

Magnesium and the metabolic syndrome: a systematic review and meta-analysis

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ABSTRACT

Purpose: Reduced serum Mg (Mg) concentrations and low intakes of Mg are proposed to be associated with metabolic syndrome (MetS) and its components or related diseases, including insulin resistance, diabetes mellitus, hypertension, dyslipidemia and cardiovascular diseases. The aim of the present study is to systematically review the published evidence on the association between Mg intake and its serum concentrations and MetS and if possible to summarize their results using meta-analysis.

Methods: PubMed, ISI Web of Science, Scopus and Google Scholar were systematically searched to identify related articles, which tried to examine the Mg intake and/or its serum concentration in relation to MetS. Fully adjusted Odds Ratios (ORs) of MetS in participants with the highest intake of Mg compared to those who had the least consumption and the mean difference in serum Mg level between patients with MetS and their controls were extracted for the meta-analysis.

Results: Totally 9 articles with 31876 participants were included in the meta-analysis regarding the association between dietary Mg intake and MetS and 8 studies, which assessed the mean level of serum Mg in 3487 individuals with and without MetS were also eligible. Our analysis showed that higher consumption of Mg is associated with lower risk of MetS (OR=0.73, CI: 0.62, 0.86, P<0.001), however, we could not find any association between serum Mg and MetS (95% CI: -0.28, 0.03, P=0.113).

Conclusion: The present systematic-review and meta-analysis showed a strong inverse association between Mg intake and MetS, but no relationship was shown between serum Mg and MetS.

Key words: Dietary Magnesium, Serum Magnesium, metabolic syndrome, diabetes mellitus

INTRODUCTION:

The metabolic syndrome (MetS) is highly widespread among developed and developing populations [1]. MetS is characterized as a cluster of risk factors that threatens public health, and increases disability, mortality, and health care costs [2]. Based on the Adult Treatment Panel III guidelines, MetS is defined as the presence of 3 or more of the subsequent characteristics: high blood pressure, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol and abdominal obesity [3]. Regardless of its definition, MetS increases the risk of diabetes and cardiovascular disease [4]. Although the role of dietary ingredients is less understood, dietary components are important in many chronic diseases and it is believed that nutrients are effective in the development of MetS [5].

Magnesium (Mg) is an essential mineral that particularly found in dietary sources such as green leafy vegetables, whole grains, legumes, and nuts [6]. As the second intracellular cation in abundance [7], Mg is a critical cofactor for hundreds of enzyme reactions, including energy metabolism, protein and nucleic acid synthesis, insulin action and insulin secretion [8, 9]. Previous studies reported that Mg deficiency is frequently (25–47%) observed in diabetic patients [10]. Rapidly growing evidence suggests that dietary Mg or Mg supplementation has valuable effects, including regulation of systemic inflammation [11] and hypertension [12], modification of lipids [13, 14], glucose and insulin metabolism [15], improvement of insulin sensitivity [16, 17] and decreasing the risk of diabetes (6).

Reduced serum Mg concentrations and low intakes of Mg are proposed to be associated with MetS and its components or related diseases such as insulin resistance [18], diabetes mellitus [19], hypertension [8], dyslipidemia [20] and cardiovascular diseases [21]; however data about the association between Mg status and MetS are conflicting. Some studies have shown a negative association between Mg intake and MetS [22] while others could not reach a significant result [23]. Furthermore, some studies compared the serum Mg concentrations between MetS patients and their controls [24, 25] that was negative [25] or non-significant association [26]; however, some studies have proposed that there may be a positive association between serum Mg concentration and MetS, too [24].

The aim of this study was to systematically review the published evidence on the association between dietary or serum Mg level and MetS and, if applicable, summarize the studies and find the possible sources of using meta-analysis.

MATERIALS AND METHODS:

Search strategy: We focused on publications considering the association between dietary or serum content of Mg and MetS. PubMed, ISI web of science, Scopus and Google scholar were systematically searched to identify related articles published up to June 2014. The following keywords that were selected from the Medical Subject Headings (MeSH) and other related terms were used for the database search: “Mg” OR "mg*" in combination with "Metabolic Syndrome X" OR "metabolic syndrome" OR "syndrome X". No language or any other limitation was incorporated in our literature search. Reference lists of related articles were considered for other potentially related papers. Titles and abstracts were separately reviewed by two authors (HKB, ASA) to find eligible articles for the present study. Any inconsistency between search results was resolved by discussion with the other authors (NS, ML).

