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Effect of egg consumption on inflammatory markers: a systematic review and meta-analysis of randomized controlled clinical trials

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Abstract

There is little evidence about whether eggs affect inflammation. The aim of this meta-analysis was to explore the effects of egg consumption on inflammation. A systematic search of online databases (Institute for Scientific Information (ISI), Scopus, Ovid, PubMed, Cochrane) was used to gather clinical trials that assessed the effect of egg consumption on circulating inflammatory biomarkers. Using a random-effects model, pooled weighted mean differences (WMD) and corresponding standard deviations (SD) were calculated. Of the 21 eligible studies found, nine trials were eligible for analysis. Eight trials assessed high-sensitivity C-reactive protein (hs-CRP), four trials assessed interleukin-6 (IL-6), and five trials assessed tumor necrosis factor- α (TNF- α). Egg consumption did not affect hs-CRP (WMD 0.24 mg/L; 95% CI: -0.43, 0.90; $I^2 = 53.8$; $P = 0.48$), IL-6 (WMD 0.20 pg/mL; 95% CI: -0.71, 1.11; $I^2 = 69.3$; $P = 0.50$), and TNF- α (WMD: -0.38 pg/mL; 95% CI: -0.87, 0.10; $I^2 = 0.00$; $P = 0.12$) relative to controls. Overall, this meta-analysis revealed that egg consumption had no significant effect on serum biomarkers of inflammation in adults.

Keywords

Egg; Inflammation; Meta-analysis; Systematic review; Randomized controlled trial

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AUTHOR CONTRIBUTIONS

MV and SS contributed to the concept of the study, planned the literature search and designed the analysis. ZSH and MKHS searched the database, checked them, and extracted the data. SS was involved in the data analysis. ZSH and MKHS wrote the article. MV and ZSC critically reviewed the manuscript. All authors edited and approved the final manuscript

SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

INTRODUCTION

Since the 1970s, the association between dietary cholesterol intake and cardiovascular disease (CVD) risk has been studied extensively. Until recently, restricting egg consumption and reducing dietary cholesterol intake to < 300 mg/day has been part of the American Heart Association (AHA) guidelines on lifestyle management.^{1–3} Although this recommendation is no longer enforced, the AHA currently recommends individuals consume as little dietary cholesterol as possible. Eggs are an inexpensive and low-calorie source of macro- and micro-nutrients, including protein, omega-3 fatty acids, folate, riboflavin, selenium, choline, and vitamins B₁₂, D, K, and A. Egg yolks are also a rich source of bioavailable xanthophyll carotenoids, specifically lutein and zeaxanthin.^{4,5} Although one egg typically contains 141–234 mg of cholesterol, there has been little evidence of a deleterious effects of eggs on cardiovascular (CV) health. Furthermore, multiple intervention-based studies have found that consumption of one egg each day had minimal effects on CVD risk in healthy individuals.^{1,6,7} A meta-analysis by Rong *et al.*, analyzing eight cohort studies, demonstrated that consumption of up to one egg each day was not associated with increased risk of coronary heart disease or stroke.⁸

Inflammation is an adaptive response by the immune system to restore functionality following a homeostatic imbalance; however, chronic and excessive inflammation can become pathological.⁹ Inflammation is a strong predictor for the development of many chronic diseases, including CVD and type 2 diabetes mellitus (T2DM).^{9–11} Diet is a common mediator between inflammation and the development of chronic diseases.^{12–14} For example, the cholesterol content of eggs has been reported to promote pro-inflammatory signaling by inducing cytotoxicity and stimulating the formation of lipid rafts in plasma membranes of leukocytes, which creates hypersensitivity to pro-inflammatory signaling.^{15,16} Interestingly, however, consumption of arginine, another nutrient found in eggs (approximately 410 mg per egg), has been shown to lower CVD risk, in part by reducing inflammation.^{17,18}

Data from clinical trials investigating the relationship between egg consumption and inflammation is mixed, and eggs have been shown to increase¹⁹ and decrease²⁰ inflammation. Authors claim that changes in inflammation may be explained by participant characteristics, such as body weight and health status. As far as we are aware, no systematic review or meta-analysis has ever examined the relationship between egg consumption and circulating inflammatory biomarkers. The purpose of the present study was to conduct a systematic review and meta-analysis of clinical trials that have assessed the relationship between egg consumption and circulating biomarkers of inflammation.

