 27

28 29 291 8 Author contributions

³⁰ 292 Dr. Minxue Shen, Dr. Xiang Chen, and Dr. Yi Xiao are joint corresponding authors and have full
 ³¹ 293 access to all the data in the study and take responsibility for the integrity of the data and the accuracy
 ³⁰ 294 of the data analysis.

- 295 Concept and design: Shen, Chen, and Xiao.36
- Acquisition, analysis, or interpretation of data: Y.J. Li, Jing, and Huang
- ³⁹ 297 Drafting of the manuscript: Y.J. Li
- $\frac{41}{42}$ 298 Critical revision of the manuscript for important intellectual content: All authors.
- ⁴³₄₄ 299 Statistical analysis: Shen, Xiao, and Y.J. Li.
- Administrative, technical, or material support: Su, J. Li, Tao, Shan, Wang, Kang, and Wu.
- 47 48 301 Supervision: Chen
- 50 302

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- **303 9 Conflict of interest**
- $_{55}^{54}$ 304 The authors declare no conflict of interest.
- 56 57 305
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Preschool antibiotics and atopic/allergic diseases

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Figure legends

- Figure 1. The prevalence of atopic and allergic diseases in exposure vs. non-exposure group of antibiotics and URTI.
- Figure 2. Association of early-life exposure to antibiotics with the risk of atopic/allergic diseases later in life. RR: risk ratio; CI: confidence interval.

Figure 3. The joint effect of URTI and antibiotics on AD after including an interaction term in the model. RR: risk ratio; CI: confidence interval.

Supplementary file captions

- Material S1. Chinese college students health survey questionnaire (Translation version in English).
- Table S1. The prevalence of atopic and allergic diseases in college students.
- id Ur. Table S2. Association of antibiotic and URTI exposure with atopic and allergic diseases in college students.

	11	70
Gender		
Male	10283	51.1
Female	9840	48.9
Income (CNY)		
<10,000	2168	10.8
10,000–29,999	4376	21.7
30,000–49,999	3465	17.2
50,000–99,999	4417	22.0
100,000–199,999	4063	20.2
≥200,000	1634	8.1
Parental highest education		
Primary school	1320	6.6
Middle school	5316	26.4
High school	5021	24.9
College and above	8466	42.1
Ethnicity		
Han Chinese	16218	80.6
Other ethnicities	3905	19.4

	_	Health seeking behavior, n (%) ^b				0) }
Disease condition	Total Ig	Ignore them	Drink water or have a rest	Receive antibiotics orally or intravenously	Receive Chinese ateq traditional traditional to the traditional to the t	Unknov
Skin		6			xt an	2
Atopic dermatitis	776	20 (2.6)	370 (47.6)	512 (65.9)	194 (25.0) a u	3 (0.3
Hand eczema	675	32 (4.7)	343 (50.8)	430 (63.7)	149 (22.0) ta A	4 (0.5
food/drug/light	456	9 (2.0)	227 (49.7)	286 (62.7)	95 (20.8) ni (5	1 (0.2
Chronic urticaria	381	8 (2.1)	158 (41.4)	257 (67.4)	100 (26.2) g	1 (0.3
Allergic skin disease ^c	833	17 (2.0)	384 (46.0)	539 (64.7)	194 (23.2) A	2 (0.2
Beyond skin					aini go	
Atopic march ^d	3139	66 (2.1)	1542 (49.1)	2081 (66.2)	بو (23.1) 728	12 (0.3
Allergic conjunctivitis	153	4 (2.6)	83 (54.2)	107 (69.9)	36 (23.5) and	0 (0)
Allergic rhinitis	2273	42 (1.8)	1135 (49.9)	1515 (66.6)	532 (23.4) si	8 (0.4
Asthma	303	7 (2.3)	154 (50.8)	206 (67.9)	70 (23.1) n i	2 (0.6
Without atopic/allergic diseases	16343	597 (3.7)	7761 (47.4)	10057 (61.5)	3058 (18.7) fechn	76 (0.4
^a Multiple selections are allowed	in the questionn	aire.			ologi	<u>،</u> د
^b Proportion ratios in populations	•				es.	י ה ס
^c Allergic skin disease includes al	llergic reactions	to food/drug/light, co	ntact dermatitis, and	urticaria.	r Age	>
 ^b Proportion ratios in populations ^c Allergic skin disease includes al 	llergic reactions	to food/drug/light, co	ntact dermatitis, and	urticaria.		


