



# Association of frequent intake of fast foods, energy drinks, or convenience food with atopic dermatitis in adolescents

Soo Ick Cho<sup>1,2</sup> · Hanjae Lee<sup>1,2</sup> · Dong Hun Lee<sup>1,2</sup> · Kyu-Han Kim<sup>1,2</sup>

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## Abstract

**Purpose** Specific food consumption, besides food allergy, may aggravate atopic dermatitis (AD). However, previous reports on the association between AD and food intake in adolescents are scarce. The aim of this study was to determine the relationship between AD and specific food consumption frequency in adolescents.

**Methods** A cross-sectional analysis using data from the Korea Youth Risk Behavior Web-based Survey 2017 was performed. The frequency of food consumption in the recent-diagnosed AD group (AD diagnosed within 12 months) compared to those in the previous-diagnosed AD (AD diagnosed more than 12 months ago) or control group were investigated.

**Results** A total of 53,373 participants were eligible for this study. The weighted prevalence of the recent-diagnosed AD and the previous-diagnosed AD was 7.39% and 18.00%, respectively. When compared with subjects with the previous-diagnosed AD, those with the recent-diagnosed AD were significantly more likely to frequently consume fast foods (odds ratio OR 1.405; 95% CI 1.150–1.717), energy drinks (OR 1.457; 95% CI 1.175–1.807), or convenience food (OR 1.304; 95% CI 1.138–1.495). Patients of the recent-diagnosed AD were significantly more likely to frequently consume fast foods (OR 1.374; 95% CI 1.155–1.634) than the control group. The differences in the frequency of specific food consumption among groups were more pronounced in high school students than in middle school students.

**Conclusions** Frequent intake of fast foods, energy drinks, and convenience food was related to the recent-diagnosed AD in adolescents. Prospective cohort and interventional studies are needed to identify causal relationships.

**Keywords** Adolescents · Atopic dermatitis · Convenience food · Energy drink · Fast food · Food

## Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic erythematous lesion usually on face or flexural areas of the body. The prevalence of AD has been reported to be up to 25% during childhood and 2–3% for adults [1]. However, recent studies showed that

the persistence of AD from childhood to adult is considerably higher than previously reported, suggesting that AD is a lifelong disease [2, 3]. In addition, a large number of newly diagnosed AD cases were reported in adolescents [4, 5]. Thus, identification of contributing factors for the provoking or persistence of AD in adolescents is important to prevent or predict adult AD. Previously, the severity, onset, or duration of AD, gender, household income, and the presence of other atopic diseases or hand eczema were shown to be related to the persistence of AD [2–4].

AD is a complex disease with clinical heterogeneity and multifaceted pathomechanisms triggered by various environmental factors in a genetically susceptible population [6–8]. Diet has been thought to play an important role in AD [7], and, in particular, the link between AD and food allergy has been well documented in infants and young children with refractory AD [9, 10]. However, the impact of food in AD appears to decline in older children and is relatively infrequent in adulthood [10–12]. In addition to

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✉ Dong Hun Lee  
ivymed27@snu.ac.kr

<sup>1</sup> Department of Dermatology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea

<sup>2</sup> Institute of Human-Environment Interface Biology, Seoul National University, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea

common culprit food, such as egg or milk, the so-called westernized food, such as fast foods or food additives, have been reported to increase the risk of AD [13–17]. Furthermore, obesity also increases the risk of AD, and weight reduction may be helpful for the prevention and management of AD [18–20]. Previous studies of AD and food were conducted mainly in children; therefore, there is a lack of studies that evaluate the effects of food on AD in adolescents.

The Korea Youth Risk Behavior Web-based Survey (KYRBWS) has been conducted annually since 2005 by Korean Centers for Disease Control and Prevention (KCDC) [21]. The survey focuses on health-risk behaviors in Korean adolescents aged 12–18 years. It is cross-sectionally designed and contains systematic questionnaires about AD and various lifestyle factors, including the frequency of specific food consumption. Previous studies using this survey demonstrated the relationship between AD and demographic, psychologic, socioeconomic or health-related factors, such as obesity, stress, depression, smoking, and physical activity [22–29].

In this study, we aimed to evaluate the relationship between AD and dietary patterns of adolescents, based on the outcome from KYRBWS in 2017.

## Methods

### Data source and patient population

KYRBWS is an annual nationwide cross-sectional survey in the Republic of Korea [21]. The raw data of KYRBWS are available in the KCDC website (<https://yhs.cdc.go.kr/>). The selection of the participants was based on a multi-stage cluster sampling design to get a highly representative nationwide sample of Korean adolescent students [21]. The result of the survey contained demographic information (age, sex, residence, height and body weight). Each subject signed an informed consent form before participating in the survey. The reliability and validity of the survey have been documented by previous studies [30, 31].

The 13th KYRBWS in 2017 initially extracted a total of 64,991 students from 400 middle schools and 400 high schools, and 62,276 (95.8%) from 799 schools voluntarily and anonymously completed the questionnaires. The contents of the questionnaires from 2017 were almost analogous to those from 2016, except for a few minor modifications, for example, regarding dietary behaviors, the frequency and types of consumption of convenience food were added in the 2017 version. The study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1809-002-967).

### Definition of AD in KYRBWS database

The questionnaires about AD consisted of two steps: first, whether AD was ever diagnosed by physicians during lifetime was identified by asking “Have you ever been diagnosed with AD by a doctor?” If the participants answered “yes”, then the additional question asked whether AD was diagnosed within 12 months. Based on the results, the subjects could be classified into three groups: “recent-diagnosed AD” who were diagnosed with AD within 12 months, “previous-diagnosed AD” diagnosed with AD during lifetime but not within 12 months, and control group with no history of AD.

### Pre-processing of data regarding the frequency of specific food consumption and other adjusting factors

In the domain of ‘dietary behaviors’, the frequency of specific food consumption in the past week were asked, including how frequent the subject eats or drinks breakfast, fruits, carbonated drinks, energy drinks, sweetened drinks (excluding carbonated drinks or energy drinks), fast foods (such as pizza, hamburger, or fried chicken), instant noodles, snacks, vegetables, milk (including processed milk) and convenience food (as substitutes for regular meals). Before conducting the statistical analysis, the frequency of food consumption was divided as follows: none, 1–4 times in the past week (occasional), and 5 or more times in the past week (frequently).

