Garlic powder intake and cardiovascular risk factors: a meta-analysis of randomized controlled clinical trials

Jin Sook Kwak[1], Ji Yeon Kim[2], Ju Eun Paek[1], You Jin Lee[1], Haeng-Ran Kim[3], Dong-Sik Park[3] and Oran Kwon[1,4§]

[1]Department of Nutritional Science and Food Management, Ewha Womans University, 52, Ewhayeodae-gil, Seodaemun-gu, Seoul 120-750, Korea
[2]Department of Food Science and Technology, Seoul National University of Science and Technology, Seoul 139-743, Korea
[3]Department of Agrofood Resources, Rural Development Administration, Jeonbuk 565-851, Korea
[4]BioFood Network, Ewha Womans University, 52, Ewhayeodae-gil, Seodaemun-gu, Seoul 120-750, Korea

BACKGROUND/OBJECTIVES: Although preclinical studies suggest that garlic has potential preventive effects on cardiovascular disease (CVD) risk factors, clinical trials and reports from systematic reviews or meta-analyses present inconsistent results. The contradiction might be attributed to variations in the manufacturing process that can markedly influence the composition of garlic products. To investigate this issue further, we performed a meta-analysis of the effects of garlic powder on CVD risk factors.
MATERIALS/METHODS: We searched PubMed, Cochrane, Science Direct and EMBASE through May 2014. A random-effects meta-analysis was performed on 22 trials reporting total cholesterol (TC), 17 trials reporting LDL cholesterol (LDL-C), 18 trials reporting HDL cholesterol (HDL-C), 4 trials reporting fasting blood glucose (FBG), 9 trials reporting systolic blood pressure (SBP) and 10 trials reporting diastolic blood pressure (DBP).
RESULTS: The overall garlic powder intake significantly reduced blood TC and LDL-C by -0.41 mmol/L (95% confidence interval [CI], -0.69, -0.12) (-15.83 mg/dL [95% CI, -26.64, -4.63]) and -0.21 mmol/L (95% CI, -0.40, -0.03) (-8.11 mg/dL [95% CI, -15.44, -1.16]), respectively. The mean difference in the reduction of FBG levels was -0.96 mmol/L (95% CI, -1.91, -0.01) (-17.30 mg/dL [95% CI, -34.41, -0.18]). Evidence for SBP and DBP reduction in the garlic supplementation group was also demonstrated by decreases of -4.34 mmHg (95% CI, -8.38, -0.29) and -2.36 mmHg (95% CI, -4.56, -0.15), respectively.
CONCLUSIONS: This meta-analysis provides consistent evidence that garlic powder intake reduces the CVD risk factors of TC, LDL-C, FBG and BP.

Nutrition Research and Practice 2014;8(6):644-654; doi:10.4162/nrp.2014.8.6.644; pISSN 1976-1457 eISSN 2005-6168

Keywords: *Allium sativum*, garlic, CVD risk factor, meta-analysis, systematic review

INTRODUCTION

Cardiovascular disease (CVD) is a prominent global public health problem. The etiology of CVD is multifactorial and exemplified by hypercholesterolemia, hypertension and diabetes mellitus (DM). Various major CVD risk factors cannot be controlled, including age, gender and family history. However, CVD is predominantly caused by risk factors that can be controlled, treated or modified, such as cholesterol, high blood pressure (BP) and diabetes [1,2].

Allium sativum, commonly known as garlic, is a plant of the family Alliaceae and is widely consumed as a spice in Korea. Garlic contains high levels of organosulfur compounds and flavonoids as well as a variety of compounds that function synergistically to provide various health benefits [3]. The body of evidence on garlic continues to grow, and numerous clinical trials have been published [4-7]. Animal studies suggest that

garlic has potential antilipidemic, antihypertensive, antiglycemic, antithrombotic and antiatherogenic properties [8-10]. However, clinical trials and reports from systematic reviews or meta-analyses present inconsistent results despite preclinical studies that suggest that garlic has potential preventive effects on CVD risk factors [4-7,11-37]. The contradiction may be attributed to variations the manufacturing process that can markedly influence the composition of garlic products. As a dietary supplement, garlic is available as dehydrated garlic powder, aged garlic extract (AGE), garlic oil (steam-distilled), garlic essential oil (ether-extracted) and garlic oil macerate, and each form contains a markedly different set of compounds [38]. Among these garlic products, dehydrated preparations are most commonly used and reportedly contain most of the constituents found naturally in whole garlic. According to a recent meta-analysis of randomized controlled clinical trials, garlic powder appeared to be more effective for reducing LDL cholesterol (LDL-C) in their

subgroup analysis of garlic preparation types [4].

In the present study, we systemically reviewed randomized clinical trials (RCTs) to assess the effects of a garlic powder or dehydrated garlic preparation on CVD biomarkers. Specifically, we examined the effects of these preparations on the classic modifiable Framingham risk measures, including systolic BP (SBP), diastolic BP (DBP), total cholesterol (TC) and LDL-C and HDL cholesterol (HDL-C) [39,40]. Additionally, given the reciprocal relationship between insulin resistance and cardiovascular risk [41], we also examined fasting blood glucose (FBG) levels. The effect of other potential confounders, such as the duration of treatment, intake level, subject type and location where the study was performed, were explored in the subgroup analyses.

MATERIALS AND METHODS

Search strategy

The study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA checklist) [42]. In this analysis, RCTs that included clinical outcomes related to CVD risk factors, such as blood cholesterol, glucose levels and BPs, were eligible. Only garlic powder intake studies were included in this analysis. Databases, such as PubMed, Cochrane, Science Direct and EMBASE, were searched for studies that were published from January 1995 to May 2014 and examined the effects of garlic powder on cholesterol, blood glucose or BP compared with placebo or positive control. The search terms used were *Allium sativum* and garlic in combination with cardiovascular-related factors, such as cholesterol, blood glucose, BP and blood circulation. The search was limited to human studies published in English, Japanese and Korean. No studies published in Korean or Japanese were identified. A manual search using the reference lists of original articles and recent reviews was also performed. Each publication was independently reviewed, and the relevant information was extracted by two authors (JSK and JYK).

Data extraction and quality assessment

Data were extracted, and quality was assessed independently by two investigators (JSK and JYK) on the basis of the quality assessment tool used for our previous systematic review and the Cochrane Collaboration [43,44]. This quality rating was based on several criteria related to study design (e.g., use of placebo control versus a non-placebo control group), data collection (e.g., the method of dietary assessment), the quality of the statistical analysis, the type of outcome measured and the characteristics of the study populations (e.g., whether selection bias was present or whether important information about the study subjects, such as age and smoking status, was gathered and reported). We assigned a score from -1 to 1 point for each quality item to yield a score ranging from -20 to 11 for a completely valid study. If the scientific study adequately addressed all or most of the criteria, it received a high methodological quality rating. The risk of bias for this analysis was assessed based on the risk of bias assessment tool for RCTs provided by the Cochrane Collaboration [43]. The risk of bias domains, such as selection bias (random sequence generation and allocation concealment), performance/detection bias (blinding of participants and personnel/blinding of outcome assessment), attrition bias (incomplete data outcome) and reporting bias (selective reporting), were identified [43].

Statistical analysis

The mean changes in biomarkers from baseline were treated as continuous variables, and the mean difference was calculated as the difference between the means in the garlic powder and the control material supplementation groups. The mean changes were calculated using the methods described in the Cochrane Handbook [43]. Briefly, the mean of the differences was equal to the difference in the means. If information was not available from the study on the standard deviations (SD) of the differences, imputation of standard deviations could be achieved by assuming a particular correlation coefficient. Forest plots were produced to visually assess the changes for each variable and the corresponding 95% confidence intervals (CIs) across the studies. A random-effect model was used to calculate the combined effect size to provide a more conservative estimation. Heterogeneity among the studies was assessed using the I^2 statistic, and considered low if $I^2 < 30\%$, moderate if $I^2 = 30\text{-}75\%$, and high if $I^2 > 75\%$ [43]. Publication bias was assessed using funnel plots and Egger's regression. Additionally, subgroup analyses were performed to investigate the potential moderator, and the groups were classified according to dosage, duration, subject and location based on median values for continuous variables. To evaluate the influence of each study on the overall effect size, a sensitivity analysis was conducted using the study removal approach. The secondary analysis was limited to studies that demonstrated high compliance; high quality or a placebo-control design; were published recently; were conducted with dietary management or were supplemented with standardized garlic powder. Furthermore, the relationships between effect size and moderators, such as dose, duration, quality of study, baseline value of risk factor and subject number, were investigated using random effects meta-regression analyses. The statistical analyses were performed using Comprehensive Meta-analysis Version 2.2, Biostat (Englewood, NJ, USA), and a *P*-value of < 0.05 was considered statistically significant.