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338x170mm (300 x 300 DPI)



Supplementary file captions

Material S1. Chinese college students health survey questionnaire (Translation version in English)

Table S1. The prevalence of atopic and allergic diseases in college students.

Table S2. Association of antibiotic and URTI exposure with atopic and allergic diseases in college students.

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Material S1. Chinese college students health survey questionnaire (English version)

Chinese college students health survey questionnaire

Informed consent

Welcome to participate in the Chinese University Student Health Survey. To promote better health management for Chinese college freshmen, you are invited to fill out a questionnaire including several parts: (A) General information; (B) Medical history, (C) Lifestyle habits, (D) Skin health, which take about 15 minutes to answer. We will provide you with reasonable health education and health management based on this information, combined with the results of the health checkup. All the information you fill in will be kept strictly confidential. Continue to fill in the following content, indicating that you and your guardian have understood and are willing to continue to cooperate with our work. Thank you!

A. General information

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0	College C) P	ostgraduate or	0	Unclear					
		a	bove							
A08. Your mother's highest education (Single selection)										
0	Primary school or	D N	liddle school	0	High school					
	blow									
0	College C) P	ostgraduate or	0	Unclear					
		a	bove							
B. Me	dical History									
B01. H	lave you ever been	spec	cifically diagnosed w	with	any of the following					
cardiov	ascular or metabolic di	iseas	es? (Multiple selection	ıs ar	e allowed)					
	Hypertension		Coronary heart		Hyperlipidemia					
			disease							
	Obesity		Fatty liver		Gout					
	Psoriasis		None of above							
В02. Н	ave you ever been di	agno	sed with any of the	follc	owing allergic diseases?					
(Multip	le selections are allow	ed)								
	Asthma		Allergic Rhinitis		Allergic					
					conjunctivitis					
	Eczema		Urticaria		None of above					
B03. H	ave you ever been dia	gnos	ed with any of the fo	llow	ing infectious diseases?					
(Multip	le selections are allow	ed)								
	Tuberculosis or other		Hepatitis B		Hepatitis C					
forms o	f tuberculosis									
	Helicobacter pylori		HIV infection		None of above					
infectio	n									
B04. H	ave you ever been dia	gnos	ed with any of the fo	llow	ing endocrine diseases?					
(Multip	le selections are allow	ed)								

	Type 1 diabetes		Type 2 diabete	es		Polycystic ovarian
						syndrome
	Hypertrichosis		Hypothyroidis	m		Hyperthyroidism
	Graves disease		l Hashimoto			None of above
			thyroiditis			
B05.Ha	ve you ever been d	liagno	sed with any of	the fol	low	ing immune diseases?
(Multip	le selections are allo	wed)				
	SLE		Scleroderma			Sjogren syndrome
	Uveitis		Rheumatoid arth	hritis		Dermatomyositis
	None of above					
B06. H	lave you ever been	n diaş	gnosed with any	y of th	e f	following hematologic
diseases	s? (Multiple selection	ns are	allowed)			
	Iron-deficiency		Megaloblastic			Thalassemia
anemia			anemia			
	Anemia		Hemophilia			leucocythemia
	Lymphadenoma		None of above			
B07. H	Iave you ever bee	en dia	ignosed with an	ny of 1	he	following mental or
neurolo	gical disorders? (Mu	ltiple	selections are all	owed)		
	ADHD and attention	on det	ficit 🛛 Depres	sive dis	ord	er 🛛 Anxiety
disorde	r					
	Schizophrenia		□ None o	of above		
B08. H	ave you ever had ar	ny of t	the following foo	od allerg	gies	? (Multiple selections
are allo	wed)					
	None		Milk	🗆 Eg	g	
	Wheat		Soybean	□ Fis	h	
					icto	anna (a a shuinn
	Nuts		Fruit	L Cr	ista	ceans (e.g., shrimp,
	Nuts		Fruit	cra	b, e	etc.)