Inclusion criteria: Observational studies published in peer reviewed journals that assessed the association between Mg intake and MetS, or studies which compared serum levels of Mg in patients with and without MetS were included in our systematic review.

Exclusion criteria: Studies that examined the association between Mg intake or serum levels of Mg with MetS in participants with polycystic ovary syndrome (PCOS) [27], cardiac syndrome [28], diabetes mellitus [29-31], morbidly obese individuals [32] were excluded from our study. One study that did not compare the Mg content of the whole diet was also excluded [33].

Data extraction: We extracted all relevant information from eligible articles, including first authors' family name, publication year, MetS definition, study design, participants' gender, age range, geographic location, total sample size, sample size in case and control studies, Mg intake, Relative Risks (RRs) or Odds Ratios (ORs) of MetS for comparison between highest and lowest category of Mg intake in models, which had the highest number of adjusted variables in the statistical model. Furthermore, we extracted the mean±SD of serum Mg levels for studies that compared serum Mg levels between participants with MetS patients and their controls. Data extraction and the quality assessment were completed by 2 authors (HKB, ASA) to guarantee equality, and one of the authors entered all of the data (HKB).

Most of the studies presented the serum Mg or Mg intake in mg/dl. In studies in which Mg concentration was not shown in mg/dl we changed other formats including mg/l [24], mmol/l [26] and meq/l [34] to mg/dl.

Data analysis

The ORs and their 95% confidence intervals (CIs) for comparing the prevalence or the incidence of MetS between groups with highest and lowest Mg intake were used to calculate

the log OR and its Standard Error (SE) as the effect size for meta-analysis [35]. RRs were considered as ORs when used in meta-analysis because only one study reported relative risks [36]. We calculated OR and its 95% CI, if a study reported the number of participants based on their Mg consumption strata. Eight studies also compared the mean \pm SD of serum Mg level in cases with MetS and their controls [24-26, 34, 37-40] that were used to calculate unstandardized mean difference as effect size to be included in a separate meta-analysis.

The overall effect was derived by using a random effects model, which takes between-study variation into account [35]. Subgroup analysis and meta-regression were incorporated to search about the possible sources of heterogeneity, if needed. Statistical heterogeneity was assessed using Cochran's Q test and I squared [41]. Sensitivity analysis was used to explore the extent to which inferences might depend on a particular study or a number of publications. Publication bias was evaluated by looking over Begg's funnel plots [42]. Formal statistical assessment of funnel plot asymmetry was done by Egger's regression asymmetry test and Begg's adjusted rank correlation test. Statistical analyses were conducted using STATA version 11.2 (STATA Corp, College Station, TX). P values less than 0.05 were considered statistically significant.

RESULTS

Study characteristics

Our search retrieved 141 articles of which 19 related articles fulfilled our inclusion criteria. Only one study that compared mean Mg intake between patients with and without MetS was included in our systematic review, but not in the meta-analysis [43]. Another study did not represent data on OR of MetS based on Mg intake, therefore the authors were asked about data by three Emails separated at least by one week, and the authors could not provide the needed data therefore we also included this article in the systematic review but not in the meta-analysis too [44]. The flow diagram of the study selection process is presented in **Figure 1**.

Among the reviewed articles, 5 were conducted in the United States [43, 45-48], 2 in Greece [34, 37], 2 in Mexico [25, 39], one in Australia [26], China [24], Taiwan [22], Italy [23], Brazil [40] South Korea [49], Saudi Arabia [50] and 3 in Iran [38, 44, 51] (Tables 1 and 2). The participants' age varied from 18 to 90 years and the study sample size varied from 117 to 11686 participants and totally 35363 individuals participated in all studies. Among the 17 studies, one study was conducted entirely by women [36], one study in men [24] and other

studies reported the association for both genders. Characteristics of included studies in connection with the association between dietary and serum Mg level are presented in Tables 1 and 2 respectively.