RESULTS

Literature search and study characteristics

A total of 1,649 potentially relevant titles and abstracts were identified from searches on PubMed, Cochrane, Science Direct and EMBASE together with other reference sources. Of the 162 articles that were collected as full text and assessed for inclusion, 27 studies met the inclusion criteria for meta-analysis (Fig. 1). The characteristics of the 27 included RCTs and their quality are described in Table 1. Twenty-two trials reported sufficient data on TC, 17 trials reported LDL-C data, 18 trials reported HDL-C data, 4 trials reported FBG data, 9 trials reported SBP data and 10 trials reported DBP data (Fig. 1). The majority of trials employed a parallel study design (n = 26); however, 1 trial used a crossover design. Among the 27 identified studies, 14 [12-14,16-18,21,23-25,28,29,31,36] reported that the garlic powder used in each trial was standardized to contain 2.5-13 µg/mg allicin or 13 µg/mg alliin, whereas the remaining studies

Table 1. Details of trials included in this meta-analysis

Reference	Design	Location	Subject	Dosage (mg)	Population size	Duration (days)	TC	LDL-C	HDL-C	FBG	SBP	DBP
Adler AJ, 1997 [11]	RCT, DB, parallel	Canada	Hypercholesterolemia	900	50	84	Y(++) / 7	Y(++) / 7	N / 6			
Anim-Nyame N, 2004 [12]	RCT, parallel	U.K.	Healthy	600	26	7					N / -4	N / -4
Ashraf R, 2005 [13]	RCT, SB, parallel	Pakistan	Type II DM	600	70	84	Y(+) / 2	Y(+) / 2	Y(+) / 2			
Ashraf R, 2011 [14]	RCT, SB, parallel	Pakistan	Type II DM	900	60	168				Y(++) / 4		
Auer W, 1990 [15]	RCT, DB, parallel	Germany	Hypertensive	600	47	84					Y(+) / -4	Y(+) / -4
Byrne DJ, 1999 [16]	RCT, DB, parallel	U.K.	Hypercholesterolemia	900	33	180	N / -3	N / -3	N / -3			
Gardner CD, 2007 [17]	RCT, parallel	U.S.A.	Hypercholesterolemia	1,400	192	134		N / 7	N / 7			
Holzgartner H, 1992 [18]	RCT, DB, parallel	Germany	Hyperlipoproteinemia	900	98	84		Y(+) / 6	Y(+) / 6		Y(++) / 6	N / 5
Isaacsohn JL, 1998 [19]	RCT, DB, parallel	U.S.A.	Hypercholesterolemia	900	50	84					N / 5	N / 5
Jain AK, 1993 [20]	RCT, DB, parallel	U.S.A.	Hypercholesterolemia	900	42	84	Y(++) / 0	Y(++) / 0	N / -1	N / -1	N / -1	N / -1
Kannar D, 2001 [21]	RCT, DB, parallel	Australia	Hypercholesterolemia	880	46	84	Y(++) / 4	Y(++) / 4	Y(-) / 2			
Kiesewetter H, 1993b [22]	RCT, DB, parallel	Germany	PAOD	800	80	84	Y(+) / -2					Y(+) / -2
Lash JP, 1998 [23]	RCT, parallel	U.S.A.	Hypercholesterolemia	1,360	35	84	Y(+) / -3	Y(+) / -3	N / -4			
Mader FH, 1990 [24]	RCT, DB, parallel	Germany	Hyperlipidaemia	800	261	120	Y(++) / 2					
Neil HA, 1996 [25]	RCT, DB, parallel	Europe	Hypercholesterolemia	900	115	180	N / 1	N / 1	N / 1			
Phelps S, 1993 [26]	RCT, DB, cross-over	U.S.A.	Healthy	600	10	14	N / -2	N / -2	N / -2			
Rahmani M, 1999 [27]	RCT, DB, parallel	Iran	Hypercholesterolemia	600	40	28	Y(++) / 3					
Santos O, 1993 [28]	RCT, DB, parallel	U.K.	Hypercholesterolemia	900	60	180	Y(++) / 0	Y(++) / 0	N / -1			
Saradeth T, 1994 [29]	RCT, DB, parallel	Europe	Healthy	600	72	105	N / -1				N / -1	N / -1
Sitprija S, 1987 [30]	RCT, DB, parallel	Thailand	Type II DM	700	40	30	N / -3		N / -3			
Sobenin IA, 2008a [31]	RCT, DB, parallel	Russia	Hypercholesterolemia	600	42	84	Y(++) / 2	Y(++) / 2	Y(+) / 2		Y(++) / 2	Y(+) / 2
Sobenin IA, 2008b-1 [32]	RCT, DB, parallel	Russia	Type II DM	600	20	28	N / 0	N / 0	N / 0	Y(+) / 1		
Sobenin IA, 2008b-2 [32]	RCT, DB, parallel	Russia	Type II DM	600	40	28	N / 0	N / 0	N / 0	N / 0		
Sobenin IA, 2010 [33]	RCT, DB, parallel	Russia	CHD	300	63	365	Y(+) / 0	Y(++) / 0	N / -1			
Superko HR, 2000 [34]	RCT, DB, parallel	U.S.A.	Hypercholesterolemia	900	50	84	N / -4	N / -4	N / -4			
Vorberg G, 1990 [35]	RCT, DB, parallel	Germany	Hypercholesterolemia	900	50	112	Y(++) / -2				Y(++) / -2	Y(++) / -2
Ziaei S, 2001 [36]	RCT, SB, parallel	Iran	Preeclampsia	800	100	56	Y(++) / -2	N / -3	Y(+) / -2		N / -3	N / -3

TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; RCT, randomized controlled trial; DB, double-blind; SB, single-blind; Y(++), significant improvement in the biomarker compared to control; Y(+), significant improvement in the biomarker compared to before the treatment; N, no significant improvement in the biomarker; DM, diabetes mellitus; PAOD, Peripheral arterial occlusive disease; CHD, coronary heart disease
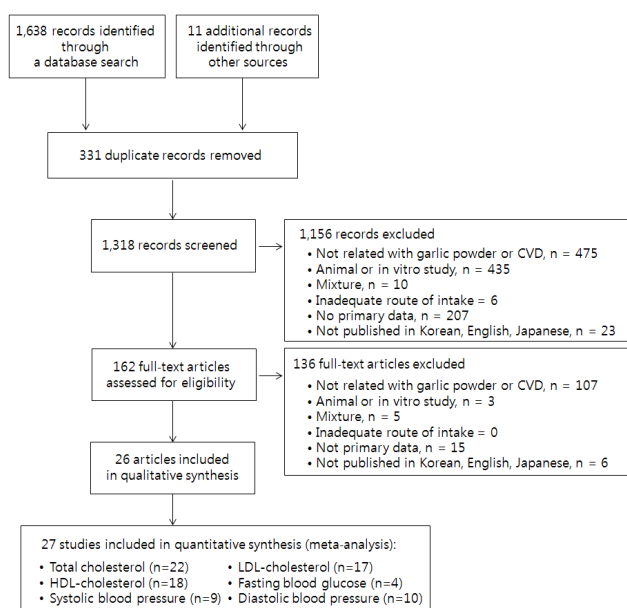
Fig. 1. Flow diagram of the article selection process.

did not provide any information about standardization. The trials ranged from 7 days to one year in duration. The studies were generally from the United States or European countries; five studies were based in Asia, and one was conducted in Australia.

The quality of the trials was generally adequate (score range: -4-7; median score: 0). (Table 1). Six trials reported adequate randomization [17-19,24,25,29], and all but six trials were double-blind, placebo-controlled trials [11,14-16,18-22,24-30, 32-35]. Eight trials did not provide information on the dietary intervention [15,16,22,24,25,33,35,36]. Compliance was assessed and reported as high in 20 trials [11-14,17-19,21,22,24,25,27-30, 32-36], and all trials applied adequate statistical analyses.