MATERIALS AND METHODS

The present study was conducted, and is reported, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²¹ The protocol of this review was registered in the PROSPERO International prospective register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO>, registration no: CRD42018105889).

Search Strategy

A systematic literature search was conducted through the following electronic databases to find controlled clinical trials examining the effect of eggs on inflammation: Ovid (www.ovid.com), Scopus preview (<https://www.scopus.com>), Institute for Scientific Information (ISI) (<https://www.webofknowledge.com>) PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), Cochrane (<https://www.cochranelibrary.com>) from database inception up to July 2018. The complete search strategy for all three databases is presented in Table S1. We searched for the words ‘egg’ and ‘inflammation’ and, as there was a possibility that the inflammatory markers could be reported as secondary outcomes of studies, we searched for a series of serum markers of CVD and obesity to ensure all eligible clinical trials were included. We also conducted a manual search of references of related reviews, systematic reviews, and meta-analyses to supplement the electronic search. Studies that were published were included with no language, gender, or publication date restrictions. An updated search was also performed in April 2019.

Study Selection

One investigator (SS) searched the databases mentioned above, and two independent investigators (ZS and MKh) screened titles, abstracts, and full text of articles that were included. Eligible studies included clinical trials in adult populations in which eggs were supplemented and circulating inflammatory biomarkers were assessed (pre- versus post-intervention or change from baseline) as primary or secondary outcomes. Circulating (plasma and serum) biomarkers of inflammation included: tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), immunoglobulin A (IG-A), high sensitivity C-Reactive Protein (hs-CRP), interleukin-1 beta (IL-1 β), soluble form of intercellular adhesion molecule (sI-CAM), vascular cell adhesion molecule-1 (VCAM-1), soluble form of E-selectin (sE-selectin), interleukin-1 (IL-1), interleukin – 8 (IL-8), monocyte chemoattractant protein-1 (MCP-1). Studies were excluded if: 1) the study population was pregnant women or 2) children, 3) the study design was unsuitable (void of a control group or lacking pre-post measurements), 4) the study included an additional intervention other than egg consumption alone (e.g. omega-6 enriched egg). The chief investigator (SS) approved all studies included in the analysis.

Data Extraction

All studies included in the analysis were investigated carefully by two separate investigators (ZS and MKh). Studies were categorized by name of the first author, publication year, country of origin, study population, total sample size, age range or mean age of the participants, number of the study participants in the experiments and control groups, study design (parallel / crossover), duration of follow up, washout period (for crossover studies), participants’ characteristics, and data reported as the outcome were extracted from each study that was included (Table 1). We extracted concentrations of circulating inflammatory biomarkers at baseline and follow-up for the experimental and control groups (mean $\pm$ standard deviation (SD), mean $\pm$ standard error (SE), mean (95% CI)). The SEs and CIs were turned into SDs.

Quality Assessment

We used the Cochrane Collaboration tool to assess the quality of eligible studies.²⁹ The risk of bias tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Within each domain, assessments are made for one or more items, which may cover different aspects of the domain, or different outcomes. We illustrated the risk of bias using the proportion of information that came from studies at low, unclear, or high risk of bias for each item in the tool. If all item met low-risk criteria, the quality was considered as 'good'; if one item met high-risk criteria, or two items were unclear, the quality was considered to be 'fair', and if two or more items were listed as having a high or unclear risk of bias, it was considered to be 'poor'.