Age, sex, height, and body weight of each subject were obtained for demographic analyses. Among the questionnaires in KYRBWS, residence (rural, small city, and large city; large cities included eleven most populated cities and one administrative capital city in Korea), sleep time, perceived stress, perception of getting enough sleep, alcohol use, socioeconomic status (SES), and other allergic diseases (asthma and allergic rhinitis) were collected for the confirmation of previously reported factors associated with AD. For five-step Likert scale questionnaires (perceived stress, perception of getting enough sleep, and SES), participants were re-categorized into three grades, i.e., mild, good, or low (grade 1 and 2 of the original scale), moderate or middle (grade 3), and severe, bad, or high (grade 4 and 5). Body mass index (BMI) was calculated from height and body weight, and subjects were categorized as follows: obese, BMI more than 25 or  $\geq$  95th percentile; overweight, BMI  $\geq$  85th percentile and  $<$  95th percentile; normal or underweight, BMI  $<$  85th percentile. Sleep time was classified into four grades (8 or more hours, more than 7 and less than 8 h, more than 6 and less than 7 h, and less

than 6 h). If alcohol was consumed within the past 30 days, it was classified as current alcohol drinking.

## Statistical methods

Pearson's Chi-square test was used for the  $2 \times 2$  analyses. To compare the frequency of specific food consumption between the recent-diagnosed AD and the previous-diagnosed AD or control group, logistic regression was conducted with or without adjustment of other related factors. The outcome of logistic regression was presented as odds ratio (OR) with 95% confidence interval (CI). Based on the multi-stage (schools and classes) cluster sampling design, the strata, cluster, and weight statements were employed for all statistical analysis. Basically, a  $p$  value  $< 0.05$  was considered statistically significant. Because the primary outcome (categorical frequency of food consumption related to AD) consisted of various choices up to 11, a Bonferroni correction was applied to multiple comparisons ( $p = 0.004545$ ). Subgroup analyses of middle school students and high school students, respectively, were also conducted for the frequency of specific food consumption with a  $p$  value  $< 0.05$

after adjustment of other related factors. All statistical tests were performed by SAS version 9.4 (SAS Institute Inc., Cary, NC).

## Results

### Prevalence of AD and distribution of AD-related factors

A total of 53,373 subjects (male 26,642; female 26,731) out of 62,276 were included in this study. (Fig. 1) Their mean age was  $15.03 \pm 1.75$  years (mean  $\pm$  standard deviation). Among them, the number of the recent-diagnosed AD patients was 3898, and that of the previous-diagnosed AD patients was 9574. The weighted prevalence of the recent-diagnosed AD and previous-diagnosed AD patients was 7.4% and 18.0%, respectively. The characteristics of AD-related factors were different among the three groups (Table 1). Univariate logistic regression analysis demonstrated that high BMI, high perceived stress, concurrent asthma or rhinitis, and low SES were statistically significant related factors for the recent-diagnosed

**Fig. 1** An illustration of selection of study population in the present study. Among a total of 62,276 participants, those without information of sleep time record ( $n = 7016$ ), height or weight ( $n = 1884$ ), and food intake record ( $n = 3$ ) were excluded. After exclusion, patients with recent-diagnosed atopic dermatitis were 3898, and those with previous-diagnosed atopic dermatitis were 9574, while the control group was 39,901

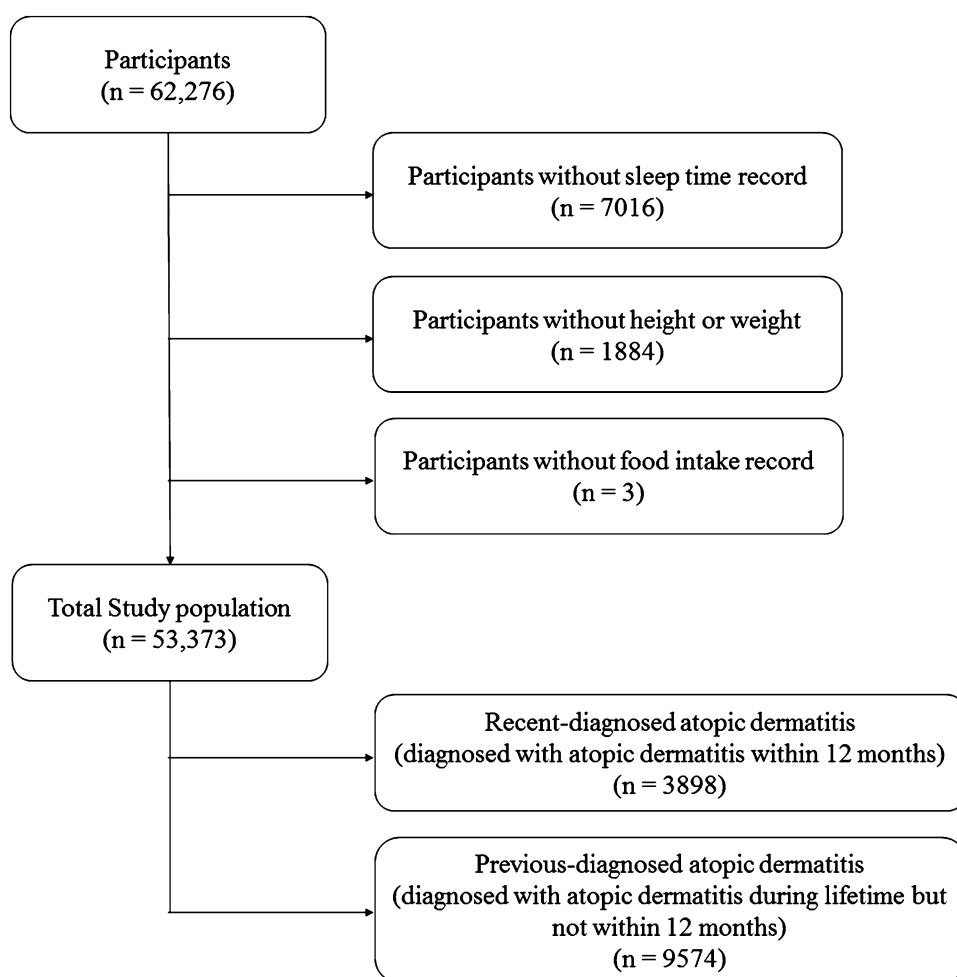


**Table 1** The demographics and characteristics of atopic dermatitis-related factors in the recent-diagnosed atopic dermatitis (diagnosed with atopic dermatitis within 12 months), the previous-diagnosed atopic dermatitis (diagnosed with atopic dermatitis during lifetime but not within 12 months) and control groups

