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**ASSOCIATION BETWEEN TEA CONSUMPTION WITH RISK OF TYPE 2 DIABETES;
SYSTEMATIC REVIEW AND META-ANALYSIS OF 14 COHORT
STUDIES UPDATE TO JUNE 2016**

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Abstract

The prevalence of the metabolic disease of diabetes type 2 is increasing day by day. A part of this increasing trend is related to environmental factors such as dietary habits. In various studies, contradictory results regarding the effects of tea consumption on the risk of diabetes type 2 have been observed. Therefore, by a systematic review of databases SID, Irandoc, Scopus, Pubmed and ISI Web of Science and meta-analysis of data, in this article we tried to investigate the relationship between the tea consumption and diabetes type 2.

In general, from between 12 articles 14 cohort studies meta-analyzed in the range of 2004 to 2015. All participants and their mean age were respectively 94 248 participants (36,653 patients and 589,783 control) and 57.3 year. The studies of >1 cup per day and ≥ 4 cup per day are of low heterogeneity and 1-3 cup per day is of high heterogeneity.

The mean of risk ratio was as follows: >1 cup: FEM = 0.99; 95% CI (0.95- 1.03), 1-3 cup per day: REM = 0.98, 95% CI (0.94-1.02), ≥ 4 cup per day:

FEM = 0.94; 95% CI (0.86-1.02). In general, FEM= 0.98, 95% CI (0.95-1.01). Consumption of ≥ 4 cup per day in relation to per day >1 cup and 1-3 cup per day decreases the risk of diabetes non-significantly 6%.

The results of this study supported the reduction of risk of diabetes type 2 due to consumption of tea.

Keywords: Tea consumption, diabetes type 2, systematic review, meta-analysis

1. Introduction

High blood glucose level due to resistance to insulin and the beta cell dysfunction can cause a metabolic disease called diabetes type 2 (T2DM) [1,2]. Diabetes is becoming an important public health challenge [3,4]. From 1980 to 2004 the population of people with diabetes in the United States has amounted to 14.7 million individuals from 5.8 million and in 2004 alone, 1.4 million new diabetics (18-79 years old) have been identified [5]. The prevalence of diabetes type 2 was equal to 2.8% in 2000 and it is predicted to reach 4.4% by 2030 [6]. The World Health Organization has predicted that diabetes will be accounted as seventh cause of death in 2030 [7]. More than 80% of them live in the countries with low- to moderate-income [8].

The International Diabetes Federation has reported that in 2013, 382 million people (8.3%) of the world population have suffered from diabetes whose 175 million people have not been diagnosed; it has predicted that almost 592 million people (10.1%) will suffered from this disease in 2035 [8]. This increasing trend has been attributed to genetic and environmental factors [9,10]. Diabetes risk factors include physical inactivity, obesity, genetics, race, age, high blood pressure, high triglycerides and lack of lipoprotein with high density [11,12].

Genetic and racial factors for diabetes type 2 were only 6% [13]. It has been proposed that the chronic oxidative stress can be effective in increasing the mechanism of insulin resistance, impaired glucose tolerance, β -cell dysfunction and diabetes type 2 [14-16]. In recent years several studies have been carried out on tea consumption, heart disease and cancers [17-20]. Tea consumption can be effective on the process of oxidative stress.

There are many evidences that the tea consumption can prevent diabetes. Green tea polyphenols (GTP) reduce free radicals and by increasing the superoxide dismutase and glutathione can reduce lipid peroxidation [21]. Tea can promote the phosphorylation of insulin-signaling proteins and increase the activity of insulin. Also green tea can increase the fat metabolism and lipolysis in healthy individuals [22]

A study that has been conducted by Polychronopoulos et al showed that green tea consumption can reduce the level of fasting blood glucose in the non-diabetic elderly [23]. The studies on the relationship between tea consumption and diabetes type 2 had had contradictory results.

Some studies have shown that the tea consumption reduces the risk of diabetes type 2 [23-27] and in some ones there was observed a significant correlation between tea consumption and risk of diabetes type 2 [28-30]. Therefore, in this

study we tried to evaluate the relationship between tea consumption and risk of diabetes type 2 by doing a systematic review and meta-analysis.

2. Materials and Methods

This study was a systematic review and a meta-analysis of the relationship between tea consumption and the risk of diabetes type 2. For finding the studies conducted in Iran and the world, the databases SID, Irandoc, Scopus, Pubmed and ISI Web of Science were used.

1.2. Selection and evaluation criteria of quality of studies

To begin with, a list of titles and abstracts of all studies available on the mentioned databases were provided by three researchers (Mi.Z, Ya.F, Ha.K) in order to avoid the researchers' bias. Titles and abstracts written between 1990 and 2016 were independently examined.