Statistical Analysis

Reported mean changes and their corresponding SDs within each study were used to estimate the overall difference in mean change across all studies, which was used as the effect size for hs-CRP. In the case of studies that did not report net changes in hs-CRP within the experimental and control groups, but did report preand post-intervention hs-CRP values, the mean changes were calculated and the SD of the mean was estimated using correlation analysis ($r = 0.61$).^{22,25,27} In the cases in which IL-6 and TNF- α were the only reported measurements of inflammation at the end of the study periods, the final measurements were pooled in the meta-analysis. All units of inflammatory biomarkers were converted to standard International System units to normalize units of measurement for each outcome prior to inclusion in the meta-analysis. The WMD and its corresponding SD was calculated for each outcome by the DerSimonian and Laird method using the random effects model.³⁰ I^2 was used to quantify inter-study heterogeneity.³¹ Potential sources of inter-study heterogeneity were investigated using subgroup analysis with a fixed-effect model. Our subgroups consisted of duration (< than 12 weeks and > than 12 weeks), quantity of eggs consumed in the intervention (1–2 eggs / day and > 2 eggs/day), study design (randomized parallel arm or cross-over), population characteristics (healthy or non-healthy), and diet adherence (normal dietary patterns or restricted diet). Sensitivity analysis was carried out to estimate the pooled effect size after excluding individual studies. Alpha was set at 0.05 and statistical significance was determined at $P < 0.05$. Publication bias was not assessed due to the number of eligible studies (< 10). Stata (version 11.0; Stata Corporation) was used to perform meta-analysis.

RESULTS

Characteristics of included studies

The process of the study selection is shown in Figure 1. After removing the duplicate articles and excluding the articles that did not meet our exclusion criteria, 21 studies remained, 12 of which were excluded.^{32–43} Figure 1 provides the rationale for exclusion of each article. Finally, nine publications (481 participants) were considered eligible for the systematic review.^{19,20,22–28} Eight studies reported circulating hs-CRP concentrations,^{20,22–28} Five studies reported circulating TNF- α concentrations,^{19,20,23,24,27} and four studies reported circulating IL-6 concentrations.^{23,24,26,27}

The characteristics of eligible studies are summarized in Table 1. Five studies were conducted in the USA,^{19,20,23,27,28} two in Australia,^{22,26} one in Mexico,²⁴ and one in the Netherlands.²⁵ The total duration of the studies included in the analysis ranged from 4 to 48 weeks. Two of these studies, which utilized a cross-over design, included a 3 week wash out period.^{23,24} The amount of egg consumption between studies varied from 1 to 3 eggs per day for the intervention groups. The mean age of the enrolled participants ranged from 18 to 77 years and all subjects were healthy,^{20,23,25,27,28} had T2DM,^{22,24,26} or metabolic syndrome.¹⁹ All studies used whole eggs as the intervention and egg whites or egg substitute as the control, with the exception of two studies that fed oatmeal²³ or lean animal protein²² as a control.

Meta-analysis

Effect of egg consumption on hs-CRP—Of the studies included in the analysis, eight trials evaluated the effect of egg consumption on hs-CRP.^{22–28,44} There was no significant difference in change in circulating hs-CRP concentration between individuals consuming eggs relative to non-egg consuming controls (MD 0.24 mg L⁻¹, 95% CI: -0.43, 0.90, $P=0.48$) with no evidence of heterogeneity between trials (I^2 : 53.8 %, Q statistics: 15.15, $P=0.03$) (Figure 2). Furthermore, subgroup analysis revealed that the duration of intervention, type of intervention in the control group, study design, population characteristics, and diet adherence did not influence the effect of eggs on hs-CRP significantly ($P>0.05$) (Table 2).

Effect of egg consumption on IL-6 and TNF- α —The overall effect of egg consumption on IL-6 was assessed in four studies.^{23,24,26,27} There was no significant difference in circulating IL-6 concentration between individuals consuming eggs relative to non-egg-consuming controls (MD 0.20 pg/mL, 95% CI: -0.71, 1.11; $P=0.67$). There was also low heterogeneity between studies ($I^2=69.3\%$, Q statistics: 9.78, $P=0.02$) (Figure S1).

No significant difference was detected for change in circulating TNF- α concentration between individuals consuming eggs relative to non-egg-consuming controls in the eligible five studies^{19,20,23,24,27} (MD -0.38 pg mL⁻¹, 95% CI: -0.87, 0.10; $P=0.12$) without evidence of heterogeneity between studies ($I^2=0.0\%$, Q statistics: 2.69, $P=0.61$) (Figure S2). The effect of eggs on these biomarkers was reported only in limited trials, so a subgroup analysis was not performed.