The effect of garlic powder on CVD risk factors

A total of 22 studies for TC (n = 1,442), 17 for LDL-C (n = 1,083) and 18 for HDL-C (n = 1,123) were reviewed for garlic powder (Table 1). The effects of garlic on the levels of TC, LDL-C and HDL-C are presented in Fig. 2. Overall, garlic powder intake significantly reduced blood TC and LDL-C by -0.41 mmol/L (95% CI, -0.69, -0.12, $P = 0.005$) (-15.83 mg/dL [95% CI, -26.64, -4.63]) and -0.21 mmol/L (95% CI, -0.40, -0.03, $P = 0.024$) (-8.11 mg/dL
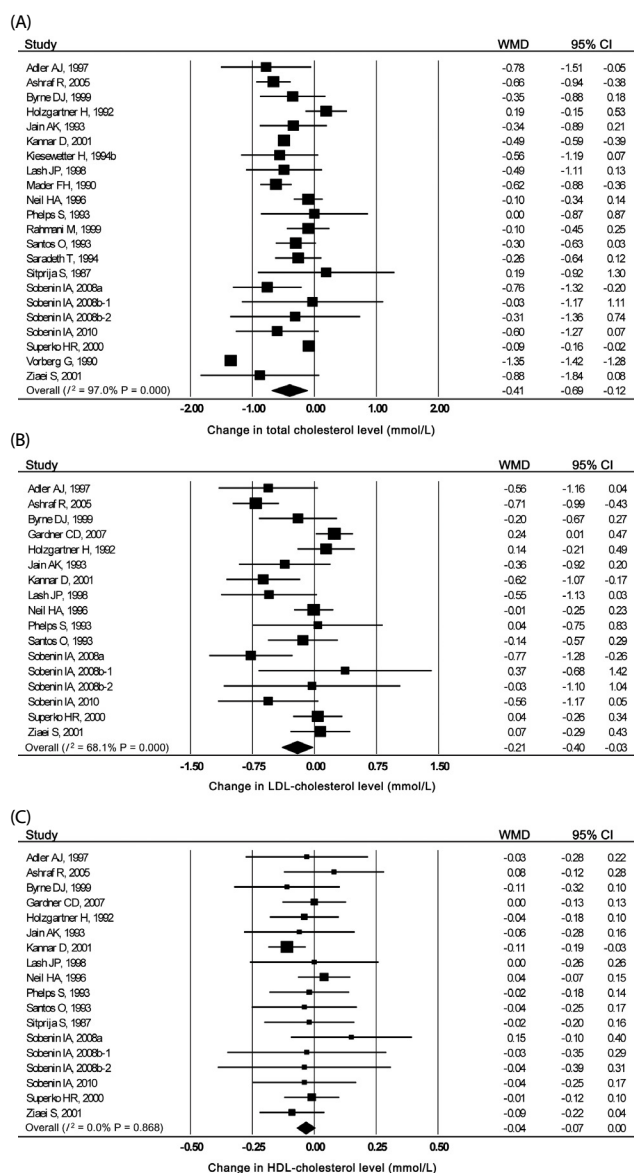
(A)

(B)

(C)

Fig. 2. Forest plot results of the effect of garlic powder on cholesterol. (A) Total cholesterol, (B) LDL-cholesterol and (C) HDL-cholesterol; WMD, weighted mean difference

Fig. 3. Forest plot results of the effect of garlic powder on fasting blood glucose; WMD, weighted mean difference

(A)

(B)

Fig. 4. Forest plot results of the effect of garlic powder on blood pressure. (A) SBP and (B) DBP; WMD, weighted mean difference

heterogeneity ($I^2 = 79.3\%$) in the garlic supplementation group compared with the control group (Fig. 4(A)). The overall pooled estimate of the effect of garlic powder on DBP was -2.36 mmHg (95% CI, -4.56, -0.15, $P = 0.036$), and the heterogeneity across studies was significant ($I^2 = 65.4\%$) (Fig. 4(B)).

Meta-regression

The effect of moderators, such as dosage, intervention duration, quality of study, baseline value or participant number, was analyzed using meta-regression. FBG was not included in these analyses given the limited number of studies. In addition, with regard to the cholesterol metabolism biomarkers, two studies [21,34] were excluded from the analysis of baseline values for TC, LDL-C and HDL-C due to lack of information. Our meta-regression analyses suggest that the effects of garlic on all of the variables were not moderated by the dosage, duration, quality or baseline value (Fig. 5-8). However, participant number was inversely associated with the effect size of LDL-C (slope = 0.004, $P = 0.020$) and DBP (slope = 0.093, $P = 0.006$) (Fig. 9).

Sensitivity / subgroup analyses

We conducted a sensitivity analysis to ascertain whether the results were driven by a single study by sequentially omitting one study at a time (data not shown). No substantial change in the effect of garlic intake on TC, LDL-C, HDL-C, SBP or DBP was noted. In the case of FBG, the effect size was largely decreased after the omission of one study [31] and became non-significant, although between-study heterogeneity was

[95% CI, -15.44, -1.16]), respectively. Heterogeneity among the studies on TC or LDL-C levels was observed ($I^2 = 97.0$ or 68.1%). However, the HDL-C level was not significantly modified by garlic supplementation ($P = 0.057$).

The mean difference in the reduction of FBG levels between the garlic powder-treated subjects and those receiving control substances was -0.96 mmol/L (95% CI, -1.91, -0.01) (-17.30 mg/dL [95% CI, -34.41, -0.18]) in 4 trials that included 162 subjects. This effect was significant ($P = 0.047$) with high heterogeneity ($I^2 = 97.6\%$, Fig. 3).