The search is done for 2 weeks from 02/15/2016 to 30/02/2016 and then the related studies were entered into the study process separately and by the blinding method of initial evaluation. The similar studies were excluded. The main criterion of inclusion of different articles to this study was a reference to tea consumption and risk of diabetes type 2.

In the second stage, the abstracts of the different selected studies were investigated by researcher using the check-list STROBE¹ that is a standard check-list. This check-list contains 43 sections and evaluates the different and varied aspects of methodology, including sampling methods, measurement of variables, statistical analysis and objectives of the study [31].

In this check-list the achievable minimum score was 40 and a maximum score 45. Finally, the top articles that had gained the minimum score (40) of the check-list questions, were entered in research and for doing meta-analysis their data were extracted. For determine Publication Bias the Funnel Plot and Egger's test were used [32].

2.2. Data extraction

In this study, 12 articles (14 cohort studies) in all of which the almost same methodology had been used and in the period 2004 to 2015 had been completed, were meta-analyzed. The important information needed to analyze the data, including information on the subject, title, type of study, time of study, score of each study in the system of NOS [scale Newcastle-Ottawa], the relative risk of diabetes type 2, the number of cases and controls and the confidence level, gender, country, mean of follow-up and measurement methods for diabetes type 2 were collected.

3.2. Quality of studies

According to qualitative evaluation criterion NOS which includes Selection, Comparability and Exposure, cohort was scored. The score range in the system NOS is from 0 to 9. In this study, all studies were classified into two groups of low score (<7) and high score (≥ 7).

4.2. Statistical synthesis and analysis of data

The meta-analysis of data was done by software Comprehensive Meta-Analysis V. 2.2.064. Studies were divided into the following three groups: less than 1 cup per day, 1 to 3 cups per day and more than or equal to 4 cups per day. For calculating the heterogeneity of the studies I^2 Higgins was used.

For doing meta-analysis, in studies in which I^2 was greater than 50% random effect model was used and ones less than 50% the fixed effect model. The subgroups included the qualitative score (high and low) and type of study. The significance level was P value <0.05 .

3. Results

1.3. Recognizing the related studies

As it is shown in Figure 1, 568 articles in total are obtained by searching the databases SID, Irandoc, Ovid, Scopus, Embase, ISI web of science and PubMed. Based on titles and abstracts and some other reasons, 389 articles were excluded in stage of Eligibility. From the remaining 146 articles, 167 articles were excluded for some reasons. Finally 12 articles remained for meta-analysis. In general, from these 12 articles 14 cohort studies were obtained (Figure 1).

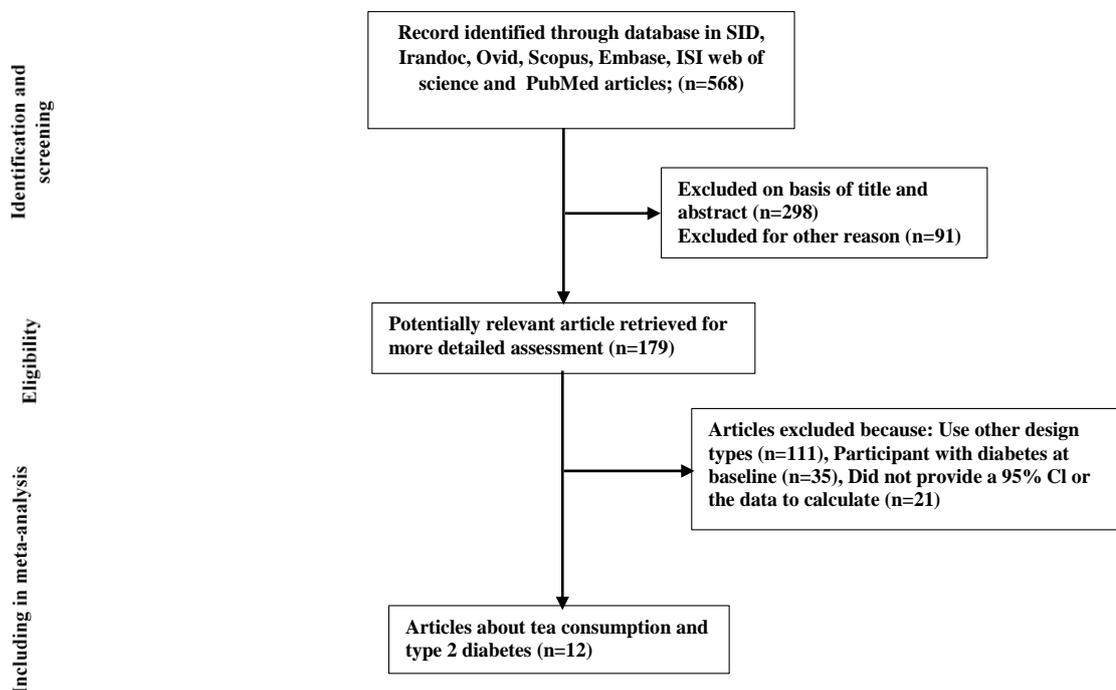


Figure1. Flow diagram for identification of relevant cohort studies.