Systematic review of Effect of egg consumption on other inflammatory markers—Additional circulating biomarkers of inflammation were measured in the eligible studies but were not taken into account for the meta-analysis as these biomarkers were reported in less than three studies. The circulating concentrations of MCP-1 were measured in two studies, one of which reported a significant reduction in the control group but no difference in the group consuming eggs.²⁰ The second study reported an increase in both the control and egg groups, with a higher increase in the control group.²⁷ The circulating concentrations of ICAM-1 and VCAM-1 were reported in three studies^{19,20,25} and all studies reported no significant change for these biomarkers after the completion of the intervention. There were also no significant changes in circulating IL-10,^{19,25} IL-8^{19,20} and SE-selectin²⁶ concentrations for the control or the egg group.

Quality assessment, sensitivity analysis, publication bias

After assessment of quality with the Cochrane Collaboration Tool the overall quality of seven studies was considered poor and two studies were considered fair (Table S2). Sensitivity analysis revealed that the effect of egg consumption on circulating inflammatory biomarkers is not substantially modified by the exclusion of a certain study.

DISCUSSION

As far as we are aware, the present study is the first systematic review and meta-analysis reporting the evidence from clinical trials investigating the effect of egg consumption on circulating concentrations of inflammatory biomarkers. The current study revealed that egg consumption does not result in measurable changes in circulating concentrations of hs-CRP, TNF α , and IL-6 in adults.

Inflammation plays a crucial intermediary role in the pathogenesis of a number of common metabolic diseases^{45,46} and an increased level of pro-inflammatory factors are thought to contribute to the development of T2DM, stroke, and CVD.⁴⁵ Dietary cholesterol from eggs could increase circulating levels of low-density lipoprotein cholesterol, a risk factor for cardiometabolic diseases including CVD and T2D.^{41,47,48} Nevertheless, the results of a recent meta-analysis do not support an egg-associated increased risk of CVD.^{45,46} Indeed, a meta-analysis reported that daily intake of up to 1 egg per day may be associated with reduced stroke risk.⁴⁹

It is important to consider how egg consumption may affect inflammation in various populations. Findings from Basu *et al.* suggested that egg consumption can increase circulating hs-CRP levels in healthy subjects but that eggs do not further increase circulating pro-inflammatory protein levels in populations that already have marked elevations in pro-inflammatory biomarkers, such as obese and insulin-resistant individuals.¹⁴ In the present meta-analysis, however, we calculated the quantitative effect of egg consumption on circulating pro-inflammatory biomarkers and considered different population characteristics in the subgroup analysis, yet found no significant association between egg intake and any of the measured pro-inflammatory biomarkers.

The neutral effect of eggs on inflammation may be explained by the abundance of particular key nutrients found in eggs. Eggs consist of many bioactive components, including phospholipids, cholesterol, lutein, zeaxanthin, antioxidants, choline, and proteins, which have a variety of pro- and / or anti-inflammatory properties.^{30,49} Dietary cholesterol has been reported to be pro-atherogenic and pro-inflammatory in multiple studies; however, most studies that have demonstrated a link between dietary cholesterol and atherogenesis have provided cholesterol in high doses, which are not representative of the cholesterol consumption one would obtain from consuming eggs.^{50,51} Importantly, eggs contain a variety of bioactive proteins that possess anti-inflammatory properties.⁵² For example, egg ovotransferrin has been reported to reduce pro-inflammatory cytokines,^{52,53} and egg lysozyme supplementation has been shown to reduce intestinal gene expression of TNF and IL6, while increasing the expression of anti-inflammatory IL4.⁵⁴ Taken together, it is

probable that the effect of egg cholesterol on circulating pro-inflammatory biomarkers may be negated by the benefits of the anti-inflammatory components of eggs.