|                                               | Recent-diagnosed atopic dermatitis ( <i>n</i> = 3898) | Previous-diagnosed atopic dermatitis ( <i>n</i> = 9574) | Control ( <i>n</i> = 39,901) |
|-----------------------------------------------|-------------------------------------------------------|---------------------------------------------------------|------------------------------|
| Age, mean $\pm$ standard deviation, years old | 15.09 $\pm$ 1.74                                      | 15.13 $\pm$ 1.72                                        | 15.01 $\pm$ 1.76             |
| Sex (%)                                       |                                                       |                                                         |                              |
| Male                                          | 1677 (43.02)                                          | 4191 (43.77)                                            | 20,774 (52.06)               |
| Female                                        | 2221 (56.98)                                          | 5383 (56.23)                                            | 19,127 (47.94)               |
| Residence (%)                                 |                                                       |                                                         |                              |
| Rural                                         | 286 (7.34)                                            | 668 (6.98)                                              | 3100 (7.77)                  |
| Small city                                    | 1903 (48.82)                                          | 4534 (47.36)                                            | 18,971 (47.55)               |
| Large city                                    | 1709 (43.84)                                          | 4372 (45.67)                                            | 17,830 (44.69)               |
| Body mass index (%)                           |                                                       |                                                         |                              |
| Normal or underweight                         | 3070 (78.76)                                          | 7814 (81.62)                                            | 32,497 (81.44)               |
| Overweight                                    | 220 (5.64)                                            | 463 (4.84)                                              | 1866 (4.68)                  |
| Obese                                         | 608 (15.60)                                           | 1297 (13.55)                                            | 5538 (13.88)                 |
| Sleep time (hours) (%)                        |                                                       |                                                         |                              |
| $\geq 8$                                      | 829 (21.27)                                           | 2063 (21.55)                                            | 10,119 (25.36)               |
| 7–8                                           | 931 (23.88)                                           | 2278 (23.79)                                            | 9818 (24.61)                 |
| 6–7                                           | 1067 (27.37)                                          | 2615 (27.31)                                            | 10,111 (25.34)               |
| <6                                            | 1071 (27.48)                                          | 2618 (27.34)                                            | 9853 (24.69)                 |
| Perceived stress (%)                          |                                                       |                                                         |                              |
| Mild                                          | 592 (15.19)                                           | 1717 (17.93)                                            | 8558 (21.45)                 |
| Moderate                                      | 1616 (41.46)                                          | 4031 (42.10)                                            | 17,082 (42.81)               |
| Severe                                        | 1690 (43.36)                                          | 3826 (39.96)                                            | 14,261 (35.74)               |
| Perception of getting enough sleep (%)        |                                                       |                                                         |                              |
| Good                                          | 840 (21.55)                                           | 2093 (21.86)                                            | 10,488 (26.29)               |
| Moderate                                      | 1235 (31.68)                                          | 3111 (32.49)                                            | 12,956 (32.47)               |
| Bad                                           | 1823 (46.77)                                          | 4370 (45.64)                                            | 16,457 (41.24)               |
| Alcohol use (%)                               |                                                       |                                                         |                              |
| Yes                                           | 600 (15.39)                                           | 1455 (15.20)                                            | 5977 (14.98)                 |
| No                                            | 3298 (84.61)                                          | 8119 (84.80)                                            | 33,924 (85.02)               |
| Concurrent asthma (%)                         |                                                       |                                                         |                              |
| Yes                                           | 266 (6.82)                                            | 207 (2.16)                                              | 703 (1.76)                   |
| No                                            | 3632 (93.18)                                          | 9367 (97.84)                                            | 39,198 (98.24)               |
| Concurrent rhinitis (%)                       |                                                       |                                                         |                              |
| Yes                                           | 1457 (37.38)                                          | 2283 (23.85)                                            | 6822 (17.10)                 |
| No                                            | 2441 (62.62)                                          | 7291 (76.15)                                            | 33,079 (82.90)               |
| Socioeconomic status (%)                      |                                                       |                                                         |                              |
| Low                                           | 645 (16.55)                                           | 1413 (14.76)                                            | 5353 (13.42)                 |
| Middle                                        | 1857 (47.64)                                          | 4537 (47.39)                                            | 18,385 (46.08)               |
| High                                          | 1396 (35.81)                                          | 3624 (37.85)                                            | 16,163 (40.51)               |

AD compared to both the previous-diagnosed AD and control (Table 2). In addition, age, female gender, sleep time, and perception of getting enough sleep were statistically significantly related in the recent-diagnosed AD compared to control.

### Relationship between AD and frequency of specific food consumption

The frequency of food or drink intake is summarized in Table 3. When compared between the recent-diagnosed

AD and the previous-diagnosed AD, frequent breakfast (OR 0.887; 95% CI 0.800–0.983), frequent consumption of carbonated beverages (OR 1.189; 95% CI 1.028–1.377), occasional consumption of energy drink (OR 1.162; 95% CI 1.060–1.274), frequent consumption of energy drink (OR 1.457; 95% CI 1.175–1.807), frequent consumption of fast foods (OR 1.405; 95% CI 1.150–1.717), frequent consumption of milk (OR 0.852; 95% CI 0.755–0.961) and frequent consumption of convenience food (OR 1.304; 95% CI 1.138–1.495) were significantly associated with the

**Table 2** Odds ratio of atopic dermatitis-related factors in the recent-diagnosed atopic dermatitis (diagnosed with atopic dermatitis within 12 months) compared to both the previous-diagnosed atopic dermatitis (diagnosed with atopic dermatitis during lifetime but not within 12 months) and control groups using univariate logistic regression analysis