A total of nine (n = 470) or ten (n = 550) studies were appropriate for the meta-analysis evaluation on whether garlic powder intake reduced SBP or DBP (Table 1). SBP was reduced by -4.34 mmHg (95% CI, -8.38, -0.29, $P = 0.036$) with significant
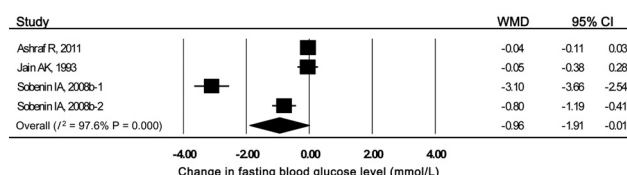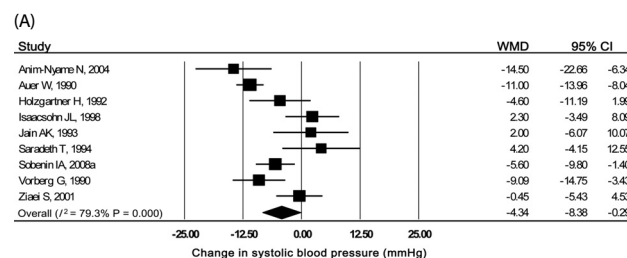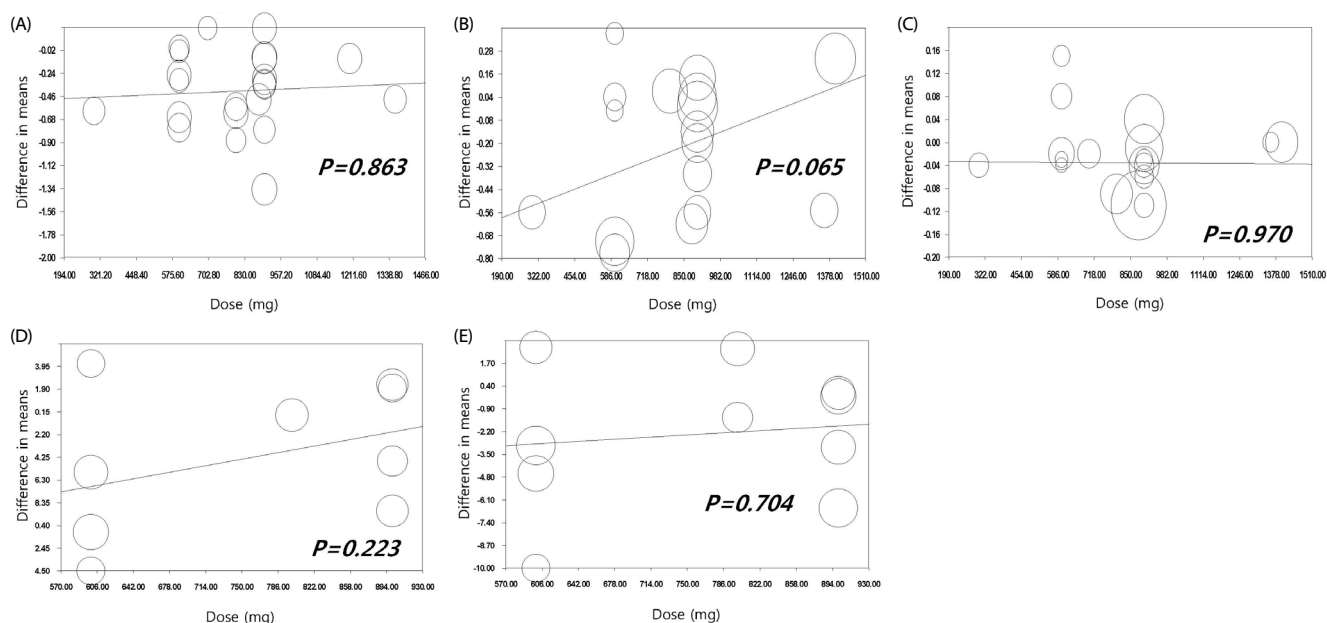
Fig. 5. Meta-regression analysis between changes in cardiovascular disease risk factors and garlic powder dosage. (A) Total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, (D) systolic blood pressure and (E) diastolic blood pressure.
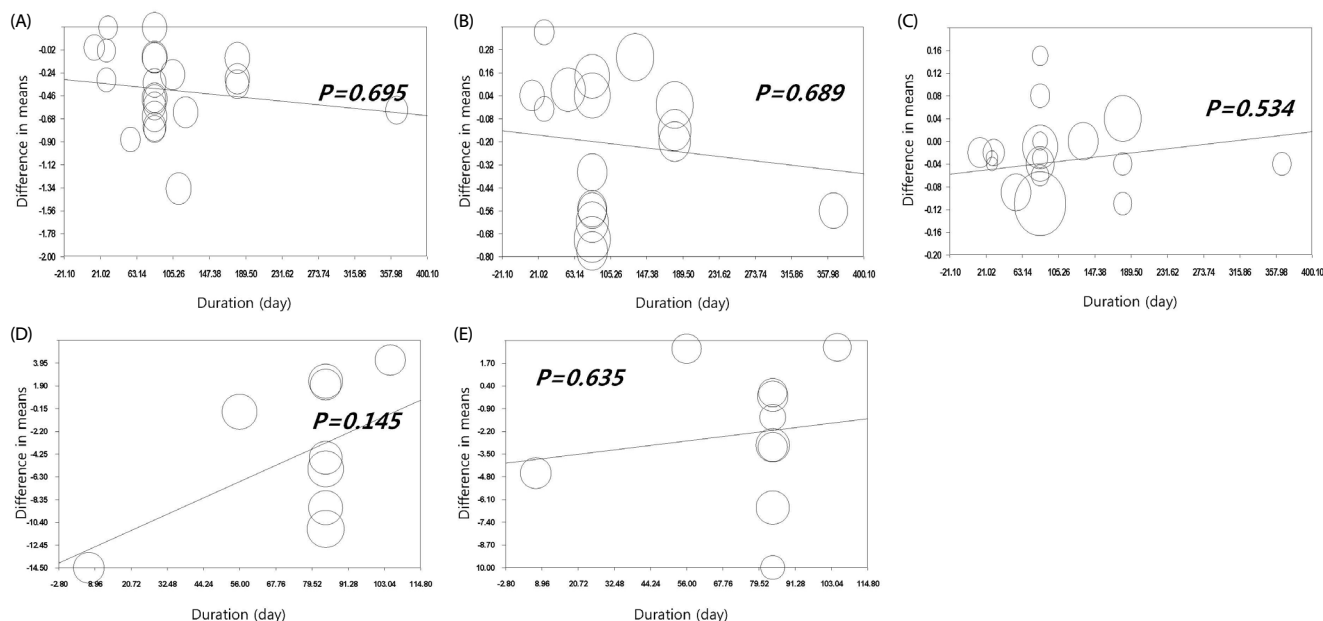

Fig. 6. Meta-regression analysis between changes in cardiovascular disease risk factors and duration of garlic powder supplementation. (A) Total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, (D) systolic blood pressure and (E) diastolic blood pressure.

markedly decreased (from 97.6 to 86.1%).

The results of the subgroup analyses are also presented in Table 2. Garlic supplementation was significantly effective in the reduction of TC levels in both the lower- and higher-dose groups ($P < 0.000$ and $P = 0.018$, respectively). In the other subgroups, garlic's effect on TC was significant in studies of longer duration (≥ 84 days, $P = 0.006$), in subjects with hypercholesterolemia ($P = 0.009$) and in other types of patients, such as those with type 2 diabetes ($P = 0.046$) or in non-Asian countries ($P = 0.012$). In contrast, the studies that were

short-term (< 84 days), performed in healthy subjects or performed in Asia did not exhibit these changes. The LDL-C values were more striking in studies that used a lower dose (≤ 800 mg, $P = 0.003$), were of long-term duration (≥ 84 days, $P = 0.012$) or involved hypercholesterolemic subjects ($P = 0.012$). No significant change in HDL-C level was demonstrated in any subgroup for dose, subject and location, however, a small increase in higher-dose groups (≥ 800 mg, $P = 0.024$) was noted. The net change in SBP for garlic supplements compared with the control material was significant for the trials that were
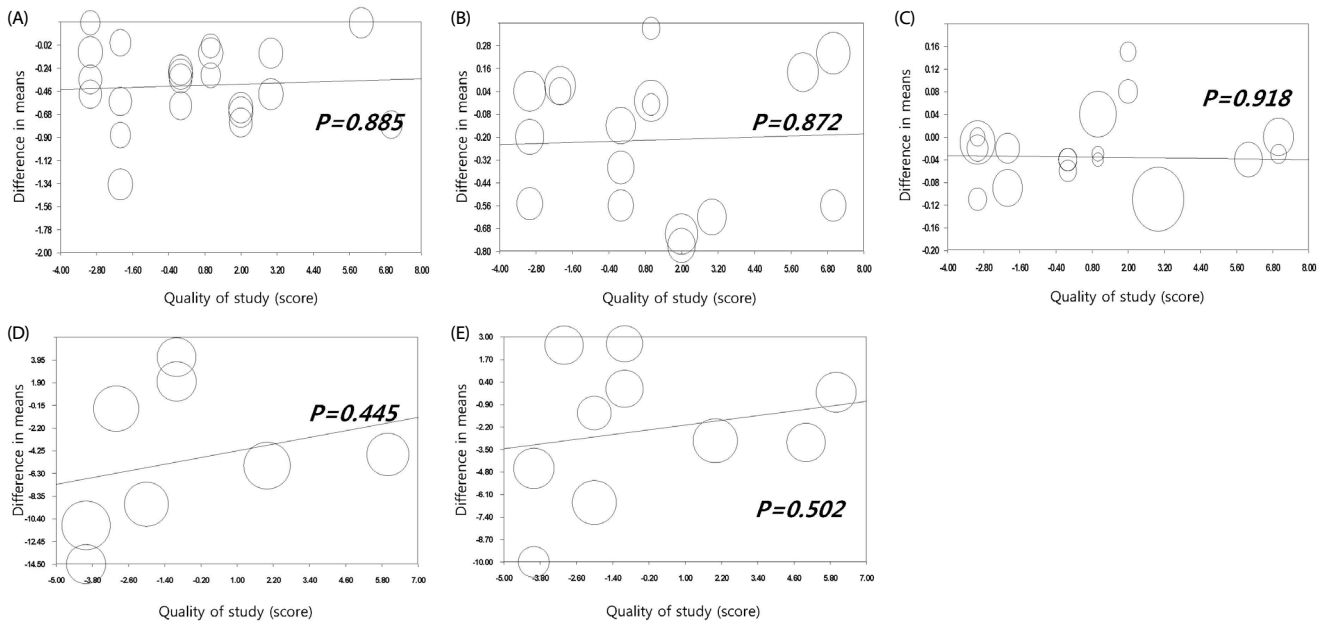
Fig. 7. Meta-regression analysis between changes in cardiovascular disease risk factors and study quality regarding garlic powder supplementation. (A) Total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, (D) systolic blood pressure and E) diastolic blood pressure.
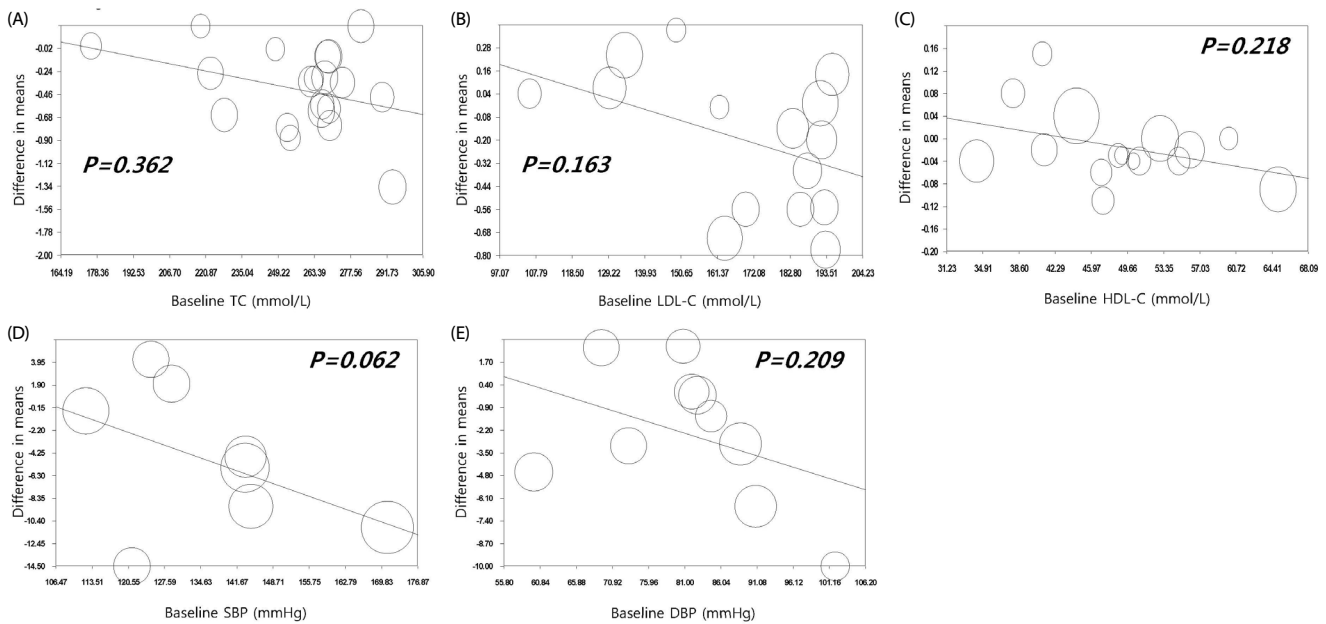

