Beverage intake and risk of Crohn disease
A meta-analysis of 16 epidemiological studies
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Abstract
Epidemiological studies were controversial in the association between beverage intake and risk of Crohn disease (CD). This study aimed to investigate the role of beverage intake in the development of CD. A systematic search was conducted in public databases to identify all relevant studies, and study-specific relative risks (RRs) and 95% confidence intervals (CIs) were pooled using a random-effects model. Sixteen studies were identified with a total of 130,431 participants and 1933 CD cases. No significant association was detected between alcohol intake and CD risk (RR for the highest vs the lowest consumption level: 0.85, 95% CI 0.68–1.08), and coffee intake and the risk (RR 0.82, 95% CI 0.46–1.46). High intake of soft drinks was associated with CD risk (RR 1.42, 95% CI 1.01–1.95), and tea intake was inversely associated with CD risk (RR 0.70, 95% CI 0.53–0.93). In conclusion, high intake of soft drinks might increase the risk of CD, whereas tea intake might decrease the risk.

Abbreviations: CD = Crohn disease, CI = confidence interval, FFQ = Food Frequency Questionnaire, IBD = inflammatory bowel disease, NOS = the Newcastle-Ottawa Scale, OR = odds ratio, RR = relative risk, UC = ulcerative colitis.

Keywords: alcohol, coffee, Crohn disease, meta-analysis, soft drinks, tea

1. Introduction
Crohn disease (CD) is a chronic inflammatory disorder of the intestinal tract, which is clinically characterized by diarrhea, abdominal pain, and extra-intestinal manifestations. During the past decades, its incidence is steadily on the rise across the world. As it relapses frequently and has a high risk of surgery, the patients suffer from a low-quality life and high medical costs. However, the etiology is still unknown, and it is hypothesized to result from a dysregulation of both the innate and adaptive immune response against the intestinal microbiome in the genetically susceptible host. In addition, growing evidence indicated that dietary factors might also play an important role in the development of CD. In the meta-analysis by Li et al, high consumption of fruit was found to be inversely associated with the risk of CD (odds ratio [OR] 0.57, 95% confidence interval [CI] 0.44–0.74). In the meta-analysis by Zeng et al, dietary intake of total carbohydrate was associated with CD risk (relative risk [RR] for per 10 g increment/d 0.991, 95% CI 0.978–1.004), whereas fiber intake was inversely associated with CD risk (RR for per 10 g increment/d 0.853, 95% CI 0.762–0.955).

During the past decades, the prevalence of westernized diet came along with an increasing incidence of CD in the regions with an originally low incidence. Thus, westernized diet was usually regarded as a potential etiological factor for CD. As 1 feature of the westernized diet, beverage intake might also play a certain role in the development of CD. However, the findings of previous epidemiological studies were inconsistent, and no meta-analyses have focused on this. Therefore, we conducted a systematic review and meta-analysis to identify the role of beverage intake in the development of CD.

2. Material and methods

2.1. Search strategy
The databases of PubMed, Embase, China Knowledge Resource Integrated Database (CNKI), and Cochrane Library databases were searched for relevant studies published up to December 1, 2018, using the key words “beverage,” “alcohol,” “wine,” “liquor,” “beer,” “coffee,” “tea,” “soda,” “soft drinks,” “diet,” “environmental factor,” “risk factor” in combination with “inflammatory bowel disease” and “Crohn disease.” Moreover, the references of related studies, reviews, and meta-analyses were also reviewed for undetected studies. This study was approved by the ethics committee of The Central Hospital of Enshi Autonomous Prefecture.

2.2. Study selection and exclusion
All the studies were reviewed independently by 2 investigators (Y. Y. and L.X.). Studies were included if they satisfied the following criteria: observational studies published originally; investigated the intake levels of at least one of the beverages (alcohol, coffee,
tea, and soft drinks) by Food Frequency Questionnaires (FFQs); had a definite diagnosis for CD cases; the association between beverage intake and CD risk was evaluated by the effect sizes of RR, OR, or hazard ratios (HRs) with 95% CI. Abstracts without full texts and review articles were excluded. In each included study, the protocol was approved by the institutional review board of each study center. Written informed consent was obtained from all patients before registration, and in accordance with the Declaration of Helsinki.

2.3. Data extraction and quality assessment
The following information was extracted from each included study: first author, publication year, area, study design, number of cases and controls, beverage types, intake categories, exposure comparison, effect sizes, and adjustment. The Newcastle–Ottawa Scale (NOS), which contained 9 terms with each term accounting for 1 score, was used to assess the methodological quality of included studies.

