Meta-Analysis of Observational Studies in Epidemiology

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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 1.01–1.98), 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.[1] During the past decades, its incidence is steadily on the rise across the world.[2] As it relapses frequently and has a high risk of surgery, the patients suffer from a low-quality life and high medical costs.[3] 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 micro-ecology in the genetically susceptible host.[4] In addition, growing evidence indicated that dietary factors might also play an important role in the development of CD.[5] 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).[6] 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).[7]

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.[8] Thus, westernized diet was usually regarded as a potential etiological factor for CD.[9] 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,

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Y.Y. and L.X. contributed equally to this study.

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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

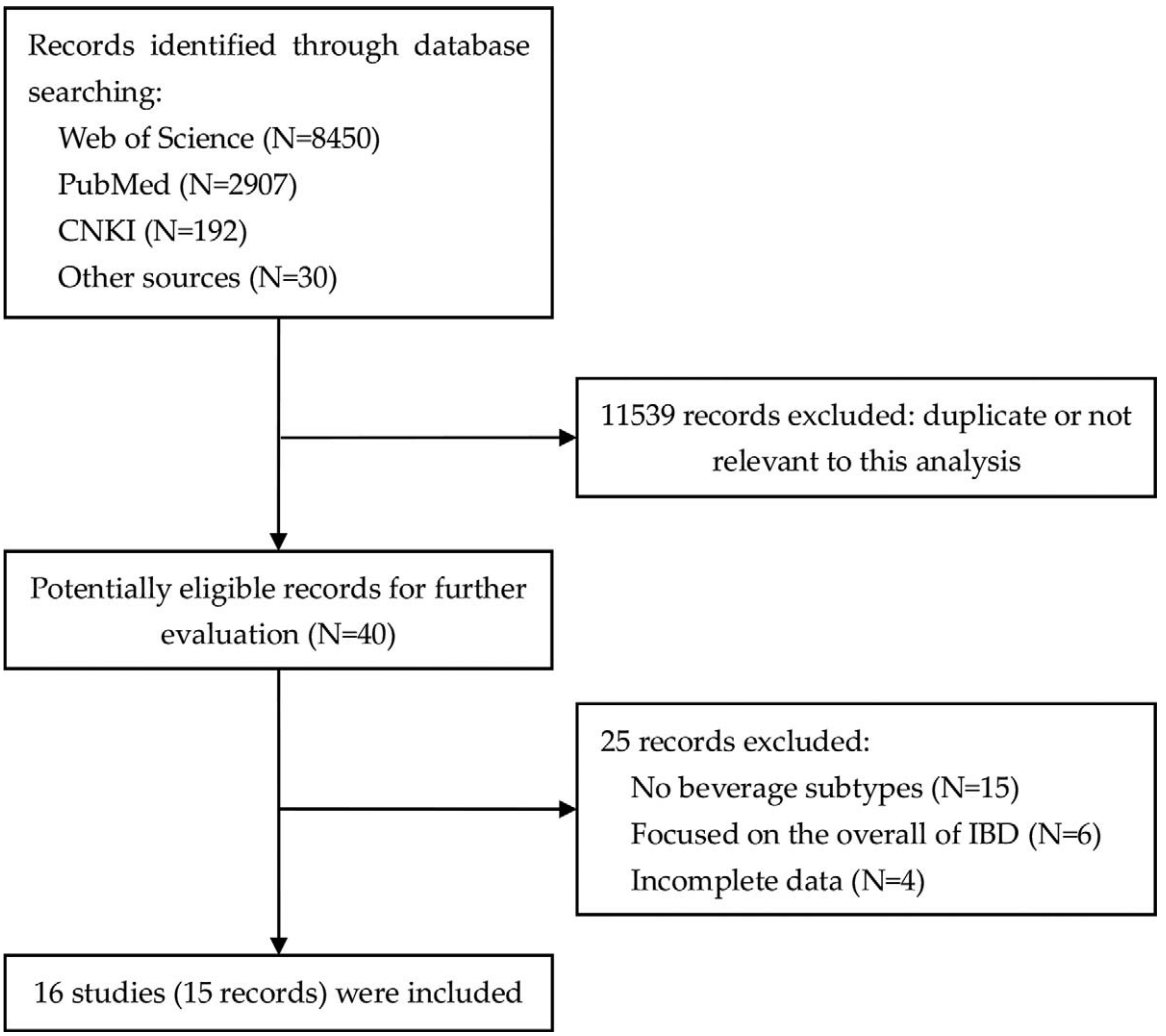

Figure 1. Flowchart of literature search.

