Dietary choline and betaine intakes and risk of cardiovascular diseases: review of epidemiological evidence

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Abstract

BACKGROUND: Cardiovascular diseases (CVD) are the most important causes of human mortality in the world. Higher intakes of choline and betaine have been shown to be associated with lower plasma homocysteine levels (the putative CVD risk factor). This study aimed to review the evidence on the association between dietary intakes of choline and betaine and traditional/novel CVD risk factors.

METHODS: We searched in PubMed website from 1990 to 2009, with the use of following keywords: "dietary choline and betaine, cardiovascular diseases, metabolic syndrome, inflammation". The cross-sectional and prospective studies as well as the clinical trials were recruited in this investigation.

RESULTS: Dietary intakes of "choline"/"choline and betaine" were not significantly associated with CVD risk; however, the higher intakes of choline and betaine were associated with higher serum concentrations of CRP, IL-6 and TNF-α. Individuals with high plasma choline levels were obese and had elevated plasma triglycerides, HDL and non-HDL cholesterol levels; whereas high plasma betaine levels were inversely associated with these biochemical markers. Both choline and betaine supplementation resulted in increased blood lipid profiles.

CONCLUSION: Although dietary intakes of choline and betaine were not significantly associated with CVD incidence, the long-term consumption of these nutrients have been shown to prevent CVD mortality by decreasing inflammation and other risk factors.

Keywords: Choline, Betaine, Cardiovascular Diseases, Metabolic Syndrome, Inflammation.

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Introduction

Cardiovascular diseases (CVD) are the major cause of mortality in the world which has a very high prevalence in developed and industrialized countries. In Iran also, cardiovascular diseases and its risk factors are increasing, so that 75% of people in Isfahan at least have one of the risk factors.[1] Increase in serum levels of inflammatory biomarkers is one of the most important risk factors in incidence of atherosclerosis and cardiovascular diseases.[2] Thus today, cardiovascular diseases are known as inflammatory diseases.[3] Metabolic syndrome also consists of a collection of cardiovascular risk factors such as abdominal obesity, dyslipidemia, impairment in blood glucose homeostasis and hypertension.[4] Studies have shown high level of total homocysteine (tHcy) in fasting status as well as after administration of oral methionine load (taking 100 mg methionine per kilogram of body weight) is an independent risk factor for CVD.[5-13] Furthermore, high level of homocysteine is associated with increase in serum levels of inflammatory markers[14,15] and metabolic syndrome components such as increase in TG and blood glucose and abdominal obesity.[16,17] Therefore, one of the nutritional strategies to reduce CVD is to lessen serum tHcy levels.[18] Choline (vitamin J) is an essential nutrient for keeping normal life of the human beings.[19,20] Adequate intake (AI) of choline for females and males over 18 years old has been considered as 42 mg/d and 550 mg/d, respectively. The tolerable upper intake level (UL) of choline for females and males over 18 y is 3500 mg/d.[20,21] Choline is synthesized in the liver by phosphatidylethanolamine N-methyltransferase (PEMT) enzyme.[19,20] Estrogen stimulates the PEMT activity[22] that is the reason females need lower levels of choline than males do.[20,21] 5-Adenosil homocysteine inhibits the activity of this enzyme.[20] Endogenous synthesis of choline alone cannot meet

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the needs of human; thus, a free-choline diet would lead to incidence of choline deficiency symptoms and organ dysfunction (including fatty liver, death of the muscle or liver cells and etc.).[19,23] Therefore, dietary intake of choline is necessary. Choline is widely found in different types of animal foods (e.g., cow liver, chicken liver, eggs, beef, shrimp, salmon and etc.) or vegetable sources (e.g. soybean, wheat bran, barley bran, large green cabbage, broccoli and etc.).[24,25] The followings are biological activities of choline: phospholipids precursors such as lecithin, sphingomyelin and choline plasmalogen,[26] neurotransmitter acetylcholine precursor,[26] and subsequently effective on improving neurological disorders and memory strength,[20,27] an important source of methyl groups,[26,28] VLDL hepatic secretion and preventing from fat accumulation in the liver,[20] a component of platelet-activating factor,[20,29] blood clots-formation factor,[20] gene expression regulators,[30] apoptosis and cell differentiation,[20] and finally, betaine synthesis precursors.[25,29]

Table 1. Brief report of studies evaluated the association between choline and betaine with cardiovascular diseases risk factors