|                                    | Recent-diagnosed atopic dermatitis to previous-diagnosed atopic dermatitis<br>Odds ratio (95% CI) | <i>p</i> value | Recent-diagnosed atopic dermatitis to control<br>Odds ratio (95% CI) | <i>p</i> value |
|------------------------------------|---------------------------------------------------------------------------------------------------|----------------|----------------------------------------------------------------------|----------------|
| Age                                | 0.991 (0.970–1.012)                                                                               | 0.410          | 1.030 (1.011–1.049)                                                  | 0.002          |
| Sex                                |                                                                                                   |                |                                                                      |                |
| Male                               | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Female                             | 1.023 (0.948–1.103)                                                                               | 0.561          | 1.413 (1.324–1.507)                                                  | <0.001         |
| Residence                          |                                                                                                   |                |                                                                      |                |
| Rural                              | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Small city                         | 0.988 (0.825–1.183)                                                                               | 0.898          | 1.086 (0.915–1.289)                                                  | 0.345          |
| Large city                         | 0.917 (0.766–1.099)                                                                               | 0.349          | 1.012 (0.853–1.200)                                                  | 0.893          |
| Body mass index                    |                                                                                                   |                |                                                                      |                |
| Normal or underweight              | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Overweight                         | 1.258 (1.067–1.483)                                                                               | 0.006          | 1.300 (1.128–1.499)                                                  | <0.001         |
| Obesity                            | 1.220 (1.098–1.356)                                                                               | <0.001         | 1.195 (1.088–1.313)                                                  | <0.001         |
| Sleep time (hours)                 |                                                                                                   |                |                                                                      |                |
| ≥ 8                                | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| 7–8                                | 0.987 (0.884–1.104)                                                                               | 0.824          | 1.118 (1.011–1.237)                                                  | 0.029          |
| 6–7                                | 1.015 (0.910–1.132)                                                                               | 0.789          | 1.270 (1.156–1.396)                                                  | <0.001         |
| < 6                                | 0.989 (0.890–1.099)                                                                               | 0.833          | 1.289 (1.174–1.415)                                                  | <0.001         |
| Perceived stress                   |                                                                                                   |                |                                                                      |                |
| Mild                               | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Moderate                           | 1.185 (1.059–1.326)                                                                               | 0.003          | 1.402 (1.268–1.549)                                                  | <0.001         |
| Severe                             | 1.332 (1.195–1.484)                                                                               | <0.001         | 1.750 (1.592–1.923)                                                  | <0.001         |
| Perception of getting enough sleep |                                                                                                   |                |                                                                      |                |
| Good                               | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Moderate                           | 0.981 (0.887–1.085)                                                                               | 0.709          | 1.184 (1.082–1.296)                                                  | <0.001         |
| Bad                                | 1.034 (0.943–1.135)                                                                               | 0.474          | 1.376 (1.267–1.495)                                                  | <0.001         |
| Alcohol use                        |                                                                                                   |                |                                                                      |                |
| Yes                                | 0.984 (0.885–1.094)                                                                               | 0.770          | 1.014 (0.922–1.114)                                                  | 0.780          |
| No                                 | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Concurrent asthma                  |                                                                                                   |                |                                                                      |                |
| Yes                                | 3.156 (2.619–3.803)                                                                               | <0.001         | 4.151 (3.577–4.816)                                                  | <0.001         |
| No                                 | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Concurrent rhinitis                |                                                                                                   |                |                                                                      |                |
| Yes                                | 1.893 (1.751–2.046)                                                                               | <0.001         | 2.858 (2.669–3.061)                                                  | <0.001         |
| No                                 | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Socioeconomic status               |                                                                                                   |                |                                                                      |                |
| Low                                | 1 (reference)                                                                                     |                | 1 (reference)                                                        |                |
| Middle                             | 0.897 (0.809–0.994)                                                                               | 0.038          | 0.857 (0.782–0.940)                                                  | 0.001          |
| High                               | 0.851 (0.763–0.950)                                                                               | 0.004          | 0.723 (0.654–0.799)                                                  | <0.001         |

recent-diagnosed AD, after the adjustment of other related factors (Table 4). After multiple testing correction, energy drinks, fast foods, and convenience foods were significantly associated with the recent-diagnosed AD.

When the recent-diagnosed AD was compared with control, frequent consumption of energy drink (OR 1.213; 95% CI 1.004–1.467), frequent consumption of fast foods (OR

1.374; 95% CI 1.155–1.634), occasional consumption of milk (OR 0.899; 95% CI 0.817–0.990), frequent consumption of milk (OR 0.867; 95% CI 0.781–0.963), and frequent intake of convenience food (OR 1.164; 95% CI 1.035–1.308) were significantly related with the recent-diagnosed AD after adjustment. Among them, only frequent intake of fast foods remained significant after Bonferroni correction.

**Table 3** Frequency of food intake in the recent-diagnosed atopic dermatitis (diagnosed with atopic dermatitis within 12 months), the previous-diagnosed atopic dermatitis (diagnosed with atopic dermatitis during lifetime but not within 12 months), and control groups