There is a possibility that eggs may affect circulating pro-inflammatory biomarkers but the various study designs included in the present analysis may have influenced the ability to detect differences. Although all of the studies included in the present analysis considered equal amounts of overall energy intake between the experimental and control groups, the amount of fat and carbohydrate intake varied significantly between the two groups in some studies,^{24,25} which was not considered as a confounding variable in the final analysis. It is also possible that the differences in BMI between subjects may have influenced the final analysis. Egg consumption has been shown to have a pro-inflammatory effect in healthy populations,⁴⁰ but in obese and overweight subjects, egg consumption has been demonstrated to have an anti-inflammatory effect.³⁰ Furthermore, increased plasma levels of the pro-inflammatory molecule, Trimethylamine *N*-oxide, plus elevated levels of leukocyte cholesterol have been reported in healthy subjects following consumption of a single egg meal.^{55,56} On the other hand, eggs have been reported to increase circulating levels of the anti-inflammatory adipokine, adiponectin, and indirectly reduce inflammation by increasing satiety.^{20,57} The majority of the study participants included in the final analysis were either obese or overweight, with exception of the study by Missimer *et al.*,²³ which also included normal-weight adults. Lastly, the study by Baumgartner *et al.*²⁵ did not document the weight or BMI of the participants in the study, which may have confounded the results of the present analysis.

The reference range for CRP is 0–10 mg L⁻¹ and >3 mg L⁻¹ for hs-CRP.⁵⁸ In the present study, the mean CRP and hs-CRP levels reported in all the eligible studies before the intervention were within the normal range. Thus, there were no differences in baseline inflammation between study participants. It is possible that in a different scenario where participants have elevated levels of hs-CRP, egg consumption may elicit anti-inflammatory effects. Thus, conducting egg consumption-based interventions in patients with inflammatory diseases such as inflammatory bowel disease or rheumatoid arthritis is warranted.

There are a number of strengths to this study. To date, this is the first meta-analysis that attempted to summarize the relationship of egg consumption and circulating biomarkers of inflammation. The present study used a systematic method following current guidelines for systematic review, including prospective registration. The Cochrane Risk of Bias tool was also used to evaluate the quality of evidence, and it was concluded that all studies included in the final analysis were of acceptable quality. Furthermore, the present analysis reported evidence from randomized controlled trials in which the effects of many potential confounders were considered, which enhances the reliability of the results relative to other observational studies. An additional point to consider is that circulating levels of inflammatory biomarkers are less reliable than intracellular levels. Thus, intracellular measurements of inflammation are warranted for more accurate detection of the relationship between egg consumption and inflammation.

There are several possible limitations in the current study. Despite low heterogeneity, the small number of clinical trials and participants available for the present analysis is a limitation that may affect the generalizability of the results. Circulating inflammatory biomarkers were reported as a secondary outcome in the majority of the studies that were analyzed; thus, the sample sizes of these studies may have not been enough to detect the intended effect of eggs on inflammation. Furthermore, the methods used to prepare the eggs were not mentioned in the eligible studies, which could have affected the inflammatory effects of eggs. Moreover, based on Cochrane Collaboration Tool, most studies were of poor quality.

Overall, this study showed no evidence for adverse or protective effects of egg consumption on inflammation in adults. However, due to the limited sample size and number of clinical trials, cautious interpretation of these results is recommended. Thus, until further investigations are conducted in this area, our results suggest that daily consumption of eggs is safe.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Summary of the search process.

Figure 2.

Forest plot of randomized controlled clinical trials illustrating weighted mean difference in serum hs-CRP (mg/dl) between the egg and control groups for all eligible studies in overall analysis. Analysis was conducted using random effects model.

Characteristics of randomized controlled trials that evaluated the effect of the egg consumption on level of serum inflammatory markers and were eligible to be included in the systematic review

Table 1.