Reference	Design	Subjects (n)	Age (y)	Duration	Exposure variable	Outcome variable	Results
Chiuve et al., 2007[50]	cross-sectional	1477 healthy women	25-42	-	Usual choline and betaine dietary intake	Serum tHcy levels	Higher intakes of choline and betaine were associated with lower plasma homocysteine levels.
Steenge et al., 2003[18]	double-blind, parallel clinical trial	36 healthy men and women	26-58	6 wk	Betaine (6 g) or folic acid (800 µg) supplementation vs. placebo	Fasting and postmethionine-loading plasma tHcy	Betaine supplementation decreased fasting and postmethionine-loading plasma tHcy, whereas folic acid decreased only fasting serum tHcy levels.
Olthof et al., 2005[47]	double-blind, cross-over clinical trial	26 healthy men	50-71	2 wk for each period	choline supplementation (2.6 g as phosphatidylcholine) vs. placebo	Fasting and postmethionine-loading plasma tHcy	Choline supplementation lowers fasting as well as postmethionine-loading plasma tHcy concentrations.
Bidulescu et al., 2007[52]	prospective	14430 healthy men and women	45-64	14 years	Usual choline and betaine dietary intake	Incident coronary heart disease	Dietary choline or choline plus betaine intake had no significant association with incidence of CVD.
Dalmeijer et al., 2008[49]	prospective	16165 healthy menopausal women	49-70	97 mo	Usual dietary intakes of folate, betaine and choline	Incident cardiovascular disease	Regular dietary intakes of folate, betaine and choline were not associated with CVD risk.
Detopoulou et al., 2008[54]	cross-sectional	3042 healthy men and women	18-89	-	Usual choline and betaine dietary intake	Concentrations of inflammatory markers	High choline-betaine intakes were associated with considerable reduction in serum concentrations of inflammatory markers.
Konstantinova et al., 2008[4]	cross-sectional	7045 women and men	48-49 and 71-74	-	plasma concentrations of choline and betaine	Metabolic syndrome components	Choline and betaine were associated in opposite directions with key components of metabolic syndrome.

Betaine (trimethylglycine) is the combination of tetragonal ammonium compound,[4] a production of choline oxidation in the inner mitochondrial membrane.[29,31]. Liver and kidney are considered as two main locations for choline oxidation.[20,31,32] Betaine usually is found in wheat bran, spinach, barley bran, shrimp, wheat bread and etc.[24,25] Due to possessing N^+ and COO^- in its molecular structure, betaine has osmolite property and it controls the intracellular osmotic pressure similar to electrolytes.[4,31] One of the other major biological activities of betaine is to transfer methyl group in betaine homocysteine methyltransferase (BHMT) reaction.[31,33] Homocysteine is located on intersection of two paths of amino acid cysteine synthesis and methionine synthesis.[34] Methyl group is resulted from folate or betaine (and/or choline which ultimately will become betaine) in reaction with converting homocysteine to methionine.[18,35] Methylation through betaine-homocysteine methyltransferase is confined to the kidney and liver while methionine synthesis is active in all body cells.[36] Many studies have shown that folic acid supplementation would reduce fasting tHcy levels both in healthy individuals[37-39] and in hyperhomocysteinemia people[40,41] while it is not very successful in controlling homocysteine levels after administration of oral methionine load.[18,42-44]. On the contrary, many studies have shown choline supplementation (2.6 g/d) and betaine supplementation (1.5-6 g/d) would reduce fasting Hcy levels[18,45-47] as well as administration of oral methionine load[18,47] both in healthy and hyperhomocysteinemia people. Moreover, there was a significant inverse correlation between high dietary choline intake[48,49] and betaine intake[48] with Hcy serum levels. Therefore, considering the suggested mechanisms and the importance of CVD, the present study aimed to review conducted researches on "association of dietary choline and betaine and cardiovascular diseases" (Table 1).

Materials and Methods

In order to review conducted studies on the association of dietary choline and betaine intakes and cardiovascular diseases, searching in PubMed was used during 1990-2009 with the use of the following keywords: dietary choline and betaine, cardiovascular diseases, metabolic syndrome, and inflammation. Totally, 74 titles were reviewed among the articles. The cross-sectional and prospective studies as well as the clinical trials were recruited in this study.