Fig. 8. Meta-regression analysis between changes in cardiovascular disease risk factors and baseline values of (A) total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, (D) systolic blood pressure and (E) diastolic blood pressure.

conducted in Europe or America ($P = 0.028$), administered a daily dose ≤ 800 mg ($P = 0.019$) and involved populations at high-risk for hypertension ($P = 0.002$). No significant effects were observed in all of the subgroups categorized by the intervention period. No group stratified by dosage exhibited a significant change in DBP. A significant DBP reduction was observed in the subgroups with a longer intervention duration ($P = 0.031$), hypertensive patients ($P = 0.010$) and locations in Europe or America ($P = 0.008$). FBG subgroup analysis was excluded given the small number of trials.

An additional sensitivity analysis limited to studies that demonstrated high compliance, high quality or placebo-control design; were published recently; were conducted with dietary management or supplemented with standardized garlic powder was performed (Table 3). The primary analysis on TC was confirmed, and the heterogeneity was improved in the analysis of high quality trials or supplemented with standardized materials (I^2: from 96.9 to 62.3 or 67.2, respectively). The significant effect on LDL-C or DBP value was not significantly different from the effect demonstrated by the comprehensive
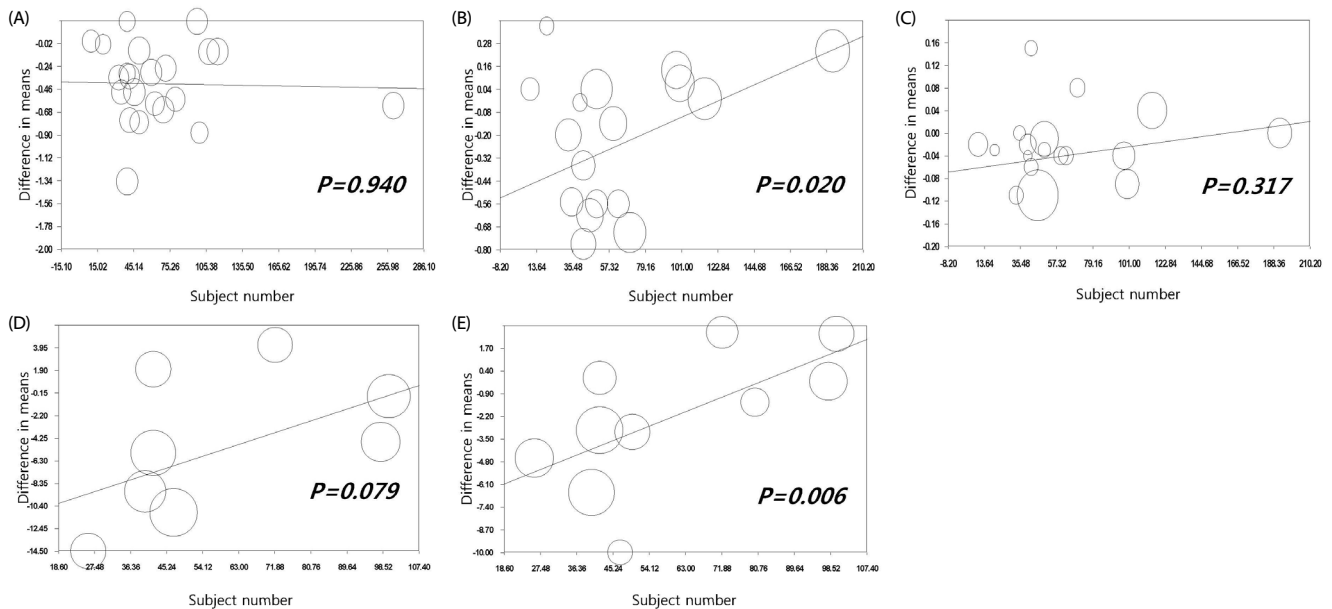
Fig. 9. Meta-regression analysis between changes in cardiovascular disease risk factors and number of participants. (A) Total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, (D) systolic blood pressure and (E) diastolic blood pressure.

Table 2. Results of subgroup analyses by dosage, duration, population and location