Table 1

Characteristics of included studies.

Study	Area	Design	Cases/controls	Type	Categories	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
				Coffee	3	≥3 vs 0 cups/d	0.3 (0.2–0.6)	
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
Russel et al, 1998[16]	Netherlands	Population-based case-control	290/616	Cola drinks	2	>1 vs. ≤1 per wk	2.2 (1.5–3.1)	Smoking, sex, age, educational level, selected nutritional factors
				Coffee	2	≥1 vs 0 per d	1.5 (0.8–2.3)	
Sakamoto et al, 2005[17]	Japan	Hospital-based case-control	126/211	Alcoholic beverages	4	Q4 vs Q1	0.50 (0.23–1.11)	Age, sex, study area, education, smoking habits
Halfvarson et al, 2006[18]	Sweden/Denmark	Population-based case-control	98/95	Coffee	3	≥3 vs 0 cups/d	2.1 (0.7–6.0)	Dizygotic and monozygotic pairs
Han et al, 2010[19]	New Zealand	Population-based case-control	315/536	Alcohol	2	≥1 vs 0 per wk	0.84 (0.62–1.15)	Age, ethnicity
Hansen et al, 2011[20]	Denmark	Hospital-based case-control	123/267	Coffee	2	≥3 vs less cups/d	0.67 (0.37–1.21)	Age, sex, ethnicity, geographic location
Jakobsen et al, 2013[21]	Denmark	Population-based case-control	59/477	Soft drinks	2	≥4 vs ≤3 times/wk	2.9 (1.0–8.5)	Age, sex, ethnicity, area of residence, socioeconomic status
Ng et al, 2015[22]	Asia-Pacific	Population-based case-control	186/940	Soft drinks	2	≥2 vs <2 times/wk	0.759 (0.386–1.491)	Sex, age, country income based on GNI
				Coffee	2	≥2 vs <2 times/wk	0.796 (0.549–1.156)	
				Tea	2	Daily vs not	0.662 (0.462–0.950)	
Niu et al, 2016[23]	China	Nested case-control	102/408	Tea	2	Yes vs no	0.76 (0.49–1.19)	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 pattern	5	Q5 vs Q1	1.2 (0.56–2.56)	Age, sex, center, date of recruitment into EPIC, daily energy intake, body mass index, smoking status
Bergmann et al, 2017[25]	Europe	Prospective	84/336	Alcohol	5	Heavy vs light	0.43 (0.13–1.47)	Age, sex, center, enrollment date, educational attainment and smoking status
Porter et al, 2017[26]	USA	Prospective	58/40749	Alcohol	3	Heavy vs no/light	1.27 (0.52–3.07)	—
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 (SMC) 2018[27]	Sweden	Prospective	143/82899	Sweetened beverage	4	Q4 vs Q1	1.05 (0.79–1.41)	Age, cohort, BMI, smoking, total caloric intake, total protein intake, total fiber intake, and nonsteroidal anti-inflammatory drug use
Khalili et al (CoSM) 2018[27]	Sweden	Prospective		Sweetened beverage	4	Q4 vs Q1	0.99 (0.87–1.12)	

BMI = body mass index, CI = confidence interval, Q = quantile, RR = relative risk.

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, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .453$), indicating no obvious association between them (Fig. 2). Egger test detected significant publication bias ($P = .992$).

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, $I^2 = 81.0\%$, $P_{\text{heterogeneity}} < .001$), suggesting no obvious association between them (Fig. 2). Egger test detected no significant publication bias ($P = .444$).

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, $I^2 = 78.1\%$, $P_{\text{heterogeneity}} < .001$) (Fig. 2). High intake of soft drinks might increase the risk of CD. Egger test detected no significant publication bias ($P = .140$).

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, $I^2 = 0.0\%$, $P_{\text{heterogeneity}} = .636$) (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 ($P_{\text{interaction}} > .05$). 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