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Images is (e.g., aspirin) Images is (free is (fre
Anticonvulsant Chemotherapy Others arugs Image:
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B10. Have you ever been allergic to any of the following environmental substances? (Multiple selections are allowed) Image: None Dust mite Animal skins Pollen Cockroach Others Cockroach Others Image: None Others B11. Do you have an excessive but bite response? (Single selection) Image: None Image: None Image: None </td
(Multiple selections are allowed) None Dust mite Mycete Animal skins Pollen House dust Cockroach Others Unclear B11. Do you have an excessive but response? (Single selection) No Yes B12. In the past year, have you had a dog, cat, or other small stuffed animal such as rabbit, guinea pig, hamster, etc.? (Multiple selections are allowed) Cat No Dog Cat No Dog Cat Other stuffed Unclear B13. Do you have a long history of close exposure to chemicals? (Multiple selections are allowed) selections are allowed) Gasoline Soli varnish Formaldehyde Gasoline Oil varnish Others Others
Image: None Image: Dust mite Image: None Image: None<
Animal skins Pollen House dust Cockroach Others Unclear B11. Do you have an excessive but response? (Single selection) No Yes B12. In the past year, have you had a dog, cat, or other small stuffed animal such as rabbit, guinea pig, hamster, etc.? (Multiple selections are allowed) Other stuffed Ot
Cockroach Others Unclear B11. Do you have an excessive but response? (Single selection) No Yes B12. In the past year, have you had a dog, cat, or other small stuffed animal such as rabbit, guinea pig, hamster, etc.? (Multiple selections are allowed) No Dog No Dog Other stuffed Unclear B13. Do you have a lowed istory of close exposure to chemicals? (Multiple selections are allowed) selections are allowed)
B11. Do you have an excessive bug bite response? (Single selection) No Yes B12. In the past year, have you had a dog, cat, or other small stuffed animal such as rabbit, guinea pig, hamster, etc.? (Multiple selections are allowed) No Dog Cat Other stuffed Unclear B13. Do you have a long history of close exposure to chemicals? (Multiple selections are allowed) selections are allowed) In None In None In Oil varnish In Oil varnish
No Yes B12. In the past year, have you had a dog, cat, or other small stuffed animal such as rabbit, guinea pig, hamster, etc.? (Multiple selections are allowed) No Dog No Dog Other stuffed Unclear B13. Do you have a long history of close exposure to chemicals? (Multiple selections are allowed) selections are allowed None Formaldehyde Oil varnish Others
B12. In the past year, have you had a dog, cat, or other small stuffed animal such as rabbit, guinea pig, hamster, etc.? (Multiple selections are allowed)
rabbit, guinea pig, hamster, etc.? (<i>Multiple selections are allowed</i>) No Dog Cat Other stuffed Unclear animals B13. Do you have a long history of close exposure to chemicals? (<i>Multiple selections are allowed</i>) selections are allowed) Oil varnish Promaldehyde Cat Cat Cat Cat Cat Cat Cat Ca
□No□Dog□Cat□Other stuffed□UnclearanimalsB13. Do you have a long history of close exposure to chemicals? (Multiple selections are allowed)(Multiple□None□Formaldehyde□□Oil varnish□Others□
Other stuffed Unclear animals B13. Do you have a long history of close exposure to chemicals? (Multiple selections are allowed) None Formaldehyde Oil varnish Others Others
animals B13. Do you have a long history of close exposure to chemicals? (Multiple selections are allowed) selections are allowed) None Formaldehyde Oil varnish Others
B13. Do you have a long history of close exposure to chemicals? (Multiple selections are allowed) None Formaldehyde Gasoline Oil varnish Others Unclear
selections are allowed) Image: Selections are allowed) Image: Selections are allowed) Image: None Image: Select
□ None □ Formaldehyde □ Gasoline □ Oil varnish □ Others □ Unclear
□ Oil varnish □ Others □ Unclear
B14. Have you used or taken any medication almost every day for the last 2 weeks?
(Multiple selections are allowed)
□ None □ Antibiotics □ Nonsteroidal
□ Hormone □ Antituberculosis anti-inflammatory
drugs drugs and analgesics
□ Others □ Clear (NSAIDS)

O No	0	Yes	0	Unclear
B16. How often do you	have	"colds and fever	s" in y	our early school yea
(before age of 7 years old)? (Sin	gle selection)		
• Rare (≤ 1 time/year)	0	Occasional	0	Often
	(2-3	times/year)	(4	or more times/year)
B17. Which way did yo	u (or	your parents) us	ually de	eal with your "cold
fever" in the early school	age y	ears? (<i>Multiple se</i>	lections	are allowed)
□ Ignore them		Drink more water	or 🗆	Receive antibiotics
	5	have a rest		orally
□ Oral Chinese		Receive antibiotics		Others
Traditional medicine		intravenously		
	ving f	requency of antil	oiotic us	e can improve or cu
B18. Which of the follow			0 (0)	la calaction)
B18. Which of the follow your "Cold or fever" in the	ne ear	ly school age year	s? (Sing	ie selection)
B18. Which of the followyour "Cold or fever" in theO Rarely, it usual	he ear	ly school age year ared O occasion	nal	ie selection)
 B18. Which of the follow your "Cold or fever" in the O Rarely, it usual without antibiotic treatment 	he ear lly cu t	ly school age year ured O occasion	s ? (<i>Sing</i> nal	ie selection)