|                           | Recent-diagnosed atopic dermatitis ( <i>n</i> = 3898) | Previous-diagnosed atopic dermatitis ( <i>n</i> = 9574) | Control ( <i>n</i> = 39,901) |
|---------------------------|-------------------------------------------------------|---------------------------------------------------------|------------------------------|
| Breakfast (%)             |                                                       |                                                         |                              |
| None                      | 697 (17.88)                                           | 1573 (16.43)                                            | 6961 (17.45)                 |
| <sup>a</sup> Occasionally | 1117 (28.66)                                          | 2618 (27.34)                                            | 11,056 (27.71)               |
| <sup>b</sup> Frequently   | 2084 (53.46)                                          | 5383 (56.23)                                            | 21,844 (54.85)               |
| Fruits (%)                |                                                       |                                                         |                              |
| None                      | 373 (9.57)                                            | 901 (9.41)                                              | 3911 (9.80)                  |
| <sup>a</sup> Occasionally | 2166 (55.57)                                          | 5444 (56.86)                                            | 22,681 (56.84)               |
| <sup>b</sup> Frequently   | 1359 (34.86)                                          | 3229 (33.73)                                            | 13,309 (33.36)               |
| Carbonated drink (%)      |                                                       |                                                         |                              |
| None                      | 865 (22.19)                                           | 2135 (22.30)                                            | 8314 (20.84)                 |
| <sup>a</sup> Occasionally | 2572 (65.98)                                          | 6489 (67.78)                                            | 27,241 (68.27)               |
| <sup>b</sup> Frequently   | 461 (11.83)                                           | 950 (9.92)                                              | 4346 (10.89)                 |
| Energy drink (%)          |                                                       |                                                         |                              |
| None                      | 2941 (75.45)                                          | 7540 (78.75)                                            | 30,550 (76.56)               |
| <sup>a</sup> Occasionally | 818 (20.99)                                           | 1799 (18.79)                                            | 8279 (20.75)                 |
| <sup>b</sup> Frequently   | 139 (3.57)                                            | 235 (2.45)                                              | 1072 (2.69)                  |
| Sweetened drink (%)       |                                                       |                                                         |                              |
| None                      | 487 (12.49)                                           | 1135 (11.86)                                            | 4996 (12.52)                 |
| <sup>a</sup> Occasionally | 2685 (68.88)                                          | 6738 (70.38)                                            | 27,825 (69.74)               |
| <sup>b</sup> Frequently   | 726 (18.62)                                           | 1701 (17.77)                                            | 7080 (17.74)                 |
| Fast food (%)             |                                                       |                                                         |                              |
| None                      | 777 (19.93)                                           | 1927 (20.13)                                            | 8094 (20.29)                 |
| <sup>a</sup> Occasionally | 2942 (75.47)                                          | 7342 (76.69)                                            | 30,442 (76.29)               |
| <sup>b</sup> Frequently   | 179 (4.59)                                            | 305 (3.19)                                              | 1365 (3.42)                  |
| Instant noodles (%)       |                                                       |                                                         |                              |
| None                      | 906 (23.24)                                           | 2254 (23.54)                                            | 8808 (22.07)                 |
| <sup>a</sup> Occasionally | 2770 (71.06)                                          | 6820 (71.23)                                            | 28,822 (72.23)               |
| <sup>b</sup> Frequently   | 222 (5.70)                                            | 500 (5.22)                                              | 2271 (5.69)                  |
| Snacks (%)                |                                                       |                                                         |                              |
| None                      | 600 (15.39)                                           | 1449 (15.13)                                            | 6567 (16.46)                 |
| <sup>a</sup> Occasionally | 2787 (71.50)                                          | 6933 (72.41)                                            | 28,770 (72.10)               |
| <sup>b</sup> Frequently   | 511 (13.11)                                           | 1192 (12.45)                                            | 4564 (11.44)                 |
| Vegetables (%)            |                                                       |                                                         |                              |
| None                      | 157 (4.03)                                            | 377 (3.94)                                              | 1574 (3.94)                  |
| <sup>a</sup> Occasionally | 1556 (39.92)                                          | 3722 (38.88)                                            | 15,963 (40.01)               |
| <sup>b</sup> Frequently   | 2185 (56.05)                                          | 5475 (57.19)                                            | 22,364 (56.05)               |
| Milk (%)                  |                                                       |                                                         |                              |
| None                      | 654 (16.78)                                           | 1431 (14.95)                                            | 5673 (14.22)                 |
| <sup>a</sup> Occasionally | 1801 (46.20)                                          | 4389 (45.84)                                            | 18,284 (45.82)               |
| <sup>b</sup> Frequently   | 1443 (37.02)                                          | 3754 (39.21)                                            | 15,944 (39.96)               |
| Convenience food (%)      |                                                       |                                                         |                              |
| None                      | 1310 (33.61)                                          | 3417 (35.69)                                            | 14,250 (35.71)               |
| <sup>a</sup> Occasionally | 2194 (56.29)                                          | 5419 (56.60)                                            | 22,478 (56.33)               |
| <sup>b</sup> Frequently   | 394 (10.11)                                           | 738 (7.71)                                              | 3173 (7.95)                  |

<sup>a</sup>Occasionally: 1–4 times in the past week

<sup>b</sup>Frequently: 5 or more times in the past week

**Table 4** Odds ratio (OR) of frequency of food intake in the recent-diagnosed atopic dermatitis (diagnosed with atopic dermatitis within 12 months) compared to the previous-diagnosed atopic dermatitis (diagnosed with atopic dermatitis during lifetime but not within 12 months) and control groups using univariate and multivariate logistic regression analyses