2.3. Characteristics of studies

General characteristics such as year of publication, country, type of study, exposure cases, the cases, the participants' age, diabetes measurement method and results, etc. have been shown in Table 1. The range of the years of publication of articles was from 2004 to 2015. A study on men and 4 studies on women and other studies on men and women were conducted. Seven studies in the United States, two studies in Great Britain, two studies in Japan, a study in Finland, a study in Singapore and a study were also international. In 12 articles 94,248 participants (36,653 patients and 589,783 controls) in general were recognized. The mean age of study participants was 57.3 year.

Table 1. Overall characteristics of articles included in the final analysis.

Source	Year	Country	Sex	Total N	Cases	T2D measures	Mean Follow-up (yr)	Ref
Salazar-Martinez	2004	USA	M	41934	1311	NDDG diagnostic criteria, self-report, confirmed by medical records	12	[33]
			F	84276	4079		18	
Song et al	2005	USA	F	37457	1593	ADA diagnostic criteria, self-report, confirmed from supplemental questionnaire and physician information	8.8	[25]
Greenberg et al	2005	USA	M/F	5127	170	Self-report of doctor's diagnosis	8.4	[24]
Van Dam et al	2006	USA	F	88259	1263	NDDG diagnostic criteria, self-report, confirmed by medical record review	10	[28]
Hu et al	2006	Finland	M/F	21385	964	WHO criteria, NHDR, NSIIDR	13.4	[34]
Iso et al	2006	Japan	M	6727	231	FSG \geq 7.8 mmol/L, or RM \geq 11.1 mmol/L, or treatment with oral hypoglycemic agents or insulin to indicate new cases of diabetes, self-report	5	[26]
			F	10686	213		5	
Pereira et al	2006	USA	F	N/A		4 follow-up mailed surveys, self-report	11	[35]
Hamer et al	2008	United Kingdom	M/F	5823	387	OGTT, diabetic medication, self-report of doctor's diagnosis	11.7	[36]
Odegaard Ao et al	2008	Singapore	M/F	22467	1189	DRICD codes, Telephone interview	5.7	
Bhupathiraju et al	2012	USA	F	74 749	7370	NDDG diagnostic criteria, self-report, confirmed by medical records	24	[37]
Connor et al	2015	UK	M/F	248264	847	self-report of doctor-diagnosed diabetes from the second health check (3 years post-baseline) or follow-up health	5	[38]
Hayashino	2011	Japan	M	4975	201	ADA and WHO diagnostic criteria, self-report without confirmation	3.4	[39]
InterAct	2012	Spain, Italy, Sweden, France, Denmark,	M/F	12403	16835	Self-report, primary care registers, secondary care registers, hospital	11.7	[40]

Germany, The Netherlands, and United Kingdom
 admissions and mortality data, confirmed by further evidence of information of incident type 2 diabetes from at least two independent sources

Based on the qualitative evaluation criterion (NOS) Newcastle-Ottawa scale in cohort studies, all studies have a score higher than 7, so they have a high quality (Table 2).

3.3. Risk of diabetes type 2 and meta-analyses

Study	Selection (Score)				Comparability (Score)	Exposure (Score)			Total Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Salazar-Martinez et al	1	1	1	1	2	0	1	1	8
Song et al	0	1	1	1	2	1	1	0	7
Greenberg et al	1	1	1	1	2	1	0	0	7
van Dam et al	1	1	1	1	2	0	1	0	7
Hu et al	1	1	1	1	2	1	1	1	9
Iso et al	0	1	1	1	2	0	1	1	7
Pereira et al	1	1	1	1	2	1	0	1	8
Hamer et al	1	1	1	1	2	1	1	0	8
Odegaard et al	0	1	1	1	2	0	1	1	7
Bhupathiraju et al	1	1	1	1	2	0	1	0	7
Connor et al	1	1	1	1	2	0	0	1	7
Hayashino et al	1	1	1	1	2	1	1	0	8
InterAct	1	1	1	1	2	1	1	0	8