C. Lifestyle Habits

C01.Do you smoke (refers to smoking at least one cigarette a day for more than six months) (*Single selection, jump to C3 if you choose "hardly"*) • Hardly • < 1 packet • 1-2 packets • > 2 packs/day /day /day
(about 20 cigarettes in a

C02. If you smoke, how many years have you smoked in total so far? (Single selection)

packect)

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0	< 1 year	0	1-3 years		$> 3 y_{0}$	ears
C03. In	n the last month	, your	frequency of	passive sn	noking is	(the involuntary
inhalati	on of smoke cau	ised by	other people	's smoking	in your l	iving or working
onviron	mont) (Single col	action i	1 1	way ahaara	"hardhi"	5 5
cirviton	inent) (single seu	ection, j	ump to CS if j	you choose	naraiy)	
0	Hardly	0	< 1 day/wee	k	O 1-2 da	ays/week
0	3-5 days/week	0	6-7 days/we	ek		
С04. Н	ow many years ha	ave you	been second-	hand smoki	ng? (Sing	le selection)
0	< 2 years	ο	2-3 years	O 4-6 year	s C	> 6 years
C05 H	ow often do you	ı drink	alcohol? (refe	erring to or	ce a wee	k for at least six
		·				in for at foult bix
months) (Single selection	ı, jump	to C9 if you c	hoose "hara	ly")	
0	Hardly	0	Once a week	κ.	O 2-4 ti	mes/week
0	5-7 times/week	0	8-10 times/v	week	o > 10 t	times/week
C06. H	ow many years ha	ave you	been drinking	g? (Single se	election)	
•	_ 1		1 2			5
0	< Tyear	0	1-Syears	- 4-Syears		> 5 years
C07. W	'hat's your main d	rink? (S	ingle selectio	<i>n</i>)		
0	Beer O	Liqueur	O Red	l wine O	Sweet	• Chinese
					wine	rice wine
C09 11	aw much de ver	drink or	avoraça acal	timo? (Sim		ion)
С00. П			i avelage edel		zie selecti	.011)
0	Less (1 bottle of	beer, o	r 50-100g oth	er types of a	alcohol)	
0	Medium (2 bottl	les of be	er, or 100g of	ther types of	alcohol)	
•	Much (three bot	tles of b	r	other types	falcohol)
U			icer, or 150g (since types ()
0	A lot (more that	in 3 bo	ttles of beer,	or more th	an 150g	of other types of
alcohol)					
n si#	Hoalth					
D. SKI	1 11741111					

D01.How many showers do you take per week in the spring and fall? (Single selection)