|                               | Recent-diagnosed atopic dermatitis to previous-diagnosed atopic dermatitis |                |                                   |                | Recent-diagnosed atopic dermatitis to control |                |                                   |                |
|-------------------------------|----------------------------------------------------------------------------|----------------|-----------------------------------|----------------|-----------------------------------------------|----------------|-----------------------------------|----------------|
|                               | Unadjusted OR (95% CI)                                                     | <i>p</i> value | <sup>a</sup> Adjusted OR (95% CI) | <i>p</i> value | Unadjusted OR (95% CI)                        | <i>p</i> value | <sup>a</sup> Adjusted OR (95% CI) | <i>p</i> value |
| <sup>b</sup> Breakfast        |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 0.979 (0.873–1.098)                                                        | 0.718          | 0.973 (0.866–1.093)               | 0.647          | 1.018 (0.924–1.121)                           | 0.720          | 0.986 (0.894–1.087)               | 0.773          |
| <sup>d</sup> Frequent         | 0.886 (0.802–0.979)                                                        | 0.017          | 0.887 (0.800–0.983)               | 0.022          | 0.937 (0.860–1.021)                           | 0.138          | 0.955 (0.875–1.043)               | 0.309          |
| <sup>b</sup> Fruits           |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 0.962 (0.839–1.103)                                                        | 0.577          | 0.993 (0.864–1.141)               | 0.921          | 0.992 (0.883–1.114)                           | 0.889          | 1.007 (0.896–1.130)               | 0.912          |
| <sup>d</sup> Frequent         | 1.011 (0.879–1.163)                                                        | 0.876          | 1.046 (0.905–1.210)               | 0.540          | 1.039 (0.919–1.174)                           | 0.542          | 1.077 (0.949–1.222)               | 0.253          |
| <sup>b</sup> Carbonated drink |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 0.984 (0.900–1.075)                                                        | 0.716          | 0.994 (0.907–1.090)               | 0.904          | 0.916 (0.847–0.991)                           | 0.028          | 0.959 (0.887–1.038)               | 0.301          |
| <sup>d</sup> Frequent         | 1.211 (1.055–1.390)                                                        | 0.006          | 1.189 (1.028–1.377)               | 0.020          | 1.038 (0.922–1.169)                           | 0.537          | 1.091 (0.963–1.236)               | 0.172          |
| <sup>b</sup> Energy drink     |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 1.176 (1.075–1.285)                                                        | <0.001         | 1.162 (1.060–1.274)               | 0.001          | 1.039 (0.962–1.122)                           | 0.329          | 1.039 (0.960–1.124)               | 0.343          |
| <sup>d</sup> Frequent         | 1.523 (1.231–1.885)                                                        | <0.001         | 1.457 (1.175–1.807)               | <0.001         | 1.332 (1.110–1.598)                           | 0.002          | 1.213 (1.004–1.467)               | 0.046          |
| <sup>b</sup> Sweetened drink  |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 0.883 (0.788–0.989)                                                        | 0.031          | 0.895 (0.798–1.004)               | 0.059          | 0.971 (0.878–1.074)                           | 0.567          | 0.973 (0.876–1.080)               | 0.604          |
| <sup>d</sup> Frequent         | 0.931 (0.812–1.067)                                                        | 0.303          | 0.928 (0.807–1.068)               | 0.296          | 0.999 (0.884–1.128)                           | 0.981          | 0.975 (0.859–1.106)               | 0.696          |
| <sup>b</sup> Fast food        |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 1.000 (0.908–1.102)                                                        | 0.996          | 1.007 (0.913–1.111)               | 0.885          | 1.024 (0.941–1.113)                           | 0.582          | 1.038 (0.953–1.131)               | 0.391          |
| <sup>d</sup> Frequent         | 1.424 (1.168–1.737)                                                        | <0.001         | 1.405 (1.150–1.717)               | <0.001         | 1.344 (1.134–1.592)                           | <0.001         | 1.374 (1.155–1.634)               | <0.001         |
| <sup>b</sup> Instant noodles  |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 0.999 (0.919–1.087)                                                        | 0.985          | 1.006 (0.923–1.097)               | 0.889          | 0.920 (0.856–0.989)                           | 0.024          | 0.951 (0.883–1.023)               | 0.179          |
| <sup>d</sup> Frequent         | 0.970 (0.813–1.157)                                                        | 0.736          | 0.952 (0.794–1.142)               | 0.597          | 0.878 (0.752–1.025)                           | 0.099          | 0.921 (0.785–1.081)               | 0.314          |
| <sup>b</sup> Snacks           |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 0.959 (0.864–1.064)                                                        | 0.433          | 0.966 (0.869–1.075)               | 0.525          | 1.046 (0.954–1.148)                           | 0.339          | 1.020 (0.928–1.121)               | 0.685          |
| <sup>d</sup> Frequent         | 1.010 (0.874–1.166)                                                        | 0.896          | 1.017 (0.878–1.179)               | 0.817          | 1.200 (1.056–1.364)                           | 0.005          | 1.107 (0.971–1.263)               | 0.129          |
| <sup>b</sup> Vegetables       |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 1.071 (0.883–1.299)                                                        | 0.485          | 1.067 (0.875–1.302)               | 0.520          | 1.035 (0.873–1.229)                           | 0.689          | 1.034 (0.869–1.230)               | 0.709          |
| <sup>d</sup> Frequent         | 1.001 (0.827–1.212)                                                        | 0.990          | 1.005 (0.825–1.224)               | 0.963          | 1.012 (0.855–1.197)                           | 0.891          | 1.035 (0.872–1.228)               | 0.693          |
| <sup>b</sup> Milk             |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 0.924 (0.827–1.032)                                                        | 0.161          | 0.938 (0.836–1.053)               | 0.276          | 0.871 (0.793–0.957)                           | 0.004          | 0.899 (0.817–0.990)               | 0.031          |
| <sup>d</sup> Frequent         | 0.853 (0.761–0.955)                                                        | 0.006          | 0.852 (0.755–0.961)               | 0.009          | 0.803 (0.728–0.886)                           | <0.001         | 0.867 (0.781–0.963)               | 0.008          |
| <sup>b</sup> Convenience food |                                                                            |                |                                   |                |                                               |                |                                   |                |
| <sup>c</sup> Occasional       | 1.056 (0.975–1.144)                                                        | 0.177          | 1.027 (0.945–1.116)               | 0.533          | 1.065 (0.992–1.143)                           | 0.082          | 0.993 (0.922–1.070)               | 0.855          |
| <sup>d</sup> Frequent         | 1.403 (1.233–1.597)                                                        | <0.001         | 1.304 (1.138–1.495)               | <0.001         | 1.349 (1.205–1.509)                           | <0.001         | 1.164 (1.035–1.308)               | 0.011          |

<sup>a</sup>Adjusted for age, sex, residence, body mass index, sleep time, perceived stress, perception of getting enough sleep, alcohol use, socioeconomic status, and other allergic diseases (asthma and rhinitis)

<sup>b</sup>Reference was none

<sup>c</sup>Occasional: 1–4 times in the past week

<sup>d</sup>Frequent: 5 or more times in the past week

### Subgroup analysis of the relationship between AD and frequency of specific food consumption

Subgroup analyses of foods with significant association with AD were performed to compare the frequency of specific food consumption by the recent-diagnosed AD

and the previous-diagnosed AD in high school students ( $n=27,464$ , mostly 15–18 years old) and middle school students ( $n=25,909$ , mostly 12–15 years old). In high school students, the recent-diagnosed AD group, as compared to the previous-diagnosed AD, showed more significant association with occasional consumption of energy drink

(OR 1.206; 95% CI 1.065–1.367), frequent consumption of energy drink (OR 1.450; 95% CI 1.104–1.904), frequent consumption of fast foods (OR 1.623; 95% CI 1.233–2.136), frequent consumption of convenience food (OR 1.314; 95% CI 1.098–1.573), while being significantly negatively associated with frequent consumption of breakfast (OR 0.847; 95% CI 0.741–0.970) after the adjustment (Table 5). In middle school students, the recent-diagnosed AD group showed more significant association with frequent consumption of energy drink (OR 1.428; 95% CI 1.001–2.039) and frequent consumption of convenience food (OR 1.262; 95% CI 1.025–1.555) while being significantly negatively associated with frequent consumption of milk (OR 0.794; 95% CI 0.667–0.945). Carbonated drink was not significantly associated with the recent-diagnosed AD in both high school and middle school students.

When the recent-diagnosed AD was compared with control, only frequent consumption of fast foods (OR 1.479;

95% CI 1.167–1.873) was significantly related to the recent-diagnosed AD in high school students. In contrast, the recent-diagnosed AD in middle school students but not in high school students was negatively associated with frequent consumption of milk (OR 0.825; 95% CI 0.701–0.971).