2.4. Statistical analysis
As the absolute incidence of CD is low, OR was roughly regarded as RR in this meta-analysis.\(^{[10]}\) To evaluate the risk of high beverage intake, we pooled the risk estimates for the highest versus the lowest intake levels. A random-effects model was used as the pooling method, which considered both within-study and between-study variation. The heterogeneity between studies was estimated by Q test and \(I^2\) statistic, and \(I^2 > 50\%\) represented substantial heterogeneity.\(^{[11]}\) Subgroup analysis was performed on cohort, study design, intake categories, and adjustment of dietary factors and smoking to evaluate the stability of the primary results. Altman and Bland test was performed to assess the difference between inconsistent subsets.\(^{[12]}\) Egger test was used to detect publication bias.\(^{[13]}\) All statistical analyses were performed using Stata SE12.0 software (StataCorp LP, College Station, TX), and all tests were sided with a significance level of .05.

3. Results
3.1. Characteristics of included studies
The search strategy identified 11,579 records: 8450 from Web of Science, 2907 from PubMed, 192 from CNKI, and 30 from other sources (Fig. 1). After eliminating duplicated and irrelevant records, 16 studies were included in the meta-analysis (Table 1).\(^{[14–28]}\) The record of Khalili et al consisted of 2 large prospective studies. Among the 16 studies, there were 10 population and/or

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**Figure 1.** Flowchart of literature search.
Characteristics of included studies.

Persson et al, 1992[14] Sweden Population-based case-control 152/305 Soft drinks 3 Daily vs less frequently 2.8 (1.6–4.9) Age, sex

Coffee 3

Reif et al, 1997[15] Israel Population/hospital-based case-control 33/144 Soft drinks 3 High vs low 1.44 (0.39–5.34) Age, sex, ethnic origin, area of residence, energy intake

≥ 3/C20–1 per wk 2.2 (1.5–3.1) Smoking, sex, age, educational level, selected nutritional factors

≥ 2.3)

Sakamoto et al, 2005[17] Japan Hospital-based case-control 126/211 Alcoholic beverages 4 Q4 vs Q1 0.50 (0.23–1.21) Age, sex, ethnic origin, area of residence, western food, fruits and vegetables, housing condition

Halfvarson et al, 2006[18] Sweden/Denmark Population-based case-control 98/95 Coffee 3 ≥–6.0) Dizygotic and monozygotic pairs

≥–3 vs less cups/d 0.67 (0.37–1.21) Age, sex, ethnicity, geographic location

≥ 2.56) Age, sex, center, date of recruitment into EPIC, daily energy intake, body mass

Jakobsen et al, 2013[21] Denmark Population-based case-control 59/477 Soft drinks 2 ≥–3 times/wk 2.9 (1.0–8.5) Age, sex

Ng et al, 2015[22] Asia-Pacific Population-based case-control 186/940 Soft drinks 2 <–<2 vs ––> 2 0.662 (0.462–1.000) Age, sex

Tea 2 Daily vs not 0.662 (0.462–1.000) Age, sex

Niu et al, 2016[23] China Nested case-control 102/408 Tea 2 Yes vs no 0.76 (0.49–1.21) Age, sex

Alcohol 2 Yes vs no 1.08 (0.64–1.82) Age, sex

Racine et al, 2016[24] Europe Nested case-control 117/468 Sugar and soft drinks 4 Q4 vs Q1 0.99 (0.87–1.12) Age, sex, center, enrollment date, educational attainment and smoking status

Bergmann et al, 2017[25] Europe Prospective 84/336 Alcohol 5 Heavy vs light 0.43 (0.13–1.42) Age, sex, education, smoking status

Porter et al, 2017[26] USA Prospective 58/40 vs no/light 1.27 (0.52–3.14) Age, sex

Cui et al, 2018[28] China Hospital-based case-control 47/47 Alcohol 2 Daily vs not 1.124 (0.273–4.631) Age, sex, ethnic origin, area of residence, western food, fruits and vegetables, housing condition

Khalili et al (CoSM) 2018[27] Sweden Prospective Sweetened beverage 4 Q4 vs Q1 0.99 (0.87–1.12) Age, sex, center, date of recruitment into EPIC, daily energy intake, body mass

Table 1: Characteristics of included studies.

Design

Area

Study

Country

Sample

Design

Cases

Controls

Intake

Comparison

RR (95% CI)

Adjustment

Persson et al, 1992[14] Sweden Population-based case-control 152/305 Soft drinks 3 Daily vs less frequently 2.8 (1.6–4.9) Age, sex, smoking

Coffee 3

Reif et al, 1997[15] Israel Population/hospital-based case-control 33/144 Soft drinks 3 High vs low 1.44 (0.39–5.34) Age, sex, ethnic origin, area of residence, energy intake

≥ 3/C20–1 per wk 2.2 (1.5–3.1) Smoking, sex, age, educational level, selected nutritional factors

≥ 2.3)

Sakamoto et al, 2005[17] Japan Hospital-based case-control 126/211 Alcoholic beverages 4 Q4 vs Q1 0.50 (0.23–1.21) Age, sex, ethnic origin, area of residence, western food, fruits and vegetables, housing condition