 ≤ 1 time per week **O** $2 \sim 4$ times per week 5~7 times per week

D0.	2. Но	ow long	do you 1	take a s	show	ver in spr	ing and	fall? (Si	ngle	selectio	on)
0	< 5	minutes		C) 5	-10 minu	ites	0	11.	-20 mir	nutes
0	21-	30 minu	tes	C) >	· 30 minu	ites				
D0	3. W	hat kind	of toile	tries do	o you	ı use mo	st? (Sing	le select	tion)		
0	Not	ne	C	D Soa	ap		O Sh	iower ge	el	0 (Others
D04	4. In	spring a	nd fall,	the ten	npera	ature of y	our bath	n is (<i>Sin</i> g	gle s	election	n)
0	Lov	v tempe	erature(<	<35 () (Close to	the	body	0	High t	temperature
	cen	tigrade)			te	emperatu	re(35-4()		40 cen	tigrade)
					c	entigrad	e)				
(Su D0 sele	0 6. He	No ow ofter	do you	ı use f	acial	cleansin	O Yo ng produ	es acts (e.g	. cle	anser, s	soap)? (Sing
(Su D0 sele	O 6. He ection	No ow ofter n) Hardly	do you	ı use f O Us	acial	cleansin	• Ye ng produ	es acts (e.g	. cle day	anser, s O ≥	soap)? (<i>Sins</i> etwice per
(Su D0 sele	0 6. He ection 0 7. He	No ow ofter n) Hardly	do you	u use f O Us	acial ually	cleansin	• Young produce of the product of th	es acts (e.g ace per o ast two	. cle day vear	anser, s • ≥ d s? <i>(Sins</i>	soap)? (Sing etwice per lay
D00 sele	0 6. Ho ection 0 7. Ho	No ow ofter n) Hardly ow often > Twice	do you have yo	u use f O Us ou was	acial ually hed	cleansin your hair	• Yo ng produ • On in the p er day	es acts (e.g nce per a ast two	. cle day year	anser, s ○ ≥ d s? <i>(Sing</i>	soap)? (Sing etwice per lay gle selection Once on
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D04 sele	0 6. He ection 7. He 0 8. In	No ow often n) Hardly \ge Twice Once ev the past	do you have yo per day very 2-6 two yea	u use f D Us ou was y days ars, wh	acial ually hed <u>c</u> 0 at ki	cleansin your hair Once p Once a nd of toi	• Yo ng produ • On • in the p er day week on letries yo	es acts (e.g nce per o ast two ast two	. cle day year	anser, s $O \ge d$ d s? (Sing O ingle set	soap)? (Sing etwice per lay gle selection Once on alternate days
D00 D00	0 6. Ho ection 7. Ho 7. Ho 8. In 8. In	No ow often n) Hardly \ge Twice Once ev the past None	do you have yo per day very 2-6 two yea O	u use f D Us ou was y o days ars, wh Shamp	acial ually hed y O at ki	cleansin your hain Once p Once a nd of toi	• Yo ng produ • On in the p er day week on letries yo champoo	es acts (e.g nce per o ast two ast two	. cle day year	anser, s $O \ge d$ d s? (Sing O ingle second + O	soap)? (Sing etwice per lay gle selection Once on alternate days election) Others
D0 sele	0 6. Ho ection 7. Ho 7. Ho 8. In 0	No ow ofter n) Hardly ow often ≥ Twice Once ev the past None	do you have yo e per day very 2-6 two yea O	u use f O Us ou was y o days ars, wh Shamp	acial ually hed <u>v</u> o at ki	cleansin your hair Once p Once a nd of toi	• Yo ng produ • On in the p er day week on letries yo ondition	es acts (e.g nce per o ast two ast two ou use is er	. cle day year	anser, s $O \ge d$ d s? (Sing O ingle second + O	soap)? (Sing etwice per lay gle selection Once on alternate days election) Others

		care	e products	
	Hair gel	□ Oth	ers	
D10. In	the last two years, how ofte	en have you dye	d your hair? (Single selection)
0	Never O	Less than once	e a year O	Once every 2 to 6
				months
0	Once every 7 to 11 O	More than one	ce a	
months		month		
D11. In	the past two years, your per	rm frequency is	(Single select	ion)
0	Never O	Less than once	e a year O	Once every 2 to 6
				months
0	Once every 7 to 11 O	More than one	ce a	
months		month		
D12. D	o you have frequent itchy sl	tin, and to what	extent (0 is no	ot itchy at all and 10
is extrem	mely itchy)?			
0 -	- 1 - 2 - 3 - 4	- 5 - 6	- 7 - 8	- 9 - 10
D13. D	o you have regular skin pai	n, and to what e	extent (0 is no	pain at all and 10 is
extreme	e pain)?			
0 -	- 1 - 2 - 3 - 4	- 5 - 6	- 7 - 8	- 9 - 10