## Discussion

In this study, we found differences in the frequency of specific food consumption by the recent-diagnosed AD group compared to that by the previous-diagnosed AD or control groups in adolescents. Recent-diagnosed AD patients were found to consume more carbonated drink, energy drink, fast foods, and convenience food but less frequent breakfast and milk compared to the previous-diagnosed AD or control subjects. Among them, energy drink, fast foods, and

**Table 5** Subgroup analysis (middle school and high school) of food behaviors related to the recent-diagnosed atopic dermatitis (diagnosed with atopic dermatitis within 12 months) compared to the previous-

diagnosed atopic dermatitis (diagnosed with atopic dermatitis during lifetime but not within 12 months) and control groups using multivariate logistic regression analysis

|                               | <sup>a</sup> Recent-diagnosed atopic dermatitis to previous-diagnosed atopic dermatitis |                |                                      |                | <sup>a</sup> Recent-diagnosed atopic dermatitis to control |                |                                      |                |
|-------------------------------|-----------------------------------------------------------------------------------------|----------------|--------------------------------------|----------------|------------------------------------------------------------|----------------|--------------------------------------|----------------|
|                               | <sup>b</sup> Middle school OR (95% CI)                                                  | <i>p</i> value | <sup>c</sup> High school OR (95% CI) | <i>p</i> value | <sup>b</sup> Middle school OR (95% CI)                     | <i>p</i> value | <sup>c</sup> High school OR (95% CI) | <i>p</i> value |
| <sup>d</sup> Breakfast        |                                                                                         |                |                                      |                |                                                            |                |                                      |                |
| <sup>e</sup> Occasional       | 0.949 (0.801–1.124)                                                                     | 0.547          | 0.989 (0.844–1.159)                  | 0.890          |                                                            |                |                                      |                |
| <sup>f</sup> Frequent         | 0.949 (0.809–1.113)                                                                     | 0.519          | 0.847 (0.741–0.970)                  | 0.016          |                                                            |                |                                      |                |
| <sup>d</sup> Carbonated drink |                                                                                         |                |                                      |                |                                                            |                |                                      |                |
| <sup>e</sup> Occasional       | 0.968 (0.844–1.110)                                                                     | 0.643          | 1.013 (0.894–1.148)                  | 0.838          |                                                            |                |                                      |                |
| <sup>f</sup> Frequent         | 1.200 (0.967–1.488)                                                                     | 0.097          | 1.167 (0.955–1.427)                  | 0.131          |                                                            |                |                                      |                |
| <sup>d</sup> Energy drink     |                                                                                         |                |                                      |                |                                                            |                |                                      |                |
| <sup>e</sup> Occasional       | 1.096 (0.957–1.254)                                                                     | 0.185          | 1.206 (1.065–1.367)                  | 0.003          | 0.970 (0.860–1.094)                                        | 0.619          | 1.090 (0.981–1.212)                  | 0.107          |
| <sup>f</sup> Frequent         | 1.428 (1.001–2.039)                                                                     | 0.050          | 1.450 (1.104–1.904)                  | 0.008          | 1.231 (0.913–1.658)                                        | 0.173          | 1.206 (0.944–1.542)                  | 0.134          |
| <sup>d</sup> Fast food        |                                                                                         |                |                                      |                |                                                            |                |                                      |                |
| <sup>e</sup> Occasional       | 0.950 (0.824–1.095)                                                                     | 0.478          | 1.059 (0.924–1.213)                  | 0.411          | 0.979 (0.864–1.109)                                        | 0.738          | 1.091 (0.969–1.227)                  | 0.149          |
| <sup>f</sup> Frequent         | 1.159 (0.868–1.548)                                                                     | 0.317          | 1.623 (1.233–2.136)                  | <0.001         | 1.245 (0.969–1.601)                                        | 0.087          | 1.479 (1.167–1.873)                  | 0.001          |
| <sup>d</sup> Milk             |                                                                                         |                |                                      |                |                                                            |                |                                      |                |
| <sup>e</sup> Occasional       | 0.857 (0.715–1.028)                                                                     | 0.096          | 0.992 (0.856–1.151)                  | 0.920          | 0.866 (0.745–1.006)                                        | 0.061          | 0.925 (0.816–1.048)                  | 0.220          |
| <sup>f</sup> Frequent         | 0.794 (0.667–0.945)                                                                     | 0.009          | 0.894 (0.757–1.055)                  | 0.184          | 0.825 (0.701–0.971)                                        | 0.021          | 0.902 (0.787–1.034)                  | 0.140          |
| <sup>d</sup> Convenience food |                                                                                         |                |                                      |                |                                                            |                |                                      |                |
| <sup>e</sup> Occasional       | 1.052 (0.924–1.198)                                                                     | 0.445          | 1.009 (0.906–1.124)                  | 0.871          | 0.966 (0.862–1.083)                                        | 0.551          | 1.013 (0.918–1.117)                  | 0.799          |
| <sup>f</sup> Frequent         | 1.262 (1.025–1.555)                                                                     | 0.029          | 1.314 (1.098–1.573)                  | 0.003          | 1.172 (0.981–1.401)                                        | 0.081          | 1.149 (0.984–1.343)                  | 0.080          |

<sup>a</sup>Adjusted for age, sex, residence, body mass index, sleep time, perceived stress, perception of getting enough sleep, alcohol use, socioeconomic status, and other allergic diseases (asthma and rhinitis)

<sup>b</sup>Among middle school students, the recent-diagnosed AD was 1864, the previous-diagnosed AD was 4390, and control group was 19,655 in each

<sup>c</sup>Among high school students, the recent-diagnosed AD was 2034, the previous-diagnosed AD was 5184, and control group was 20,246 in each

<sup>d</sup>Reference was none

<sup>e</sup>Occasional: 1–4 times in the past week

<sup>f</sup>Frequent: 5 or more times in the past week

convenience food remained significant after multiple testing correction.

Intake of fast foods is a controversial risk factor for AD. A recent systematic review and an International Study of Asthma and Allergies in Childhood (ISSAC) phase 3 study showed that frequent intake of fast foods was associated with severe eczema [13, 14], while some studies failed to show a significant relationship [32–34]. These studies with non-significant outcome were conducted in relatively young children. In contrast, Ellwood et al. [13] reported that eczema in childhood was significantly associated with the consumption of fast foods, although this association was more pronounced in adolescents aged 13–14 years than in children aged 6–7 years. Unlike young children, adolescents are more likely to be affected by fast foods, because they have more independence and control over their diet [13] and may be exposed to fast foods for a longer period of time. Similarly, in the present study, only fast food was significantly associated with the recent-diagnosed AD in older adolescents. Unlike other foods, such as energy drink or convenience food, the association of fast foods in the recent-diagnosed AD was evident in comparison with not only the previous-diagnosed AD, but also the control group after adjustment of BMI and other possible confounding factors. Fast foods are associated with poor diet quality and high calorie intake, with food additives, such as preservatives and colorants [14, 35, 36]. Besides, exposure to fast foods is a well-known risk factor for obesity in adolescents [35, 36]. Recent studies reported that obesity is strongly associated with AD worldwide, especially in North America and Asia [18–20]. Taken together, fast foods would influence AD both directly and indirectly.