Totally 9 articles with 31876 participants were included in the meta-analysis regarding the association between dietary Mg intake and MetS [22, 23, 36, 45, 47, 49-52]. The results of our analysis showed that higher consumption of Mg is associated with lower risk of MetS (OR=0.73, CI: 0.62, 0.86, P<0.001) (**Figure 2**). However, there was a slight level of heterogeneity between studies (Cochrane Q test, P=0.149, I-squared=32.4%). When the methodology of included studies was carefully reviewed, we noticed that a study done by McKeown et al [47] used BMI higher than 31 kg/m² for men and 27 kg/m² for women as an index for abdominal obesity while other studies defined MetS based on ATP III, therefore we removed this study from our analysis and the heterogeneity significantly decreased (Cochrane Q test, P=0.429, I-squared=0.5%) while the association remained significant (OR=0.78, CI: 0.69, 0.88, P<0.001) (**Figure 3**).

Our preliminary analysis on 8 studies [24-26, 34, 37-40], which assessed the mean serum Mg in 3487 individuals with and without MetS (**Figure 4**) indicated that serum Mg level in MetS participants is about 0.1 mg/dl lower compared to normal population (95% CI: -0.36, -0.03, P=0.023), but there was a significant heterogeneity among studies (Cochrane Q test, P<0.001, I-squared=98.5%). Among included studies two had used IDF [37, 40], one used Chinese Diabetes Society's [24] criteria to define MetS and a study done by Guerrero-Romero [25] had excluded individuals with hypertension and diabetes from the study population. Therefore, these 4 studies were removed from our analysis, but the heterogeneity remained significant (Cochrane Q test, P=0.000, I-squared=96.2%) (**Figure 5**). Moreover, removing these articles turned the association between serum levels of Mg and MetS into non-significant one (95% CI: -0.28, 0.03, P=0.113). Furthermore, we tried to find the source of heterogeneity using subgroup analysis based on the participant's age, sex, criteria used to define MetS, studies' design and country of origin. We also incorporated meta-regression to examine if publication year, participants' mean age can describe the high level of heterogeneity between the included studies; however, none of these methods were successful to find the source of heterogeneity.

Sensitivity analysis showed that removing none of individual studies trying to examine the association between dietary or blood levels of Mg intake and MetS could significantly change the overall effects. Although Begg's funnel plot showed that the distribution of calculated

effect sizes, is slightly asymmetric (**Figure 6.A**), the asymmetry tests did not provide any evidence of publication bias (Begg's test, $P=0.245$, Egger's test, $P=0.140$). The same result was found for studies investigated the difference between blood levels of Mg between patients with MetS and healthy population (Begg's test, $P=0.621$, Egger's test, $P=0.210$) (**Figure 6.B**).

DISCUSSION

The present systematic review and meta-analysis showed that increased Mg consumption is associated with lower risk of MetS. Moreover, although the heterogeneity was high, our analyses showed that patients with MetS have lower levels of blood Mg concentrations than healthy controls. Our results provide strong evidence about the favorable protective role of Mg intake in MetS. To the best of our knowledge, there is no systematic review and meta-analysis trying to evaluate the association between Mg and the MetS.

It must be kept in mind that we could not include two studies [43, 44] regarding the association between dietary Mg intake and MetS because they did not provide the essential data. However, all these studies have mentioned an inverse association between dietary Mg intake and MetS in their results. Morrell et al. [43] compared individuals with 2 or more criteria for MetS and participants without any MetS criteria and found a significant difference in their Mg intake (251 vs 269 mg). Mirmiran et al [44] observed a negative association between dietary Mg and MetS Z-score in obese individuals and high fiber consumers, but this association was not significant in normal weight participants or in low fiber consumption. After adjustment for other covariates, no significant association was found between Mg intake and MetS. This study indicated that the association between Mg intake and MetS cannot be independent of fiber, Ca and K, and other nutrients' intake.

Although studies are not entirely consistent about the possible mechanisms, the beneficial effect of Mg on MetS is related to its potential effect on MetS components. Previous studies demonstrated that low dietary intake of calcium, Mg, and fiber may be associated with insulin resistance and supplementation with Mg and calcium improved insulin sensitivity [53, 54]. Another study demonstrated that Mg supplementation in elderly patients improved insulin action [53]. Furthermore, it has been shown in a study done by He et al that Mg intake had been associated with all components of MetS [55]. In another study, Mg intake was negatively associated with components of MetS particularly waist circumference, fasting

blood glucose, and HDL cholesterol level [52]. Mg intake was also inversely linked to the plasma C-reactive protein (CRP) concentration, as it has been hypothesized that a probable positive effect of Mg intake might be associated with its roles in improving systemic inflammation [36].