Page 31 of 31				BMJ Open		jopen-20 1 by copy		
1 2 3 4 5	Table S1. The prevalence of	f atopic and allergi	c diseases in coll	ege students		20-047768 on 2′ /right, including		
6		N Provelence		URTI, n (%)		1 Sep	Antibiotics, n (%)	
9 10	Disease	(%) ^a	Rare	Occasional	Frequent	Raregi Raregi Raregi eigi	Often,orally	Often, intravenously
10 11	Skin					2021. 1eme		
12 13	Atopic dermatitis	776 (3.86)	174 (2.99)	459(3.99)	143(5.1)	6 33.39)	263(4.11)	164(4.79)
14	Hand eczema	675(3.35)	145 (2.49)	407(3.54)	123(4.38)		243(3.79)	122(3.57)
15 16 17	Allergic reactions to food/drug/light	456(2.27)	121(2.08)	255(2.22)	80(2.85)	adea(2.06) d data n	152(2.37)	92(2.69)
18 19	Chronic urticaria	381(1.89)	96(1.65)	207(1.8)	78(2.78)		133(2.08)	78(2.28)
20	Allergic skin disease ^b	833(4.14)	217(3.73)	460(4)	156(5.56)		285(4.45)	167(4.88)
21 22	Beyond skin					omjo trair		
23	Atopic march ^c	3139(15.6)	687(11.79)	1825(15.88)	627(22.34)	37 <mark>2</mark> (13.33)	1101(17.19)	666(19.47)
24 25	Allergic conjunctivitis	153(0.76)	32(0.55)	84(0.73)	37(1.32)	and 63 0.61)	54(0.84)	36(1.05)
26 27	Allergic rhinitis	2273(15.6)	486(8.34)	1327(11.55)	460(16.39)	sing 98 (9.56)	809(12.63)	480(14.03)
28	Asthma	303(1.51)	46(0.79)	171(1.49)	86(3.06)	ar 60 (11) (1.08)	117(1.83)	75(2.19)
30 31 32 33 34 35 36 37 38 39 40 41	^a The total prevalence of atopic and ^b Allergic skin disease includes alle ^c Atopic march refers to atopic der	l allergic diseases in our ergic reactions to food/dr matitis, allergic asthma,	study population. rug/light, contact den allergic rhinitis, and	rmatitis, and urticaria. allergic conjunctivitis. 10		ine 11, 2025 at Agence Bibliograph hnologies.		
42 43 44		For peer re	view only - http://b	mjopen.bmj.com/site	/about/guidelines.xh	ique de l		

June 11, 2025 at Agence Bibliographique de l

ble S2. Association of antibioti	c and URTI exp	BMJ (bosure with atopic ar	Open Id allergic diseases	jopen-2020-047768 on ets 4 by copyright, including to the state in college state	5	Page 3
D'acces		URTI, aRR (95%CI) ^a	ı.	for u	Antibiotics, aRR (95%)	CI) ^a
Disease	Rare	Occasional	Frequent	Rare / occave i on all	Often, orally	Often, intravenously
Skin				er 202 elater		
Atopic dermatitis	Reference	1.32 (1.09, 1.54)	1.59 (1.27, 1.98)	Reference t	1.18 (1.01, 1.39)	1.36 (1.14, 1.62)
Hand eczema	Reference	1.32 (1.08, 1.56)	1.60 (1.26, 2.02)	e Sown Reference e	1.27 (1.08, 1.49)	1.17 (0.95, 1.44)
lergic reactions to food/drug/light	Reference	1.10 (0.92, 1.28)	1.30 (1.04, 1.63)	ndceur Referenceur	1.15 (0.97, 1.37)	1.36 (1.12, 1.65)
Chronic urticaria	Reference	0.97 (0.76, 1.17)	1.58 (1.21, 2.05)	Reference B	1.13 (0.90, 1.40)	1.39 (1.09, 1.78)
Allergic skin disease ^b	Reference	1.04 (0.89, 1.20)	1.46 (1.22, 1.76)		1.16 (1.01, 1.34)	1.33 (1.13, 1.57)
Beyond skin				р://Ы 3, АН1		
Atopic march ^c	Reference	1.39 (1.26, 1.52)	2.08 (1.85, 2.34)	Referenter op	1.35 (1.24, 1.48)	1.55 (1.40, 1.71)
Allergic conjunctivitis	Reference	1.89 (1.13, 2.66)	3.49 (2.05, 5.96)	Reference b	1.58 (1.08, 2.32)	2.72 (1.75, 4.23)
Allergic rhinitis	Reference	1.43 (1.27, 1.59)	2.13 (1.86, 2.43)	Reference co	1.39 (1.26, 1.53)	1.56 (1.39, 1.74)
Asthma	Reference	2.56 (1.69, 3.43)	4.89 (3.20, 7.47)	Referentere o	1.92 (1.52, 2.43)	2.10 (1.64, 2.70)

^a Adjusted for the fixed effects of gender, income, education, passive smoking, and ethnicity and the random effect of university.
 ^b Allergic skin disease includes allergic reactions to food/drug/light, contact dermatitis, and urticaria.
 ^c Atopic march refers to atopic dermatitis, allergic asthma, allergic rhinitis, and allergic conjunctivitis.

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