Interestingly, the association with energy drinks in AD was rarely reported. We found that the recent-diagnosed AD group consumed energy drink more frequently than the previous-diagnosed AD or control group. Patients with AD frequently suffer from sleep disturbance, and poor sleep quality was related to disease severity [37–41]. They may also have psychological comorbidities, such as anxiety or depression [42–45]. On the other hand, excessive caffeine intake causes sleep disorders like insomnia, anxiety, and even depression [46–49]. Overall, an excessive intake of energy drink in patients with AD may trigger a vicious cycle through sleep disturbances or psychological comorbidities. Besides, caffeine interferes with the absorption of minerals and vitamins, such as vitamin B and folate [50, 51], which might be associated with increased risk of AD and other atopic diseases [52]. The precise mechanism underlying the association of AD and energy drinks remains to be elucidated. Energy drinks have been widely consumed recently by adolescents [53–55]. In addition to other potentially adverse health effects [47, 56], adolescent patients with AD need to be cautious of excessive intake of energy drinks.

The recent increase in the consumption of convenience food is due to good accessibility and ease of eating. It is characterized by high fat content and contains many flavorings and food additives [57, 58]. Clinical relevance of food additives with AD has been relatively low, but has been reported in several publications, especially in adult patients [15, 17, 59]. Further research is needed to elucidate the roles of convenience food with nutritional imbalance and food additives on adolescent AD.

Our findings indicate that skipping breakfast, carbonated drinks, and milk are also related to AD to some degree, although not significant, after multiple testing correction. Skipping breakfast is reported to be associated with obesity in children [35]. In addition, regular school breakfast participation led to improvement in anxiety and depression [60]. Carbonated drinks are also strongly related to obesity in adolescence [61]. Many carbonated drinks contain caffeine, and were reported to be the more frequent caffeine source in children and adolescents than coffee [62, 63]. Previous studies reported that consumption of milk has a protective effect on AD [13, 32, 33, 64, 65]. However, patients with AD may tend to avoid milk, which is one of the most common foods causing food allergy [9, 66, 67]. Since there is a negative correlation between milk intake and soft drinks intake [61], consumption of carbonated beverages or high caffeinated beverages may be low in subjects with high milk intake.

This study has some limitations. First, the definitions of recent-diagnosed or previous-diagnosed AD were based on a survey. Second, the severity of AD was not able to be evaluated in the survey. Thus, we were unable to evaluate the association of food consumption habits with the severity of AD. Third, the frequency of food intake was checked during the past week; therefore, it was difficult to assess the long-term food intake. Fourth, responses or exposures to food in other countries may have racial or cultural differences. However, this study is meaningful in that it is a large-scale study that has investigated an association between food and recent-diagnosed AD in adolescents.

In conclusion, we found that frequent intake of fast foods, energy drinks, and convenience food was associated with the recent-diagnosed AD patients in adolescent. The association of food consumption patterns with AD was stronger in high school students than in middle school students. Proper education regarding food consumption may help prevent the progression or the persistence from childhood AD to adolescent AD by limiting fast foods, high caffeinated drinks, and convenience food intake. Future studies will be required to verify the association of AD with specific foods in adolescents.

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## Compliance with ethical standards

**Conflict of interest** The authors have nothing to declare.

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STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

|                              | Item No | Recommendation                                                                                                                                                                                               | Page No  |
|------------------------------|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Title and abstract           | 1       | (a) Indicate the study’s design with a commonly used term in the title or the abstract                                                                                                                       | 2        |
|                              |         | (b) Provide in the abstract an informative and balanced summary of what was done and what was found                                                                                                          | 2        |
| Introduction                 |         |                                                                                                                                                                                                              |          |
| Background/rationale         | 2       | Explain the scientific background and rationale for the investigation being reported                                                                                                                         | 3        |
| Objectives                   | 3       | State specific objectives, including any prespecified hypotheses                                                                                                                                             | 3        |
| Methods                      |         |                                                                                                                                                                                                              |          |
| Study design                 | 4       | Present key elements of study design early in the paper                                                                                                                                                      | 4        |
| Setting                      | 5       | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection                                                                              | 4        |
| Participants                 | 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants                                                                                                                  | 4,5      |
| Variables                    | 7       | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable                                                                     | 4-5      |
| Data sources/<br>measurement | 8*      | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group                         | 4        |
| Bias                         | 9       | Describe any efforts to address potential sources of bias                                                                                                                                                    | 4        |
| Study size                   | 10      | Explain how the study size was arrived at                                                                                                                                                                    | 6        |
| Quantitative variables       | 11      | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why                                                                                 | 4-5      |
| Statistical methods          | 12      | (a) Describe all statistical methods, including those used to control for confounding                                                                                                                        | 5        |
|                              |         | (b) Describe any methods used to examine subgroups and interactions                                                                                                                                          | 5        |
|                              |         | (c) Explain how missing data were addressed                                                                                                                                                                  |          |
|                              |         | (d) If applicable, describe analytical methods taking account of sampling strategy                                                                                                                           | 5        |
|                              |         | (e) Describe any sensitivity analyses                                                                                                                                                                        |          |
| Results                      |         |                                                                                                                                                                                                              |          |
| Participants                 | 13*     | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed            | 6        |
|                              |         | (b) Give reasons for non-participation at each stage                                                                                                                                                         | 6        |
|                              |         | (c) Consider use of a flow diagram                                                                                                                                                                           | 6        |
| Descriptive data             | 14*     | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders                                                                     | 6,20,21  |
|                              |         | (b) Indicate number of participants with missing data for each variable of interest                                                                                                                          |          |
| Outcome data                 | 15*     | Report numbers of outcome events or summary measures                                                                                                                                                         | 6,22-26  |
| Main results                 | 16      | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 6, 27-30 |

|                          |    |                                                                                                                                                                            |         |
|--------------------------|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
|                          |    | (b) Report category boundaries when continuous variables were categorized                                                                                                  | 4.5     |
|                          |    | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period                                                           |         |
| Other analyses           | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses                                                                             | 7,31-33 |
| <b>Discussion</b>        |    |                                                                                                                                                                            |         |
| Key results              | 18 | Summarise key results with reference to study objectives                                                                                                                   | 8       |
| Limitations              | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias                 | 9       |
| Interpretation           | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8-9     |
| Generalisability         | 21 | Discuss the generalisability (external validity) of the study results                                                                                                      | 8-9     |
| <b>Other information</b> |    |                                                                                                                                                                            |         |
| Funding                  | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based              |         |

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).