A previous meta-analysis showed that Mg supplementation significantly increased serum or plasma Mg levels [56]. The nutrition guidelines of the American Diabetes Association (ADA) recommended Mg supplementation for diabetic individuals with low serum Mg level [57]. Although, this meta-analysis could not find a strong association between serum Mg and metabolic syndrome, it has been indicated that low serum Mg is a significant predictor of dyslipidemia and hypertension [58]. Also, serum Mg was inversely associated with waist circumference and triglyceride (TG) level [59]. It has been revealed that Mg may regulator lipid level [60], glucose metabolism and insulin activity [61] and also has antioxidant [8], anti-inflammatory [36] and anti-hypertensive [62] effects. Several mechanisms have been suggested to explain the favorable effects of Mg on features of the MetS or its components. It has been previously suggested that higher Mg intake and intracellular Mg was affiliated in insulin stimulation and influence insulin secretion [16, 63] by preserving pancreatic β -cell function via its consequence on calcium homeostasis and oxidative stress [8]. Moreover, Mg is necessary for the stimulation and transcription of some enzymes and nuclear proteins that are participated in the glycolytic pathway, Krebs cycle, and release of insulin. Besides, the insulin function is completely dependent on Mg, as it is responsible for the activation of the β -subunit of the insulin receptor, and the motivation of substrates and proteins in the insulin-signalling pathway [64]. It also regulates cellular glucose metabolism via its role as a co-factor [65].

Similarly, Mg acts as a co-factor for several critical enzymes involving lipid metabolism. Mg has been reported to raise HDL and reduce LDL cholesterol and TG via restraining the action of lecithin cholesterol acyltransferase (LCAT) [66] and HMG-CoA reductase and increasing lipoprotein lipase (LPL) activity [67]. It has been assumed that Mg, in the intestine, by forming an un-absorbable soap with fatty acids and cholesterol, can decrease their absorption, reduce energy intake from the diet and may have advantages for weight maintenance because of this capability [68].

Several pathways have been associated with the antihypertensive effects of Mg. Initially, Mg as a calcium antagonist, inhibits the intracellular calcium mobilization [62]; moreover, by

means of motivating the action of Na–K ATPase or rising sodium excretion in urine, reduces the unfavorable effect of sodium [62]. Furthermore, it reduces catecholamines release [62] and improve systemic inflammation [36].

Serum Mg is the most common test for assessing Mg status and it is valuable for clinical purpose, such as rapid assessment of critical changes in Mg status [69]. However, it should be noted that Mg is an intracellular cation and only one percent of Mg is in the extra-cellular fluid, therefore only about 0.3% of total body Mg is found in the serum. Therefore, some researchers have been considered serum mg levels as a poor indicator of body magnesium status [70]. Moreover, in some people with chronic magnesium deficiency who have deficient body Mg, their serum levels might be within the normal range [69]. It could be a possible reason for not finding a significant association between serum Mg and MetS in the current study. Serum Mg levels are higher in vegetarians and vegans (in comparison with omnivorous), after endurance exercises and also during the third trimester of pregnancy [71]. By the way, because serum Mg measurement is feasible and inexpensive, serum Mg concentration is still used as a standard method for assessing the Mg status in patients [72].

The present study has several limitations that should be considered. We could find only one prospective cohort study, which was trying to find the association between Mg intake and MetS risk and other included studies were cross-sectional in design. All included studies, which tried to compare serum levels of Mg between MetS patients and healthy controls, were case-control in design. It's well known that retrospective studies are prone to recall bias; therefore prospective studies trying to find these associations are strongly recommended.

Moreover, in the analysis of Mg intake and MetS risk, although we used the highest adjusted model, most of the studies could not control the dietary factors that are associated with MetS and it is difficult to entirely separate the effect of Mg from other dietary nutrients such as calcium, potassium and fiber.

Finally, our analysis on the mean serum level of Mg in individuals with and without MetS demonstrated a significant heterogeneity among studies and we could not find the possible source of heterogeneity in several subgroup analyses and meta-regression.