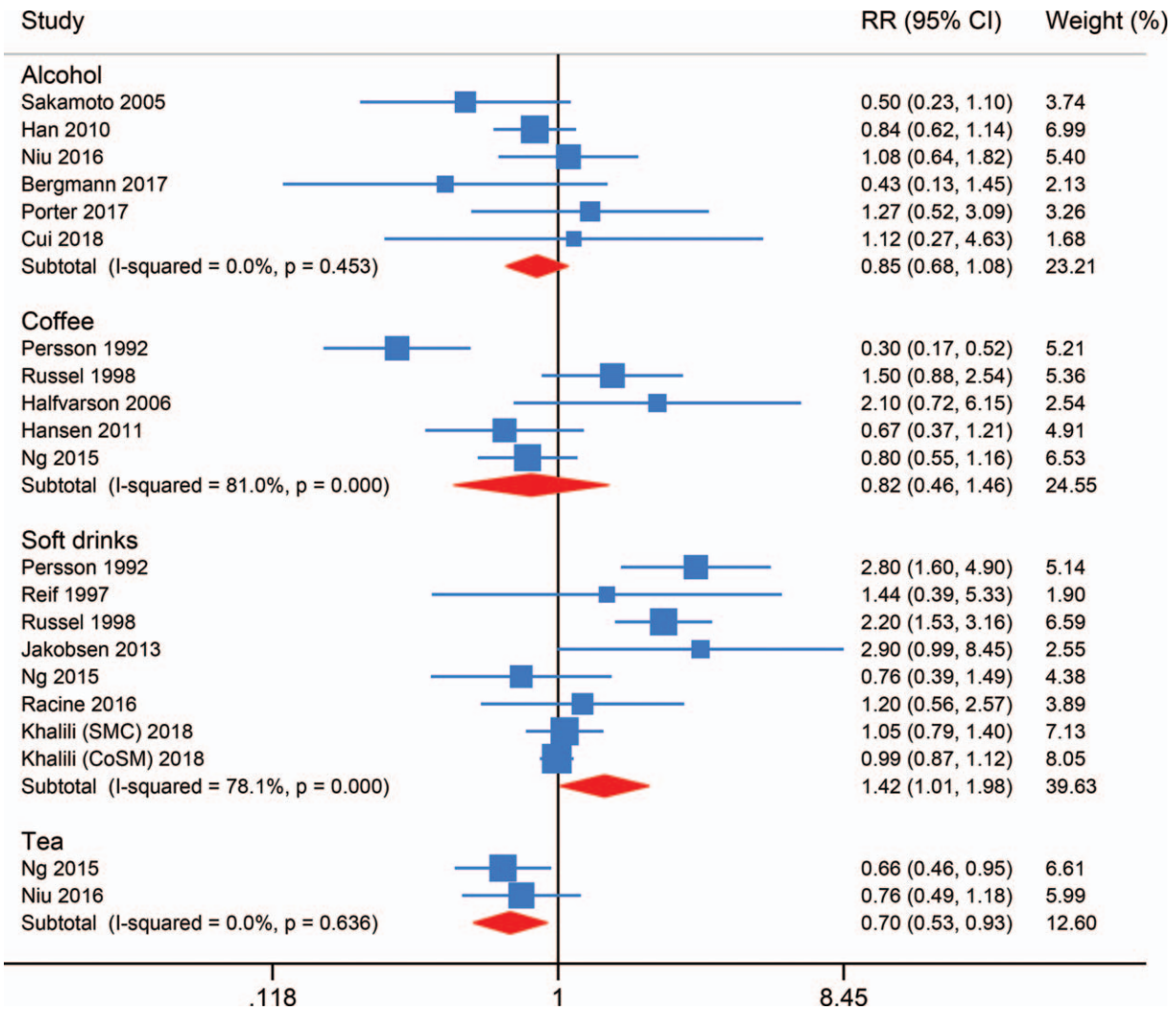

Figure 2. Forest plot of beverage intake and risk of Crohn disease.

Table 2

Subgroup analysis of beverage intake and risk of Crohn disease.

	Alcohol		Coffee		Soft drinks		Tea	
Subgroups	**RR (95% CI)**	**$P_{interaction}$**	**RR (95% CI)**	**$P_{interaction}$**	**RR (95% CI)**	**$P_{interaction}$**	**RR (95% CI)**	**$P_{interaction}$**
Cohort								
Asian	0.84 (0.50–1.43)	.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)		0.67 (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.[30] 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.[31]

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.[32] 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).[33]

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.[34,35] 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.[36,37] In the study by Opstelten et al, IBD patients consumed more carbonated beverages, and sugar and sweets than individuals from a general population ($P < .05$).[38] 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 0.70, 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.[39–41] Moreover, the presence of antioxidants in tea might also reduce the formation of free radicals that damaged cells in the body.[42] 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.[43] 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.
Formal analysis: Yanhua Yang.
Investigation: Lili Xiang.
Methodology: Lili Xiang.
Software: Lili Xiang.
Supervision: Jianhua He.
Writing – original draft: Yanhua Yang.
Writing – review & editing: Jianhua He.

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