	Dose		Duration		Population			Location	
	< 800	≥ 800	< 84	≥ 84	Healthy	Patient	Patient with other complications	Asia	Other
TC (mmol/L)									
No. of studies	8	14	5	17	2	15	5	4	18
Sample size	357	1085	210	1232	82	1080	280	318	1124
Effect size	-0.48*	-0.43*	-0.22	-0.45*	-0.22	-0.45*	-0.41*	-0.40	-0.41*
95% CI	-0.67, -0.29	-0.80, -0.07	-0.68, 0.23	-0.76, -0.13	-0.56, 0.13	-0.79, -0.11	-0.82, -0.01	-0.82, 0.04	-0.74, -0.10
I^2 (%)	3.3	98.1*	0.0	97.7*	0.0	98.0*	0.0	62.7*	97.6*
LDL-C (mmol/L)									
No. of studies	6	11	4	13	1	13	3	2	15
Sample size	245	788	170	863	10	863	160	170	863
Effect size	-0.48*	-0.10	0.08	-0.27*	0.04	-0.27*	0.09	-0.33	-0.18*
95% CI	-0.80, -0.16	-0.27, 0.07	-0.22, 0.39	-0.49, -0.06	-0.75, 0.83	-0.49, -0.06	-0.24, 0.42	-1.09, 0.44	-0.36, -0.00
I^2 (%)	36.6	53.6*	0.0	74.7*	0.0	74.7*	0.0	90.9*	56.3*
HDL-C (mmol/L)									
No. of studies	7	11	5	13	1	13	4	3	15
Sample size	285	788	210	863	10	863	200	210	863
Effect size	0.01	-0.05*	-0.05	-0.03	-0.02	-0.03	-0.06	-0.03	-0.04
95% CI	-0.07, 0.09	-0.09, -0.01	-0.13, 0.03	-0.07, 0.01	-0.18, 0.14	-0.07, 0.01	-0.16, 0.04	-0.13, 0.06	-0.08, 0.00
I^2 (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SBP (mmHg)									
No. of studies	4	5	2	7	2	4	3	1	8
Sample size	140	330	126	344	98	180	192	100	370
Effect size	-7.11*	-2.12	-7.09	-3.75	-5.17	-8.08*	0.95	-0.45	-4.87*
95% CI	-13.08, -1.15	-6.44, 2.19	-20.84, 6.66	-8.28, 0.79	-23.50, 13.15	-11.30, -4.86	-2.47, 4.37	-5.43, 4.53	-9.21, -0.53
I^2 (%)	80.7*	60.2*	88.0*	79.7*	89.9*	49.4	0.0	0.0	79.0*
DBP (mmHg)									
No. of studies	4	6	2	8	2	4	4	1	9
Sample size	140	410	126	424	98	318	134	100	450
Effect size	-3.35	-1.68	-1.13	-2.66*	-1.21	-4.40*	-0.42	2.52	-2.91*
95% CI	-7.09, 0.40	-4.77, 1.40	-8.11, 5.84	-5.08, -0.24	-8.25, 5.84	-7.75, -1.05	-2.92, 2.09	-1.87, 6.91	-5.05, -0.77
I^2 (%)	67.8*	69.8*	82.7*	63.7*	79.9*	71.7*	9.4	0.0	59.6*

CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure;
* $P < 0.05$

Table 3. Restriction sensitivity and heterogeneity analyses

|		High compliance	High quality	publication year >= 2000	diet intervention "yes"	standardized "yes"	Alliin content > 1.0%	Placebo controlled
TC (mmol/L)	No. of studies	15	14	8	15	11	9	21
	Sample size	1163	1087	431	783	899	764	1344
	Effect size	-0.42*	-0.36*	-0.46*	-0.30*	-0.39*	-0.37*	-0.24*
	95% CI	-0.76, -0.07	-0.51, -0.21	-0.73, -0.20	-0.47, -0.13	-0.55, -0.22	-0.55, -0.19	-0.73, -0.15
	I^2 (%)	98.0*	61.8*	87.9*	78.7*	66.6*	72.5*	97.1*
LDL-C (mmol/L)	No. of studies	11	12	9	13	10	8	16
	Sample size	84	838	623	755	758	623	935
	Effect size	-0.17	-0.26*	-0.25	-0.24*	-0.23	-0.24	-9.38*
	95% CI	-0.39, 0.05	-0.51, -0.02	-1.51, 0.13	-0.49, -0.00	-0.48, 0.02	-0.53, 0.05	-0.44, -0.05
	I^2 (%)	75.0*	75.6*	80.9*	73.7*	79.3*	82.6*	68.4*
HDL-C (mmol/L)	No. of studies	12	12	9	14	10	8	17
	Sample size	924	838	623	795	758	623	975
	Effect size	-0.04	-0.03	-0.05	-0.04*	-0.03	-0.02	-0.04
	95% CI	-0.08, 0.00	-0.08, 0.01	-0.10, 0.00	-0.08, -0.00	-0.08, 0.01	-0.08, 0.04	-0.07, 0.00
	I^2 (%)	0.0	0.0	0.0	0.0	13.5	28.1	0.0
FBG (mmol/L)	No. of studies	2	3	3	3	2	0	4
	Sample size	100	120	120	120	102	-	162
	Effect size	-0.40	-1.29	-1.29	-1.29	-0.04	-	-0.96*
	95% CI	-1.14, 0.35	-2.78, 0.20	-2.78, 0.20	-2.78, 0.20	-0.11, 0.02	-	-1.91, -0.01
	I^2 (%)	93.0*	98.4*	98.4*	98.4*	0.0	-	97.6*
SBP (mmHg)	No. of studies	6	3	3	4	5	4	8
	Sample size	386	190	168	216	338	238	372
	Effect size	-3.58	-2.81	-6.13	-5.15	-4.10	-5.19	-4.28
	95% CI	-8.71, 1.56	-7.74, 2.12	-12.72, 0.46	-10.97, 0.66	-8.97, 0.77	-11.18, 0.80	-8.77, 0.21
	I^2 (%)	74.2*	59.2	76.5*	73.5*	68.3*	69.7*	81.8*
DBP (mmHg)	No. of studies	7	3	3	4	5	4	9
	Sample size	466	190	168	216	338	238	452
	Effect size	-1.81	-2.34*	-1.94	-2.80	-0.91	-1.73	-2.61*
	95% CI	-4.68, 1.07	-4.27, -0.41	-5.57, 1.70	-4.52, -1.09	-3.61, 1.80	-4.42, 0.97	-5.00, -0.23
	I^2 (%)	70.7*	0.0	68.4*	0.0	60.2*	52.8	66.7*

* $P < 0.05$
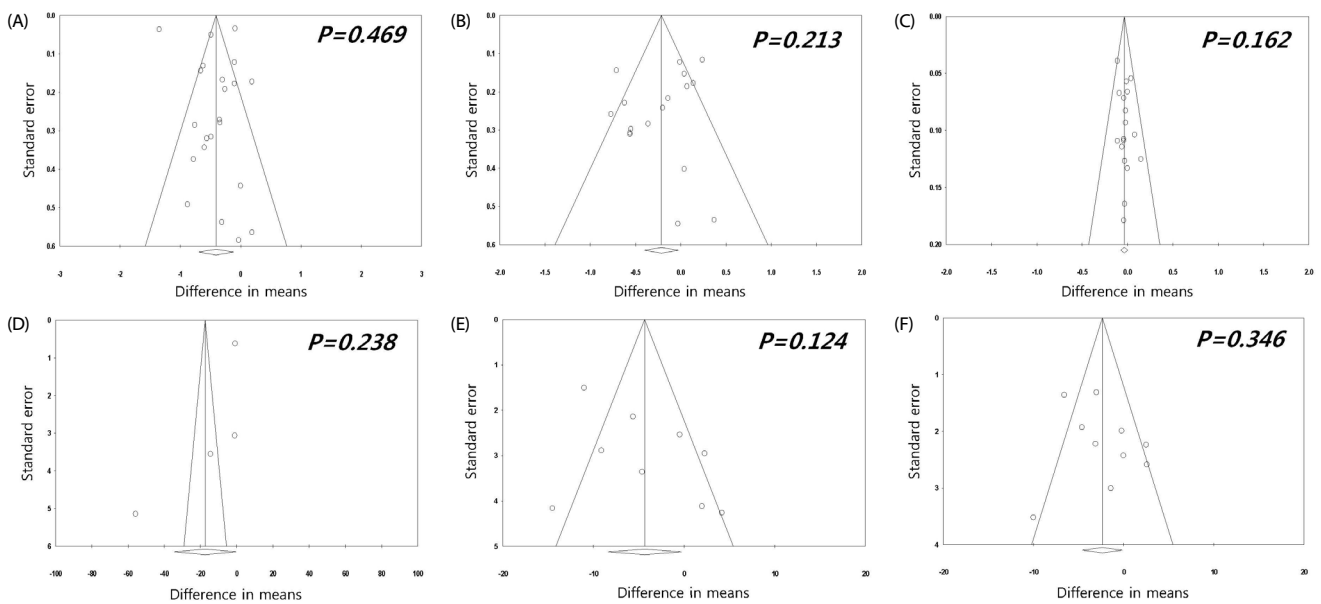
Fig. 10. Funnel plot showing the effects of the garlic powder intervention on changes in (A) total cholesterol, (B) LDL-cholesterol, (C) HDL-cholesterol, (D) fasting blood glucose, (E) systolic blood pressure and (F) diastolic blood pressure.

meta-analyses restricted to studies that demonstrated high compliance, were recently published, were supplemented with standardized materials or used garlic powder with a high alliin content. The pooled effects of garlic on HDL-C were not altered when analyses were limited, with the exception of recently published studies. Contrary to the pooled results, the sensitivity test revealed no significant effect on FBG or SBP in all restricted categories.