The association of choline and betaine intakes with serum homocysteine levels

Some of the studies had evaluated the association of choline and betaine intakes with serum tHcy levels. Chiuve et al. in 2007, in a cross-sectional design studied 1477 women in the Nurses Health Study.[50] In this study, the association between choline and betaine intakes with tHcy levels was investigated using linear regression model. After adjusting the effect of folate intake, it was indicated that the highest quintile of choline and betaine intake compared to the lowest quintile, had been associated with 8% reduction in tHcy levels (p value = 0.07). Moreover, the choline from glycerophosphocholine and phosphocholine had a significant inverse correlation with tHcy levels. This inverse correlation in women who received folate < 400 μg/d was more evident than women who received folate ≥ 400 μg/d (p value for interaction for glycerophosphocholine = 0.03), and in average, alcohol intake > 15g/d was evident more than low intake or lack of intake of alcohol (< 15g/d) (p value for interaction for glycerophosphocholine = 0.02 and for phosphocholine = 0.04). The strongest dose-dependent response was seen in women consuming low-methyl diet (high alcohol and low folate intake) (p value for interaction for glycerophosphocholine = 0.002 and for phosphocholine = 0.001). Therefore, according to the results of this study, it seems that increase in total choline and betaine as well as choline intake from water-soluble compounds, glycerophosphocholine and phosphocholine, were associated with reduction in tHcy levels. Besides, homocysteine remethylation would be more dependent on the betaine path, when methyl group sources were low resulted from inadequate folate or high alcohol consumption. Steenge et al. also in a double-blind clinical trial on 36 healthy men and women with no history of CVD, who had slight increase in serum homocysteine levels, reviewed the effect of daily betaine supplementation (6 gr) in comparison with folic acid (800 micrograms folic acid plus 6 gr placebo) and placebo (6 gr) on fasting serum homocysteine levels and after administration of oral methionine for 6 weeks.[17] Oral methionine administration test was done (receiving 100 mg per kilogram of the body weight) before and after the six weeks of supplementation. Fasting homocysteine levels decreased by 1.8 μmol/L in those who received betaine supplement (95% CI -3.6, 0.0; P < 0.05) and by 2.7 μmol/L in those who received folic acid supplement (95% CI -4.5, -0.9, P < 0.05) whereas, fasting homocysteine levels was increased by 0.5 μmol/L in those who received placebo. Furthermore, in comparison with placebo, betaine supplementation reduced area under the homocysteine-time curve after administration of oral methionine load by 221 μmol.24h/L (95% CI -425, -16, P < 0.05) while folic acid supplementation had no effects. Therefore, according to the obtained results of this study, it seems that betaine can be useful in controlling homocysteine

levels after intake of methionine in those who had a slight increase in their homocysteine levels. However, the effect of betaine on reducing CVD risk has not been determined yet, considering its potential in sustaining circulating homocysteine concentrations. Many other studies have shown that betaine supplementation decreases homocysteine concentrations.[45,46] On the other hand, since choline is the betaine synthesized precursor,[29,31] some studies have discussed the effect of phosphatidylcholine supplement (the form of choline in the foods) on fasting homocysteine concentration as well as after administration of oral methionine load. Olthof et al. in 2005 in Netherland, in a double-blind, placebo-controlled, cross-over study reviewed twenty six 50-71 year-old healthy men.[47] These subjects were randomly assigned to either the choline group (2.6 g/d choline intake as phosphatidylcholine) or the placebo group (oil mixture). Treatment duration in each period lasted for two weeks. Fatty acids composition and lipid content was similar in both treatments. Oral methionine administration test was done at the first and the last days of each supplementation period. Finally, it was indicated that phosphatidylcholine supplementation, compared to placebo, was associated with 18% reduction of fasting homocysteine serum concentrations (-3 μmol/L; 95% CI, -3.9, -2.1 μmol/L). Moreover, after intake of 1.5 g/day choline as phosphatidylcholine at the first day, total homocysteine levels was decreased after administration of oral methionine load (-4.8 μmol/L; 95% CI, -6.8, -2.8 μmol/L). Furthermore, phosphatidyl choline supplementation for two weeks -in comparison with placebo- reduced homocysteine levels after administration of oral methionine load to 29% (-9.2 μmol/L; 95% CI, -11.3, -7.2 μmol/L). Generally, it seems that high dose of choline intake as phosphatidyl choline supplementation can reduce fasting homocysteine levels as well as after administration of oral methionine load in healthy males who had slight increase in homocysteine serum levels. Provided that high concentration of homocysteine is the cause of cardiovascular disease, high levels of choline intake would lower the risk of CVD.