The studies of >1 cup per day and ≥4 cup per day are of low heterogeneity and 1-3 cup per day is of high heterogeneity (Figure 2). The highest and lowest percentage of weight in studies belonged >1 cup for the studies of Boggs et al and Hayashino et al, 1-3 cup per day for Hammer et al and Iso et al and ≥4 cup per day for Bhupathiraju et al and Van Dam et al. Mean of risk ratio for studies consists of: > 1 cup: FEM = 0.99; 95% CI (0.95-1.03), 1-3 cup per day: REM = 0.98, 95% CI (0.94-1.02), ≥4 cup per day: FEM = 0.94; 95% CI (0.86-1.02). In general FEM = 0.98, 95% CI (0.95-1.01) was the case in our observations (Figure 2).

Table-2. Methodological quality of studies included in the final analysis based on the Newcastle-Ottawa scale for assessing the quality of cohort.

Group by N-Cup	Study name	Statistics for each study					Risk ratio and 95% CI	Relative weight
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value		
<1 cup/day	Salazar-Martinez et al	0.990	0.909	1.079	-0.230	0.818		21.54
<1 cup/day	Song et al	1.010	0.859	1.188	0.120	0.904		5.99
<1 cup/day	Van Dam et al	0.830	0.669	1.029	-1.698	0.089		3.42
<1 cup/day	Iso et al	0.970	0.835	1.127	-0.398	0.690		7.04
<1 cup/day	Pereira et al	1.070	0.948	1.208	1.096	0.273		10.80
<1 cup/day	Odegaard Ao et al	0.990	0.869	1.128	-0.151	0.880		9.24
<1 cup/day	Bhupathiraju et al	0.910	0.781	1.061	-1.205	0.228		6.72
<1 cup/day	InterAct	0.930	0.809	1.069	-1.022	0.307		8.15
<1 cup/day	Hayashino et al	0.830	0.562	1.225	-0.938	0.348		1.04
<1 cup/day	Boggs et al	1.030	0.953	1.113	0.744	0.457		26.08
<1 cup/day		0.990	0.951	1.030	-0.502	0.615		
>=4 cups/day	Hayashino et al	0.930	0.746	1.159	-0.645	0.519		15.19
>=4 cups/day	Salazar-Martinez et al	0.720	0.517	1.003	-1.940	0.052		6.70
>=4 cups/day	Song et al	0.880	0.635	1.220	-0.767	0.443		6.92
>=4 cups/day	Van Dam et al	0.640	0.399	1.027	-1.850	0.064		3.30
>=4 cups/day	Iso et al	0.670	0.474	0.948	-2.265	0.024		6.14
>=4 cups/day	Pereira et al	1.090	0.812	1.463	0.573	0.566		8.50
>=4 cups/day	Bhupathiraju et al	1.080	0.895	1.303	0.804	0.422		20.95
>=4 cups/day	Connor et al	0.680	0.517	0.895	-2.756	0.006		9.81
>=4 cups/day	InterAct	1.580	1.107	2.254	2.522	0.012		5.84
>=4 cups/day	Hayashino et al ..	1.060	0.859	1.308	0.543	0.587		16.66
>=4 cups/day		0.943	0.865	1.027	-1.350	0.177		
1-3 cups/day	Salazar-Martinez et al	0.810	0.560	1.171	-1.121	0.262		1.44
1-3 cups/day	Song et al.	1.020	0.907	1.147	0.332	0.740		14.30
1-3 cups/day	Greenberg et al	0.730	0.504	1.058	-1.663	0.096		1.42
1-3 cups/day	Van Dam et al..	0.900	0.767	1.056	-1.292	0.196		7.67
1-3 cups/day	Hu et al	1.080	0.911	1.281	0.884	0.377		6.73
1-3 cups/day	Iso et al	0.700	0.369	1.327	-1.093	0.274		0.48
1-3 cups/day	Pereira et al	1.050	0.911	1.211	0.671	0.502		9.65
1-3 cups/day	Hamer et al	1.000	0.919	1.088	0.000	1.000		27.25
1-3 cups/day	Bhupathiraju et al	0.940	0.841	1.051	-1.087	0.277		15.74
1-3 cups/day	InterAct	0.830	0.693	0.994	-2.023	0.043		6.01
1-3 cups/day	Boggs et al	1.100	0.951	1.272	1.287	0.198		9.30
1-3 cups/day		0.983	0.941	1.028	-0.738	0.461		
Overall		0.982	0.955	1.010	-1.259	0.208		

<1 cup/day; I²=0%, P= 0.53
 1-3 cup/day; I²=66%, P=0.002
 ≥4 cup/day; I²=31%, P=0.147
 Overall= I²=40%, P=0.011

Figure 2. Forest plots of relative risk with 95% CI of tea consumption with risk of type 2 diabetes.