We conducted an additional analysis to investigate the gender-specific effects of garlic powder on blood lipid values with 2 trials (n = 163) for females and 3 trials (n = 155) for males (data not shown). The effect size of TC was greater in both the female (-0.81 mmol/L [-31.27 mg/dL], P = 0.018) and male groups (-0.72 mmol/L [-27.80 mg/dL], P = 0.000) than in the primary analysis, with improved heterogeneity (I^2 = 0.0). Garlic's effect on LDL-C was significant only in the male group (-0.63 mmol/L [-24.32 mg/dL], P = 0.000), showing low heterogeneity (I^2 = 0.0). However, no significant change in HDL-C level was demonstrated for either gender, which was consistent with the primary analysis. Blood pressure and FBG were not evaluated in the gender-specific analysis, as limited numbers were obtained for this part of the study.

Publication bias

Publication bias was evaluated by funnel plots and Egger's regression test. The plots exhibited a typical funnel shape, and Egger's regression test suggested no evidence of substantial publication bias (P > 0.05) (Fig. 10).

DISCUSSION

This meta-analysis demonstrated the efficacy of garlic powder intake on CVD risk factors using 27 RCTs that collectively included 1,649 participants. To the best of our knowledge, this meta-analysis is the first to present the finding that garlic consumed as a powder preparation improved multiple CVD risk factors. Garlic powder supplementation significantly reduced blood TC, LDL-C and FBG levels, along with SBP and DBP compared with control substances. Although the HDL-C data did not achieve statistical significance, overall these data support the potential cardiovascular benefits of garlic powder. Garlic contains various sulfur compounds, such as ɣ-glutamyl-S-allyl-L-cysteines and S-allyl-L-cysteine sulfoxide, which are organosulfur compounds that are processed or metabolized into diallyl sulfide, diallyl disulfide, diallyl trisulfide, diallyl tetrasulfide, ajoene and S-allyl cysteines; these compounds have been shown to exert cardiovascular effects/benefits [45]. Garlic preparations may be categorized as powders, oils, AGE or raw (not processed), and the chemical profile may vary according to these preparation types, including the active compounds. S-allyl cysteine has been identified as the active and stable component of AGE. However, the active component in garlic powder is less well established given that the commonly named allicin, an alliin derivative, is volatile [6,45,46]. The strength of our analysis is derived from the meta-analysis that exclusively focused on garlic powder and therefore excluded a major confounder attributed to garlic product preparation variability.

We demonstrated a -0.41 mmol/L (-15.83 mg/dL) and -0.21 mmol/L (-8.11 mg/dL) reduction in blood TC and LDL-C levels, respectively, in subjects who received garlic powder compared with the controls. An elevated blood cholesterol level is one of the major risk factors for CVD. Roberts [47] reviewed evidence regarding the 10 factors identified by the National Cholesterol Education Program (NCEP) and concluded that elevated serum TC levels (> 3.9 mmol/L (150 mg/dL)), specifically an elevated serum LDL-C level, is the only absolute, unequivocal, independent atherosclerotic risk factor. Serum cholesterol levels are frequently used as secondary/surrogate outcome measures of CVD disease progression. In the case of blood TC levels, our findings were consistent with those of previous meta-analyses that evaluated the hypocholesterolemic effect of garlic and resulted in an effect size ranging from -0.77 to -0.19 mmol/L (-29.73 ~ -7.33 mg/dL) for the TC level [4,6,37]. The results of the sub-analyses of garlic preparations in previous studies support the consistency with which "garlic powder" intake significantly reduced blood TC levels by -0.36 to -0.31 mmol/L (-13.90 ~ -11.97 mg/dL) [4,6,37]. Recently, meta-analyses investigating garlic consumption with respect to blood LDL-C or HDL-C levels reported conflicting findings. Ried et al. [4] demonstrated that garlic intake significantly improved these end points, whereas three meta-analyses questioned the robustness of such findings and the reported clinical effectiveness [6,7,37]. In contrast to the previous meta-analyses, our meta-analysis exclusively included garlic powder intake to avoid confounders. Furthermore, the amount of garlic powder intake could be compared in the present study. Interestingly, a lower dosage (< 800 mg/day) demonstrated a more profound effect on LDL-C in the subgroup analysis. In agreement with the previous meta-analysis, a longer duration was more effective in improving blood cholesterol levels.

This study is the first to conduct a meta-analysis of the effects of garlic powder intake on blood glucose metabolism. In the four included studies in which the subjects had type II DM or hypercholesterolemia, the FBG level was significantly decreased by -0.96 mmol/L (95% CI, -1.91, -0.01; P = 0.047) (-17.30 mg/dL [95% CI, -34.41, -0.18]). Garlic powder supplementation also exerted a small but significant hypotensive effect on both SBP (-4.34 mmHg, P = 0.036) and DBP (-2.36 mmHg, P = 0.036). The effect size for all subjects was -7.7 ~ -4.6 mmHg for the SBP levels and -5.0 ~ -2.4 mmHg for the DBP levels, which were similar to the decreased levels reported in previous meta-analyses [5,48]. However, the meta-analysis of hypertensive subjects (SBP ≥ 140 mmHg) demonstrated a potent effect size with a -16.33 mmHg decrease for SBP and -9.28 mmHg for DBP [49]. We also observed more profound effect sizes than were observed for the total analysis in our subgroup analysis, which demonstrated a -8.08 mmHg decrease for SBP and -4.40 mmHg for DBP. In agreement with the meta-analysis results of blood lipid levels, the lower dosage group exhibited a higher effect size for SBP; however, the duration of intake did not appear to be a potent moderator of BP levels in the subgroup analysis. Although a significant reduction of LDL-C was observed only in the male group, it is difficult to generalize that garlic is more effective in males than females due to the limited number of study in this analysis.

This systematic review, the most comprehensive to date,

included moderate- to high-quality RCTs that investigated the effect of garlic powder on cardiovascular risk factors, such as blood lipids, FBG and BP, thereby allowing for meaningful subgroup analyses by dosage, trial duration and baseline levels. Certain limitations of this analysis should be noted. Due to the high heterogeneity in meta-analyses, the resulting effect sizes should be interpreted with some degree of caution despite the lack of publication bias. The reason for the heterogeneity was explored using meta-regression, subgroup analyses and sensitivity analyses. However, no factors, such as dose, duration, subject type, location and study quality, significantly changed heterogeneity, implying the presence of additional factors that might explain the high variability between the studies. How a lower dose of garlic powder affects LDL-C and SBP is still unclear. Additionally, a number of trials with short duration or with a limited number of included participants might influence the results of the present meta-analysis. The available data were insufficient to establish conclusive effects on FBG given the inclusion criterion of studies exclusively limited to garlic powder.

In summary, the present analysis revealed that garlic powder preparations could be considered a general heart and cardiovascular tonic with cholesterol (particularly LDL-C), FBG and BP regulatory properties. Thus, these preparations might be considered a healthy functional food and a dietary supplement for conventional diets. Because the Korean mean daily intake of garlic powder (1.9 g, which is equivalent to 4.7 g of fresh garlic) covers the effective dosage (0.3 - 1.4 g), clinical benefits on ordinary dietary intake of garlic is suggested. However, the 33% of the Korean population whose consumption level of garlic is below the effective dosage should take an additional dietary, garlic supplement. Further trials on the effects of garlic on cardiovascular risk factors should include information on the active ingredients in standardized garlic preparations. Additionally, meta-analyses examining other garlic preparations, such as AGE or garlic oil, and cardiovascular risk factors might be needed to explore the preventive effects of garlic intake.