Conclusions

The present systematic-review and meta-analysis showed a strong inverse association between Mg intake and MetS. However, our results about the relationship between serum

Mg, as a measure of body Mg, and MetS were highly heterogeneous. Therefore, our results should be discussed with more caution. Assessing the body Mg with a better indicator of body storage such as magnesium retention test that shows the stored body Mg might reveal more accurate result.

AUTHORS CONTRIBUTION

HKB, ASA, ML and NS contributed in conception, design, statistical analyses, data interpretation and manuscript drafting. HKB and ASA contributed in database search, and data extraction. All authors contributed in preparing and approval of the final manuscript for submission.

Conflict of interest

The authors declare no conflict of interest.

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Table 1: Characteristics of studies investigating the association between dietary Mg intake and metabolic syndrome

Author, year (country)	Metabolic syndrome definition	Study design	Sample size	Age range (years) Or mean-SD	sex	Adjusted OR or RR	Adjusted variables
Bo et al, 2006 (Italy) [23]	(ATP III)	cross-sectional	1658	64-45	both	1.03 (0.62, 1.70)	age, sex, BMI, smoking, alcohol, Physical activity, calories, fat, fiber
Ford et al, 2007 (US) [45]	(ATP III)	cross-sectional	7669	20<	both	0.56 (0.34, 0.92)	age, sex, race, education, smoking, CRP, alcohol, Ph A, Family history coronary disease, vit and sup intake, diabetes history, fat, CHO, fiber, total energy
He et al, 2006 (US) [52]	(ATP III)	cohort	4637	30-18	both	0.63 (0.47–0.84)	age, sex, race, education, smoking, Ph A, FH diabetee, alcohol, BMI, fiber, PUFA, SFA, CHO, total energy . model4: model 3 plus MetS components minus BMI
Song et al, 2005 (US) [36]	(ATP III)	cross-sectional	11686	45<	female	0.65 (0.52–0.83)	age, calorie, smoking, PhA, alcohol, FH myocardial infarction, fat, cholestrol, folate, glycemic load
Noori et al, 2010 (Iran) [51]	(ATP III)	cohort	160	18<	both	1.73 (0.38-7.85)	age, sex, smoking, PhA, Dialysis mode, dose of stroid, FH diabetes and stroke, calorie, BMI, fiber
McKeown et al, 2008 (US) [47]	(ATP III)	cross-sectional	535	60<	both	0.36 (0.19,0.69)	age, sex, race, education, marital status, smoking, alcohol, PhA, BMI, calorie, SFA, lipid medication, BP medication except for model with BP
Huang et al, 2012 (Taiwan) [22]	(ATP III)	cross-sectional	210	65<	both	0.49 (0.17-1.43)	-

Morrell et al, 2012 (USA) [43]	American Heart Association	cross-sectional	2722	18-24	both	-	-
Mirmiran et al, 2012 (Iran) [44]	(ATP III)	cross-sectional	2504	18-74	both	-	age, gender, smoking, PhA, fiber, SFA, K, Ca, Na, fish and food groups age
Choi et al, 2013 (South Korea) [49]	(ATP III)	cross-sectional	2084	> 19	Men	0.81 (0.53-1.23)	
			3052	> 19	Women	0.90 (0.62-1.30)	
Al-Daghri et al, 2013 (Saudi Arabia) [50]	IDF	cross-sectional	185	19-60	both	0.50 (0.25-1.00)	-

Table 2: Characteristics of studies investigating the association between serum Mg level and metabolic syndrome.