4. Discussion

Meta-analysis of 14 cohort studies showed that consumption of ≥ 4 cup per day more than that of > 1 cup per day and 1-3 cup per day reduces non-significantly the risk of diabetes by 6%. In the study of meta-analysis done by Yali Jing et al the reduction of the risk of diabetes type 2 was 20% and in the study of Yang et al was 16% that they were many more than ours. Unlike our study, in the study of Yang et al the reduction of the risk of diabetes was not significant [42, 41]. Two studies showed that there is not any relationship between tea consumption and diabetes type 2 [34, 36].

The study of Hammer et al showed that the consumption of more than 3 cups tea per day can reduce the risk of diabetes type 2, after adjustment for sex, age, race and socio-economic status [36].

2 studies of Conner et al and Iso et al showed that the tea consumption more than 4 cups per day reduces significantly the risk of diabetes type 2 in relation to the groups that consume less than 1 cup and between 1 and 3 cups per day [26, 38]. However, the study of Interact showed that tea consumption does not cause the risk of diabetes type 2, but increases the risk of diabetes type 2 by 58% [40].

The study of Babu et al showed that consumption of green tea (300 mg / kg BW/day) can reduce blood glucose [43]. The study of Wu et al also showed that taking 0.5 grams per day of green tea can significantly reduce the fasting hyperglycemia [44]. Other studies also showed that consumption of 0.5 grams of green tea for 12 weeks can significantly reduce the fasting plasma glucose levels, insulin, triglyceride and free fatty acids [45].

On the other hand, the study of Islam et al showed that taking 23 grams per day of green tea can increase insulin concentration in the blood of mice [46]. As it can be seen in Figure 3, despite the inverted funnel plot, the results of Eggers' test showed that the Publication Bias is considerable in the studies (Intercept: -1.31, 95% Ci (-2.2, -0.36)).

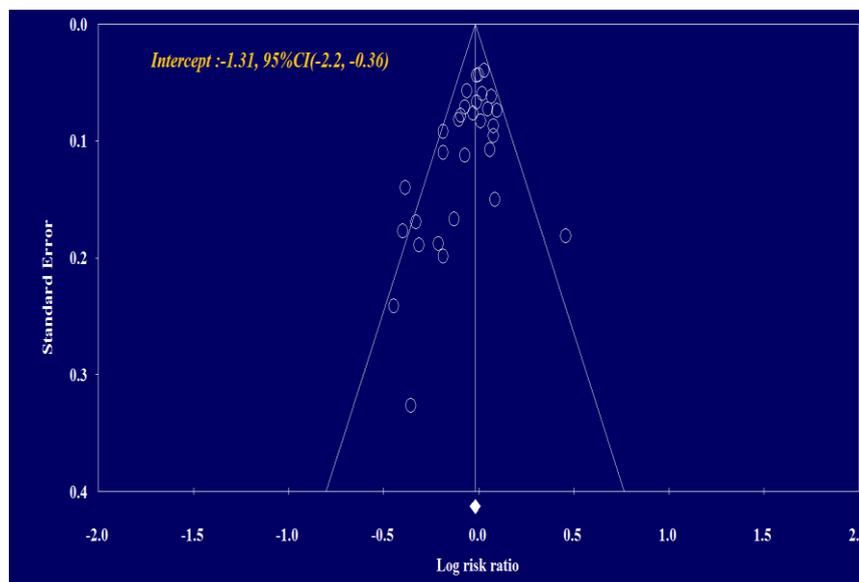


Figure 3. Begg's funnel plot of publication bias test.

The limitations of study included: limitation of language (except English and Persian languages), lack of case-control studies, lack of a single valid method for measuring the amount of tea consumption, existence of many confounding in observational studies including: non-identifying the type of tea in some studies, such as green tea, brown tea, oolong tea, the caffeine tea and the tea without caffeine.

Although the studies have shown that the caffeine reduces the risk of diabetes type 2 [47], due to lack of data the intervening role of caffeine in diabetes type 2 was not adopted in studies. The confounding effect on heterogeneity by meta-regression was not taken into account.

5. Conclusions

Meta-analysis results of this study showed that the tea consumption reduces non-significantly the risk of diabetes type 2 (p value > 0.05). Therefore, more studies are needed to draw conclusions with regard to the subgroups such as sex, economic status and so on.

The results of this study supported the reduction of the risk of diabetes type 2 due to consumption of tea.

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