First author, year	Country	Design	Duration, week	Participants, n	Population	Mean age,y	Mean BMI, kg/m ²	Egg diet	Control diet	Inflammatory outcomes	Specific diet adherence
Pearce, 2010 ²²	Australia	parallel	12	65 (29m/36f)	T2MD	59	34	2 egg/day	100 gr lean animal pro	hs-CRP	High Protein Diet+energy restricted
Ratliff, 2008 ²⁰	USA	parallel	12	28(m)	healthy	40–70	N/A	640 mg chol (3 egg/day)	egg substitute	hs-CRP, TNF- α	carbohydrate restricted diet
Missimer, 2017 ²³	USA	cross-over	4	50 (25m/25f)	healthy	18–30	18.5–30	2 egg/day	oatmeal (384 gr/d)	hs-CRP, TNF- α , IL-6	normal
Ballesteros, 2015 ²⁴	Mexico	cross-over	5	29 (10m/19f)	T2DM	53.5 $\pm$ 8.3	30.8 $\pm$ 6.4	1 egg/day+2 cups (472 mL) of lactose-free milk/day	oatmeal (40 gr/d)+ 2 cups (472 mL) of lactose-free milk/day	hs-CRP, TNF- α , IL-6	normal
Baumgartner, 2013 ²⁵	the Netherlands	parallel	12	77 (34m/43F)	healthy	18–65	N/A	one to two eggs per week + 1 egg/day	one to two eggs per week	hs-CRP	normal
Fuller, 2018 ²⁶	Australia	parallel	12	128 (59m/69f)	prediabetes or T2DM	18y	25	high-egg diet (12 eggs/week)	low egg (<2 eggs/week)	hs-CRP, IL-6	weight-loss diet
Blesso, 2013 ¹⁹	USA	parallel	12	37 (12m/25f)	Metabolic Syndrome	51.9 $\pm$ 7.7	30.5 $\pm$ 5.3	3 eggs equal to additional 534 mg of dietary cholesterol	3 egg substitute equal to additional 0 mg of dietary cholesterol	TNF- α	carbohydrate restricted diet
Wright, 2018 ²⁷	USA	parallel	12	22 (12m/10f)	healthy	70 $\pm$ 5	31.3 $\pm$ 3.2	3 eggs/day	0 eggs and egg products	hs-CRP, TNF- α , IL-6	High protein in the intervention and normal in the control group
Aljohi, (2019) ²⁸	USA	parallel	48 (1 year)	45 (14m/32f)	aged-related macular degeneration	75.5 $\pm$ 1.82	29.35 $\pm$ 1.67	12 eggs per week	0 whole egg products	hs-CRP	normal

Table 2.
Results of meta-analysis on effects of egg consumption on serum hs-CRP in various subgroups

Study group	Number of participants	Meta-analysis			Heterogeneity		
		WMD (95%CI)	P effect	Q statistic	P within group	I ² (%)	P between group
Overall	435	0.24 (-0.43, 0.91)	0.48	15.15	0.034	53.8	-
Gender							
Male	105	-2.29 (-6.37, 1.79)	0.27	2.93	0.09	65.9	
Female	77	0.8 (0.12, 1.48)	0.02	0.00	-	-	0.004
Both	407	0.33 (-0.23, 0.90)	0.25	10.27	0.114	41.6	
Duration							
Long-term intervention (12 weeks)	365	0.54 (-0.20, 1.27)	0.15	9.65	0.09	48.2	0.03
Short-term intervention (less than 12 weeks)	70	-0.67 (-1.65, 0.30)	0.18	0.62	0.43	0.0	
Interventions (int group)							
One to two eggs per day	385	0.30 (-0.54, 1.15)	0.48	9.89	0.08	49.4	0.58
More than two eggs per day	50	-1.81 (-7.23, 3.60)	0.51	4.94	0.03	79.8	
Intervention (cont group)							
One egg per day	97	-0.19 (-1.31, 0.94)	0.75	0.00	0.98	0.0	
More than one egg per day	338	0.35 (-0.51, 1.20)	0.42	14.09	0.02	64.5	0.30
Study design							
Parallel study	365	0.54 (-0.20, 1.28)	0.15	9.65	0.09	48.2	0.03
Cross-over study	70	-0.67 (-1.65, 0.30)	0.18	0.62	0.43	0.0	
Population characteristic							
Healthy	222	-0.1 (-1.08, 0.87)	0.84	10.5	0.03	61.9	0.51
T2DM	213	0.74 (-0.48, 1.97)	0.23	4.2	0.12	52.4	
Diet adherence							
Normal diet	192	-0.21 (-1.02, 0.61)	0.62	3.50	0.32	14.2	0.09
Non-normal diet	243	0.58 (-0.50, 1.67)	0.29	8.70	0.03	65.5	