Halfvarson et al, 2006[18] Sweden/Denmark Population-based case-control 98/95 Coffee 3 ≥–6.0) Dizygotic and monozygotic pairs

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≥ 2.56) Age, sex, center, date of recruitment into EPIC, daily energy intake, body mass

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Tea 2 Daily vs not 0.662 (0.462–1.000) Age, sex

Niu et al, 2016[23] China Nested case-control 102/408 Tea 2 Yes vs no 0.76 (0.49–1.21) Age, sex

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Cui et al, 2018[28] China Hospital-based case-control 47/47 Alcohol 2 Daily vs not 1.124 (0.273–4.631) Age, sex, ethnic origin, area of residence, western food, fruits and vegetables, housing condition

Khalili et al (CoSM) 2018[27] Sweden Prospective Sweetened beverage 4 Q4 vs Q1 0.99 (0.87–1.12) Age, sex, center, date of recruitment into EPIC, daily energy intake, body mass

hospital-based case-control, 2 nested case-control, and 4 prospective cohort studies, with a total of 130,431 participants and 1933 CD cases. In study quality assessment, the quality scores ranged from 6 to 8, with an average of 7.25.

3.2. Alcohol intake and CD risk

Six studies evaluated the association between alcohol intake and CD risk. The pooled RR for the highest versus the lowest intake was 0.85 (95% CI 0.68–1.08, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.453$), indicating no obvious association between them (Fig. 2). Egger test detected significant publication bias ($P = 0.992$).

3.3. Coffee intake and CD risk

Five studies evaluated the association between coffee intake and CD risk. The pooled RR for the highest versus the lowest intake was 0.82 (95% CI 0.46–1.46, $I^2 = 81.0\%$, $P_{\text{heterogeneity}} < 0.001$), suggesting no obvious association between them (Fig. 2). Egger test detected no significant publication bias ($P = 0.444$).

3.4. Soft drinks intake and CD risk

Eight studies evaluated the association between soft drinks intake and CD risk, among which 1 focused on the subtype of cola drinks. The pooled RR for the highest versus the lowest intake was 1.42 (95% CI 1.01–1.98, $I^2 = 78.1\%$, $P_{\text{heterogeneity}} < 0.001$) (Fig. 2). High intake of soft drinks might increase the risk of CD. Egger test detected no significant publication bias ($P = 0.140$).

3.5. Tea intake and CD risk

Two studies evaluated the association between tea intake and CD risk. The pooled RR for the highest versus the lowest intake was 0.70 (95% CI 0.53–0.93, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = 0.636$) (Fig. 2). High intake of tea might decrease the risk of CD.

3.6. Subgroup analysis

Subgroup analysis was performed on cohort, study design, intake categories, and adjustment of dietary factors and smoking to evaluate the stability of the primary results (Table 2). As the results were influenced by these factors except for the tea, Altman and Bland test was conducted to evaluate the difference between inconsistent subsets. Finally, no significant difference was found between these subsets ($P_{\text{interaction}} > 0.5$). This indicated the inconsistency in subgroup analyses might contribute to the limited number of included studies, and the primary results were stable in general.

4. Discussion

The etiology of CD was still unknown, and it was hypothesized to result from multiple factors, like the ethnicity of Caucasian, and environmental factors of smoking, early-life antibiotic use, breastfeeding, childhood pet exposure, and urban residence.[29] Dietary factors were also known to be associated with CD. To our knowledge, this is the first meta-analysis to investigate the association between beverage intake and CD risk, and 4 most common daily subtypes were analyzed, respectively. For alcohol intake, it was not associated with CD risk (RR 0.85, 95% CI 0.68–1.08). However, alcohol could cause direct mucosal injury and increase bacterial translocation, and it was usually regarded
Table 2
Subgroup analysis of beverage intake and risk of Crohn disease.