Author	Metabolic syndrome definition	Study design	Sample size	Age range case	Age range control	sex	No MS Serum Mg mean±SD	MS Serum Mg mean±SD	Adjusted variable
Evangelopoulos et al, 2008 (Athens) [37]	IDF	Cross sectional	117	67.0	65.0	both	1.99 ± 0.24 N=35	1.83 ± 0.23 N= 82	-
Ghasemi et al, 2010 (Iran) [38]	ATP III	Cross sectional	137	60-90	60-90	both	2.16±0.03 (n=77)	2.08±0.03 (n=60)	Sex- and creatinine, high TG, high WC, hypertension, and low HDL-C, hyperglycemia and diabetes
Guerrero-Romero et al, 2002 (Mexico) [25]	ATP III	Case control	576	42.3	41.5	both	2.20±0.20 (n=384)	1.80±0.30 (n=192)	-
Guerrero-Romero et al, 2006 (Mexico) [39]	ATP III	Case-control	441	44.0	43.0	both	2.1 ± 0.3 (n = 294)	1.8 ± 0.4 (n = 147)	-
Kalaitzidis et al, 2005 (Greece) [34]	ATP III	Cross sectional	255	48.8	48.7	both	2.04±0.36 (n = 191)	1.92±0.36 (n = 64)	-
Simmons et al, 2010 (Australia) [26]	ATPIII	Cross sectional	1453	53	53		2.02±0.14 (n=1168)	2.02±0.17 (n=363)	-
Yu et al, 2012 (China) [24]	Chinese Diabetes Society's	Cross sectional	379	57-24	57-24	male	1.93 ± 0.28 (n=149)	2.09 ± 0.28 (n=52)	-
Lima et al, 2009 (Brazil) [40]	IDF	cross sectional	129	45.7±11.8	45.7±11.8	both	2.43± 0.43 (n=57)	1.80 ± 0.18 (n=72)	-

Legends of Figures

Figure 1. The Study selection process.

Figure 2. Meta-analyses of studies examining dietary magnesium intake and MetS.

Figure 3. Meta-analyses of studies examining dietary magnesium intake and MetS after removing study done by McKeown et al [47] which used BMI higher than 31 kg/m² for men and 27 kg/m² for women as an index for abdominal obesity

Figure 4. Meta-analyses of studies examining serum magnesium level and MetS.

Figure 5. Meta-analyses of studies examining serum magnesium level and MetS after removing two had used IDF [37, 40], one used Chinese Diabetes Society's [24] criteria to define MetS and a study done by Guerrero-Romero [25] which had excluded individuals with hypertension and diabetes from the study population.

Figure 6. A) Begg's funnel plot (with pseudo 95% confidence interval) in Log OR versus standard error of Log OR for studies that reported the OR of Mg intake. B) Begg's funnel plot (with pseudo 95% confidence interval) in mean difference (MD) versus standard error of mean difference for studies that reported the serum Mg.

Figure 1.