The association of dietary choline, betaine and folate intake with CVD

Considering the increase of atherosclerosis risk in low choline and betaine intake, due to dysfunction in homocysteine-methylation pathway and choline's antioxidant properties,[51] investigating the association of dietary choline and betaine intake and incidence of CVD is of high importance. Bidulescu et al. in 2007 in the U.S. in a prospective study for 14 years followed up 14430 two-race 45-64 year-old women and men from Atherosclerosis Risk in Communities study (ARIC) who had no history of CVD.[52] In this study, nutrient intake was assessed using food frequency questionnaire (FFQ) including 66 food items based on the choline and betaine content in common foods database composed with the U.S. Department of Agriculture (USDA).[53] Moreover, they used Cox Regression Model to calculate incidence risk of coronary heart disease (CHD) and also regression standardized method to eliminate the effect of regression errors. One thousand seventy two incidences of CHD were seen during 14 years of follow-up (1987-2002). After adjusting the effect of confounding factors (age, sex, education, race, diabetes status, menstrual status, total energy intake, folate, methionine, B_6, cholesterol, saturated fatty acids, animal fats, fiber and animal protein), they realized that dietary choline or choline plus betaine intake had no significant correlation with incidence of CVD [(95% CI), HR for the highest quartile of choline intake, and choline plus betaine intake in comparison with the lowest quartile was 1.09 (0.79-1.50) and 1.14 (0.83-1.56), respectively]. The researchers of this study came to realize that high dietary choline and betaine intake did not prevent from incidence of CHD. However, to confirm or reject this finding, they emphasized for necessity of conducting more studies in other communities. Dalmeijer et al.[49] in 2008 in the Netherland during a prospective study followed-up 16165 49-70 year-old-menopausal women from the European Prospective Study on Cancer and Nutrition (EPIC) for 97 months, who had no history of CVD. In this study, nutrient intake using FFQ was assessed as 178 food items. Assessing folate intake was implemented using the Netherland's National food table, and choline and betaine intake using USDA food table. The incidence of CHD and cerebrovascular accident (CVA) had been controlled through the Netherland Health Care Information Center. During 97 follow-up months, 717 incidences of CVD were seen (493 cased of CHD and 224 cases of CVA). After adjusting the effect of confounding factors, there was found no significant association between dietary folate, betaine and choline intake with the risk of CVD [(95% CI) HR for the highest in comparison with the lowest quartile was 1.23 (0.75-2.01) and 0.9 (0.69-1.71) and 1.04 (0.71-1.53), respectively]. Moreover, in the subsample of the study population with 903 subjects, high folate and choline intake significantly was associated with reduction of tHcy levels. Therefore, according to the obtained results of this study, dietary choline, betaine and folate intake had no association with the risk of CVD in Dutch menopausal women. However, the effect of higher doses of dietary choline

and betaine intake (e.g., supplementation or fortification) has not been identified yet.

The association of dietary choline and betaine intakes with serum concentrations of inflammatory biomarkers

Inflammation plays a crucial role in progression of atherosclerosis and cardiovascular diseases. The concentrations of inflammatory biomarkers increased in patients with hyperhomocysteinemia.[14] Therefore, effort for reducing inflammatory response through reducing homocysteine levels can be effective in controlling cardiovascular diseases. Detopoulou et al. [54] in 2008 in a cross-sectional study on 3042 individuals (1514 males and 1528 females) from the ATTICA study aged 18-89 years, who had no history of CVD, evaluated the association between dietary choline and betaine intakes and markers of low-grade systemic inflammation. After adjusting the effect of medical variables, lifestyle and socio-demographic status, they realized that in comparison with the lowest tertile (< 250 mg/d), the highest tertile of choline intake (> 310 mg/d) was associated with 22% reduction of C-reactive protein (CRP) concentrations ($P < 0.05$), 26% reduction of interleukin-6 (IL-6) concentrations ($p < 0.05$) and 6% reduction of tumor necrosis factor-α (TNF-α) concentrations ($P < 0.01$). Accordingly, the highest tertiles of betaine intake (> 350 mg/d) in comparison with the lowest tertiles (< 260 mg/d) was associated with 10% reduction in Hcy concentrations ($P < 0.01$), 19% reduction in CRP concentrations ($P < 0.01$) and 12% reduction in TNF-α concentrations ($P < 0.05$). Moreover, they realized that incidence rate of hypercholesterolemia in those who were at the highest tertiles of choline intake significantly was lower than those with the lowest tertiles (22% vs. 32%) whereas the prevalence of hypercholesterolemia in those who had the highest tertiles of betaine intake significantly was higher than those with the lowest tertiles (32% vs. 24%). Besides, in this study, the subjects had been divided into four groups of high choline-betaine intakes, high choline and low betaine intakes, low choline and high betaine intakes and low choline-betaine intakes. The lowest levels of Hcy ($P = 0.05$), TNF-α ($P = 0.03$) and IL-6 ($P = 0.09$) was seen in those who had high choline-betaine intakes. Furthermore, CRP levels also had been reduced in high choline-betaine intakes; however, CRP levels was lower in those who had high choline and low betaine intakes ($P = 0.04$). Therefore, according to the obtained results of this study, high choline-betaine intakes was associated with considerable reduction in serum levels of inflammatory markers; Zeisel[55] believed that the low prevalence of CVD among people who follow Mediterranean diet, might be attributed to the presence of high choline-betaine intakes of such a diet. However, further studies are required to confirm or reject such results.