| Subgroups          | Alcohol  |          | Coffee   |          | Soft drinks |          | Tea      |          |
|--------------------|----------|----------|----------|----------|-------------|----------|----------|----------|
|                    | RR (95% CI) | P_interaction | RR (95% CI) | P_interaction | RR (95% CI) | P_interaction | RR (95% CI) | P_interaction |
| Cohort             |          |          |          |          |             |          |          |          |
| Asian              | 0.84 (0.50–1.13) | .997 | 0.73 (0.49–1.09) | .761 | 0.74 (0.37–1.49) | .07 | 0.68 (0.51–0.90) | — |
| Caucasian          | 0.85 (0.64–1.12) |          | 0.85 (0.36–1.97) |          | 1.54 (1.07–2.21) |          | — |          |
| Design             |          |          |          |          |             |          |          |          |
| Population-based   | 0.89 (0.70–1.15) | .297 | 0.87 (0.42–1.84) | .584 | 1.05 (0.87–1.28) | .153 | — | — |
| Hospital-based     | 0.61 (0.30–1.20) | .67 | 0.37–1.21 |          | 1.74 (0.90–3.36) |          | 0.70 (0.53–0.93) | — |
| Intake categories  |          |          |          |          |             |          |          |          |
| ≥3                 | 0.67 (0.35–1.31) | .422 | 0.75 (0.11–5.03) | .833 | 1.27 (0.91–1.78) | .556 | — | — |
| <3                 | 0.90 (0.70–1.17) |          | 0.93 (0.59–1.45) |          | 1.64 (0.76–3.56) |          | 0.70 (0.53–0.93) | — |
| Adjusted by dietary factors |          |          |          |          |             |          |          |          |
| Yes                | 1.12 (0.27–4.63) | .696 | 1.50 (0.89–2.54) | .061 | 1.27 (0.90–1.80) | .503 | — | — |
| No                 | 0.84 (0.64–1.11) |          | 0.69 (0.37–1.28) |          | 1.79 (0.71–4.51) |          | 0.70 (0.53–0.93) | — |
| Adjusted by smoking |          |          |          |          |             |          |          |          |
| Yes                | 0.48 (0.25–0.93) | .066 | 1.50 (0.89–2.54) | .061 | 1.27 (0.88–1.83) | .478 | — | — |
| No                 | 0.93 (0.72–1.19) |          | 0.69 (0.37–1.28) |          | 1.71 (0.81–3.62) |          | 0.70 (0.53–0.93) | — |

CI=confidence interval, RR=relative risk.
as the cause for intestinal inflammation. The inconsistency might result from the difference between experimental studies and epidemiological studies, and the latter was confused by more factors. Just like fat intake, it was associated with experimental colitis, but epidemiological studies found an insignificant association with CD risk. Coffee intake also showed an insignificant association with CD risk (RR 0.82, 95% CI 0.46–1.46). In vivo, mice treated with caffeine displayed a delayed response towards dextran sulfate sodium (DSS)-induced colitis. We thought coffee intake might play different roles in the etiology and disease activity. For the inflammatory mucosa, it might play a protective role, but its role in pre-illness intestinal tract might be affected by multiple factors. As for the other subtype of inflammatory bowel diseases (IBD), coffee intake was also found in an insignificant association with ulcerative colitis (UC) (RR 0.58, 95% CI 0.33–1.05).

For the consumption of soft drinks, it was associated with CD risk (RR 1.42, 95% CI 1.01–1.98). Soft drinks had been a highly visible and controversial public health issue, which were also viewed by many experts as a major contributor to obesity and related chronic diseases. Soft drinks are rich in carbohydrate, especially sugar, and high sugar intake has been experimentally found in association with inflammation induction and gut microbiota alteration. In the study by Opstelten et al, IBD patients consumed more carbonated beverages, and sugar and sweets than individuals from a general population (P < .05). Thus, low intake of soft drinks might help decrease the incidence of CD, especially among the children. For CD patients, this strategy might help decrease the disease activity and the risk of relapse. For tea consumption, it had a reverse association with CD (RR 0.79, 95% CI 0.53–0.93). Animal studies found that tea alone or in combination with sulfasalazine could reduce inflammatory changes in experimental colitis, indicating a protective role of tea in CD. Moreover, the presence of antioxidants in tea might also reduce the formation of free radicals that damaged cells in the body. Thus, high intake of tea might help decrease the incidence of CD, especially among the adults. For CD patients, this strategy might help decrease the disease activity and the risk of relapse.

This meta-analysis had several strengths. First, this is the first meta-analysis to investigate the association between beverage intake and CD risk. Second, we evaluated the four most daily subtypes. There were also several limitations. First, the results based on case-control studies were prone to introduce considerable bias, particularly recall bias and interviewer bias. Second, there existed considerable heterogeneity in the meta-analyses of coffee and soft drinks, which might contribute to the limited number of included studies. Third, not all potential confounders were adjusted in every study. As health involves a dynamic process of adaptation to a constantly changing environment, supporting health and well-being is a multidimensional act that can be promoted and maintained by different ways of living, curative actions, mental interactions, public interventions, and global developments and crises, and also by the design of the setting. Thus, environmental and social problems can lead to alcohol intake or intake of soft drinks, and different social circumstances can lead to the change of behaviors. In the future, we think a large-scale prospective designed study which considers these factors is needed to validate the role of beverage intake in the development of CD.

5. Conclusions
In conclusion, high intake of soft drinks might increase the risk of CD, while tea intake might decrease the risk.

Author contributions
Data curation: Yanhua Yang.
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Methodology: Lili Xiang.
Software: Lili Xiang.
Supervision: Jianhua He.
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Writing – review & editing: Jianhua He.

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