REFERENCES

1. World Health Organization; World Heart Federation; World Stroke Organization. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization; 2011.
2. Verschuren WM, Jacobs DR, Bloemberg BP, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Nedelijković S, Nissinen A, Toshima H. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five-year follow-up of the seven countries study. JAMA 1995;274:131-6.
3. Amagase H. Clarifying the real bioactive constituents of garlic. J Nutr 2006;136:716S-25S.
4. Ried K, Toben C, Fakler P. Effect of garlic on serum lipids: an updated meta-analysis. Nutr Rev 2013;71:282-99.
5. Silagy CA, Neil HA. A meta-analysis of the effect of garlic on blood pressure. J Hypertens 1994;12:463-8.
6. Zeng T, Guo FF, Zhang CL, Song FY, Zhao XL, Xie KQ. A meta-analysis of randomized, double-blind, placebo-controlled trials for the effects of garlic on serum lipid profiles. J Sci Food Agric 2012;92:1892-902.
7. Khoo YS, Aziz Z. Garlic supplementation and serum cholesterol: a meta-analysis. J Clin Pharm Ther 2009;34:133-45.
8. You SJ, Ahn BK, Kang CW. Effects of dietary garlic powder on growth performance and mRNA expression of hepatic HMG-CoA reductase in broiler chickens. J Anim Sci Technol 2009;51:307-14.
9. Kim-Park S, Ku DD. Garlic elicits a nitric oxide-dependent relaxation and inhibits hypoxic pulmonary vasoconstriction in rats. Clin Exp Pharmacol Physiol 2000;27:780-6.
10. Al-Qattan KK, Thomson M, Al-Mutawa'a S, Al-Hajeri D, Drobiova H, Ali M. Nitric oxide mediates the blood-pressure lowering effect of garlic in the rat two-kidney, one-clip model of hypertension. J Nutr 2006;136:774S-776S.
11. Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. Am J Clin Nutr 1997;65:445-50.
12. Anim-Nyame N, Sooranna SR, Johnson MR, Gamble J, Steer PJ. Garlic supplementation increases peripheral blood flow: a role for interleukin-6? J Nutr Biochem 2004;15:30-6.
13. Ashraf R, Aamir K, Shaikh AR, Ahmed T. Effects of garlic on dyslipidemia in patients with type 2 diabetes mellitus. J Ayub Med Coll Abbottabad 2005;17:60-4.
14. Ashraf R, Khan RA, Ashraf I. Garlic (Allium sativum) supplementation with standard antidiabetic agent provides better diabetic control in type 2 diabetes patients. Pak J Pharm Sci 2011;24:565-70.
15. Auer W, Eiber A, Hertkorn E, Hoehfeld E, Koehrle U, Lorenz A, Mader F, Merx W, Otto G, Schmid-Otto B. Hypertension and hyperlipidaemia: garlic helps in mild cases. Br J Clin Pract Suppl 1990;69:3-6.
16. Byrne DJ, Neil HA, Vallance DT, Winder AF. A pilot study of garlic consumption shows no significant effect on markers of oxidation or sub-fraction composition of low-density lipoprotein including lipoprotein(a) after allowance for non-compliance and the placebo effect. Clin Chim Acta 1999;285:21-33.
17. Gardner CD, Lawson LD, Block E, Chatterjee LM, Kiazand A, Balise RR, Kraemer HC. Effect of raw garlic vs commercial garlic supplements on plasma lipid concentrations in adults with moderate hypercholesterolemia: a randomized clinical trial. Arch Intern Med 2007;167:346-53.
18. Holzgartner H, Schmidt U, Kuhn U. Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate. Arzneimittelforschung 1992;42:1473-7.
19. Isaacsohn JL, Moser M, Stein EA, Dudley K, Davey JA, Liskov E, Black HR. Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial. Arch Intern Med 1998;158:1189-94.
20. Jain AK, Vargas R, Gotzkowsky S, McMahon FG. Can garlic reduce levels of serum lipids? A controlled clinical study. Am J Med 1993;94:632-5.
21. Kannar D, Wattanapenpaiboon N, Savige GS, Wahlqvist ML. Hypocholesterolemic effect of an enteric-coated garlic supplement. J Am Coll Nutr 2001;20:225-31.
22. Kiesewetter H, Jung F, Jung EM, Blume J, Mrowietz C, Birk A, Koscielny J, Wenzel E. Effects of garlic coated tablets in peripheral arterial occlusive disease. Clin Investig 1993;71:383-6.
23. Lash JP, Cardoso LR, Mesler PM, Walczak DA, Pollak R. The effect of garlic on hypercholesterolemia in renal transplant patients. Transplant Proc 1998;30:189-91.
24. Mader FH. Treatment of hyperlipidaemia with garlic-powder tablets. Evidence from the German Association of General Practitioners'

multicentric placebo-controlled double-blind study. Arzneimittel-forschung 1990;40:1111-6.

25. Neil HA, Silagy CA, Lancaster T, Hodgeman J, Vos K, Moore JW, Jones L, Cahill J, Fowler GH. Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis. J R Coll Physicians Lond 1996;30:329-34.

26. Phelps S, Harris WS. Garlic supplementation and lipoprotein oxidation susceptibility. Lipids 1993;28:475-7.

27. Rahmani M, Tabari AK, Niaki K, Allahaverdian S, Sheikholeslami M. Effect of dried garlic supplementation on blood lipids in mild and moderate hypercholesterolemic patients. Arch Iran Med 1999;2: 19-23.

28. De A Santos O, Gruenwald J. Effect of garlic powder tablets on blood lipids and blood pressure: a six month placebo controlled, double blind study. Br J Clin Res 1993;4:37-44.

29. Saradeth T, Seidl S, Resch KL, Ernst E. Does garlic alter the lipid pattern in normal volunteers? Phytomedicine 1994;1:183-5.

30. Sitprija S, Plengvidhya C, Kangkaya V, Bhuvapanich S, Tunkayoon M. Garlic and diabetes mellitus phase II clinical trial. J Med Assoc Thai 1987;70 Suppl 2:223-7.

31. Sobenin IA, Andrianova IV, Demidova ON, Gorchakova T, Orekhov AN. Lipid-lowering effects of time-released garlic powder tablets in double-blinded placebo-controlled randomized study. J Atheroscler Thromb 2008;15:334-8.

32. Sobenin IA, Nedosugova LV, Filatova LV, Balabolkin MI, Gorchakova TV, Orekhov AN. Metabolic effects of time-released garlic powder tablets in type 2 diabetes mellitus: the results of double-blinded placebo-controlled study. Acta Diabetol 2008;45:1-6.

33. Sobenin IA, Pryanishnikov VV, Kunnova LM, Rabinovich YA, Martirosyan DM, Orekhov AN. The effects of time-released garlic powder tablets on multifunctional cardiovascular risk in patients with coronary artery disease. Lipids Health Dis 2010;9:119.

34. Superko HR, Krauss RM. Garlic powder, effect on plasma lipids, postprandial lipemia, low-density lipoprotein particle size, high-density lipoprotein subclass distribution and lipoprotein(a). J Am Coll Cardiol 2000;35:321-6.

35. Vorberg G, Schneider B. Therapy with garlic: results of a placebo-controlled, double-blind study. Br J Clin Pract Suppl 1990;69:7-11.

36. Ziaei S, Hantoshzadeh S, Rezasoltani P, Lamyian M. The effect of garlic tablet on plasma lipids and platelet aggregation in nulliparous pregnants at high risk of preeclampsia. Eur J Obstet Gynecol Reprod Biol 2001;99:201-6.

37. Reinhart KM, Talati R, White CM, Coleman CI. The impact of garlic on lipid parameters: a systematic review and meta-analysis. Nutr Res Rev 2009;22:39-48.

38. Staba EJ, Lash L, Staba JE. A commentary on the effects of garlic extraction and formulation on product composition. J Nutr 2001;131:1118S-1119S.

39. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180-7.

40. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.

41. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006;113:1888-904.

42. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

43. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [Internet]. Oxford: The Cochrane Collaboration; 2011 [updated 2011 March; cited 2014 June 1]. Available from: www.cochrane-handbook.org.

44. Kim JY, Kwon O. Garlic intake and cancer risk: an analysis using the Food and Drug Administration's evidence-based review system for the scientific evaluation of health claims. Am J Clin Nutr 2009;89:257-64.

45. Zeng T, Zhang CL, Zhao XL, Xie KQ. The roles of garlic on the lipid parameters: a systematic review of the literature. Crit Rev Food Sci Nutr 2013;53:215-30.

46. Rahman K, Lowe GM. Garlic and cardiovascular disease: a critical review. J Nutr 2006;136:736S-740S.

47. Roberts WC. Atherosclerotic risk factors--are there ten or is there only one? Am J Cardiol 1989;64:552-4.

48. Ried K, Frank OR, Stocks NP, Fakler P, Sullivan T. Effect of garlic on blood pressure: a systematic review and meta-analysis. BMC Cardiovasc Disord 2008;8:13.

49. Reinhart KM, Coleman CI, Teevan C, Vachhani P, White CM. Effects of garlic on blood pressure in patients with and without systolic hypertension: a meta-analysis. Ann Pharmacother 2008;42:1766-71.