The association of plasma choline and betaine and metabolic syndrome components

Metabolic syndrome includes a collection of cardiovascular risk factors. Studies have shown that tHcy levels would increase with some of the metabolic syndrome components such as abdominal obesity, dyslipidemia, increase in blood glucose and blood pressure.[16,17] Some studies have been shown that betaine supplementation (4-6 g/d) increased total cholesterol levels, LDL-C, TG while choline supplementation (2.6 g/d) increased TG levels.[46,56] Therefore, according to the association of homocysteine and cardiovascular diseases,[5,13] and role of choline in metabolism of blood lipids[20] and betaine function as osmolite,[31] the present study aimed to review the association between choline and betaine plasma levels with cardiovascular risk factors including metabolic syndrome components. Konstantinova et al. [4] in 2008 in Norway, during a cross-sectional study, investigated the blood sample of 7045 women and men with the ages of 48-49 and 71-74 years. The mean serum levels of choline and betaine were 9.9 μmol/L and 39.5 μmol/L, respectively. Choline and betaine serum levels were lower in women than in men and also were lower in those at the age of 48-49 years than those at 71-74 years ($P < 0.0001$). Choline serum levels had a positive association with serum TG, serum glucose, body mass index (BMI), body fat percentage, waist circumference, ($P < 0.0001$ for all the above) and physical activity ($P < 0.05$) and it had a negative association with HDL-C ($P < 0.05$) and cigarette smoking ($P < 0.0001$). While betaine serum levels had negative association with non-HDL-C, TG, BMI, body fat percentage, waist circumference, systolic and diastolic blood pressure ($P < 0.0001$ for all the above) and smoking ($P < 0.05$), and it had a positive association with HDL-C ($P < 0.01$) and physical activity ($P < 0.0001$). Therefore, the obtained results of this study showed that metabolic syndrome profiles are associated with high choline and low betaine serum levels; i.e. choline and betaine are associated with metabolic syndrome components in two diverging directions.

Discussion

With reviewing studied researches on dietary choline and betaine intake and cardiovascular diseases, it can be concluded that the dietary choline and betaine intake had no significant association with incidence of

CVD.[49,52] However, more intakes of these substances were associated with significant reduction of serum inflammatory markers.[54] High dietary choline and betaine intakes, similar to supplementation, would reduce tHcy levels in healthy and hyperhomocysteinemia people.[45-49] Moreover, choline and betaine serum levels are associated with metabolic syndrome components in diverging directions.[4] Many mechanisms have been suggested for the above observations; it seems that high choline intake would increase expression and activity of betaine-homocysteine methyltransferase enzyme (BHMT) in the liver and kidney; this enzyme, with transferring methyl group, would convert homocysteine to methionine and would lead to reduction in tHcy levels.[18,57,58] Choline also is a betaine precursor; that is the reason high choline and betaine intake is associated with reduction in homocysteine levels.[45-47] The presence of choline in the form of phosphatidyl choline is essential for normal secretion of VLDL from the liver [20]. Therefore, choline intake would lead to cholesterol and TG transport from the liver to the vessels.[46,52,55,59] On the other hand, betaine-homocysteine methyltransferase enzyme (BHMT), in addition to remethylation of homocysteine, would cause increase in hepatic synthesis of ApoB mRNA and subsequently ApoB synthesis and VLDL secretion [60]. Therefore, high betaine intake would be associated with increase in total cholesterol levels, LDL-C and TG [46]. Several mechanisms have been suggested to justify the association between choline and betaine with inflammatory markers serum levels; high Hcy levels is associated with concentrations of inflammatory markers.[14,15] High choline and betaine intakes would reduce Hcy levels and consequently inflammatory markers concentration.[54] On the other hand, Rivera et al. announced that choline and betaine cause inhibition of macrophages activity and reduction of NFk-B[61]. And since these two factors are the causing factors of inflammation, therefore choline and betaine intake can reduce inflammatory markers serum levels through this mechanism. According to suggestions of some other studies,[62-64] high choline intake and subsequently betaine synthesis in mitochondrial membrane would improve mitochondrial membrane and followed by protection against oxidative stress and inflammation. Moreover, based on theories of Kim et al.[65] and Grimble,[66] other metabolites of choline and betaine such as glycine and serine also can be used for synthesis of glutathione. Furthermore, Detopoulou[54] announced that higher choline and betaine intake increases *S*-adenosylmethionine (SAM) concentrations and reduces *S*-adenosylhomocysteine (SAH) concentrations that the ratio of them regulates the majority of methyltransferases activities. Increase in SAM inhibits nitric oxide synthesis,[66] reduces NFk-B production,[67] increases synthesis of glutathione,[68] activates synthetase-B cystathionine enzyme and subsequently increases synthesis of cysteine and glutathione from cystathionine.[69] Besides, choline and betaine affect the inflammation status through methylation of promoter gene areas which regulate the levels of inflammatory markers.[70] Mitochondrial dysfunction in metabolic syndrome caused to decay choline dehydrogenase pathway which may be explained by the observed association between choline and betaine with metabolic syndrome components.[4,71,72] Furthermore, Loscalzo[59] believed that the high values of choline and betaine would change cells phenotype via increase in methylation and consequently causes atherosclerotic plaque progression while some other researchers believed antioxidant properties of choline can reduce inactivation of endothelial and subsequently the risk of vascular blockages.[51,52] Since high tHcy levels is considered as one of the CVD risk factors, we would also review the mechanism of effect of Hcy on atherosclerosis,[73] homocysteine oxidation products like active oxygen species have peroxidation property which can damage endothelial tissue.[73] Moreover, homocysteine reduces peroxidase glutathione enzyme expression.[73] On the other hand, homocysteine increases DNA synthesis in vascular smooth muscle cells.[73] The combination of homocysteine with nitric oxide and formation of S-nitrosohomocysteine can accumulate platelets and thrombosis.[73] Besides, it would lead to reduction of biology access of nitric oxide.[73] Homocysteine also increases the likelihood of blood coagulation through increasing the lipoprotein to fibrin connection, reduction in protein C activity (anti-coagulation) and reduction in anti-thrombin III activity.[74] It should be noted that the number of studies on the dietary intakes of choline and betaine were very limited due to inaccessibility to the amount of choline and betaine in foods until recent years.[24,25] Cross-sectional design of some of these studies confounded the possibility assessment of causality relationship.[54] Due to inaccessibility to national composition tables, international food-composition tables have been used in most of the studies.[49,54] Choline and betaine intake range was limited in most communities, therefore the difference of intakes have not been observable and comparable between the first and fourth quartiles.[49] Despite the possibility of impact of choline and betaine endogenous synthesis on the results, none of these studies had controlled these factors.[54] Stimulating choline endogenous

synthesis by estrogen would result in confounding results in women before menopausal age.[22] Besides, it is also possible that dietary choline and betaine and/or different compounds with choline have different effect on studied factors.[3,54] Since wheat bran is the main source of betaine, the observed useful association with atherosclerosis and inflammatory process might have been due to other whole wheat compounds.[4] Therefore, conducting further prospective studies in this area, using national food-composition tables, considering the effect of endogenous and dietary choline and betaine separately, examining the effect of choline and betaine supplementation on inflammation and accurate controlling of confounding factors such as estrogen, fiber and etc. are recommended for future studies.

Conclusion

Although dietary intakes of choline and betaine were not significantly associated with CVD incidence, the long-term consumption of these nutrients have been shown to prevent CVD mortality by decreasing inflammation and other risk factors.

Conflict of Interests

Authors have no conflict of interests.

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