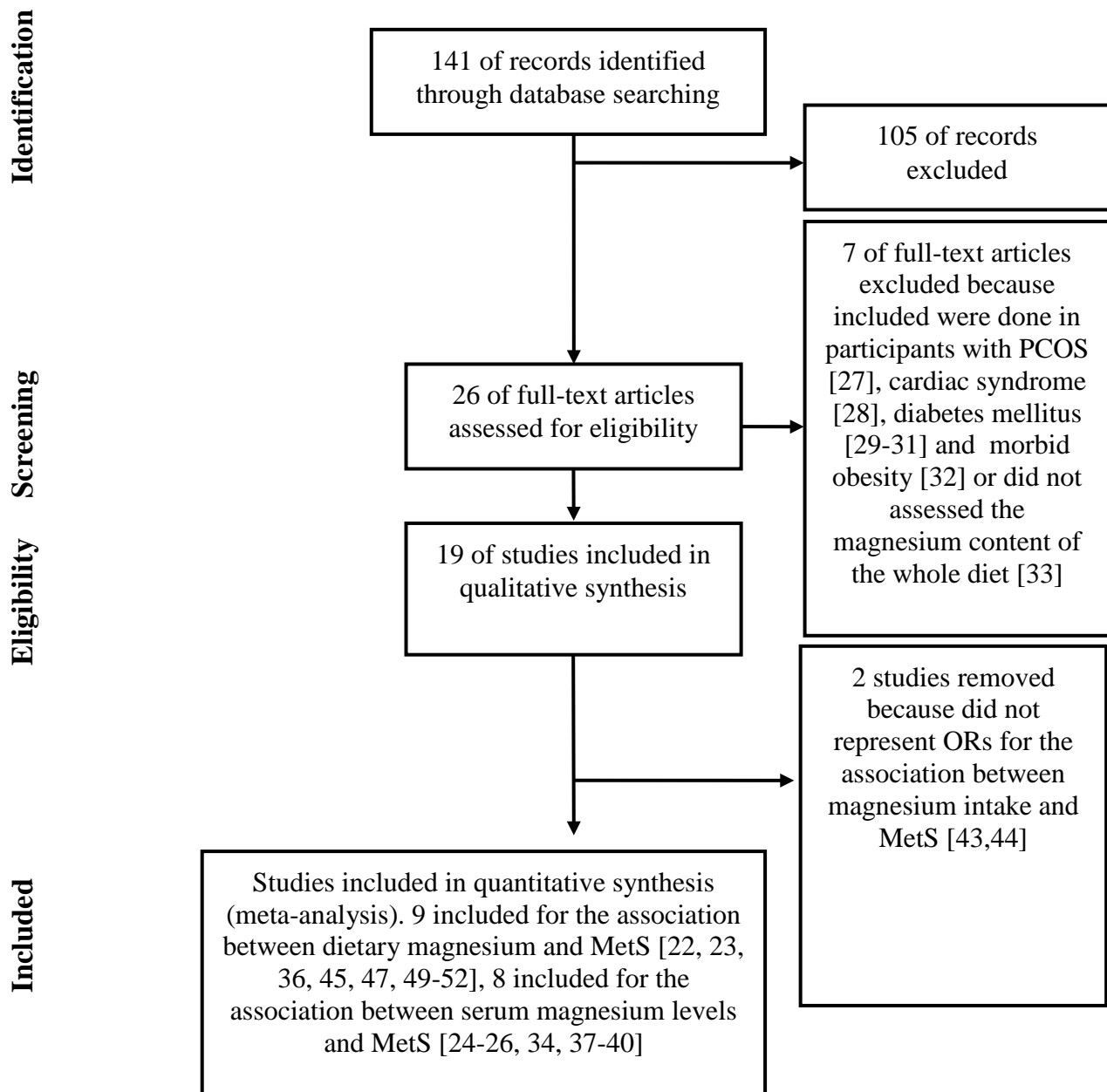


Figure 2.

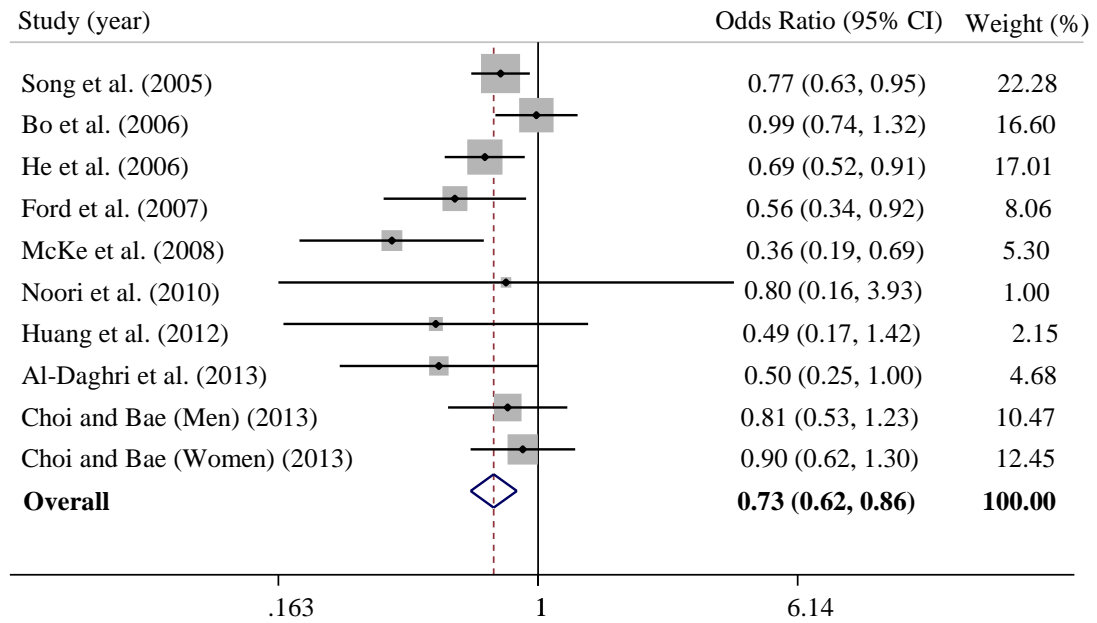


Figure. 3.

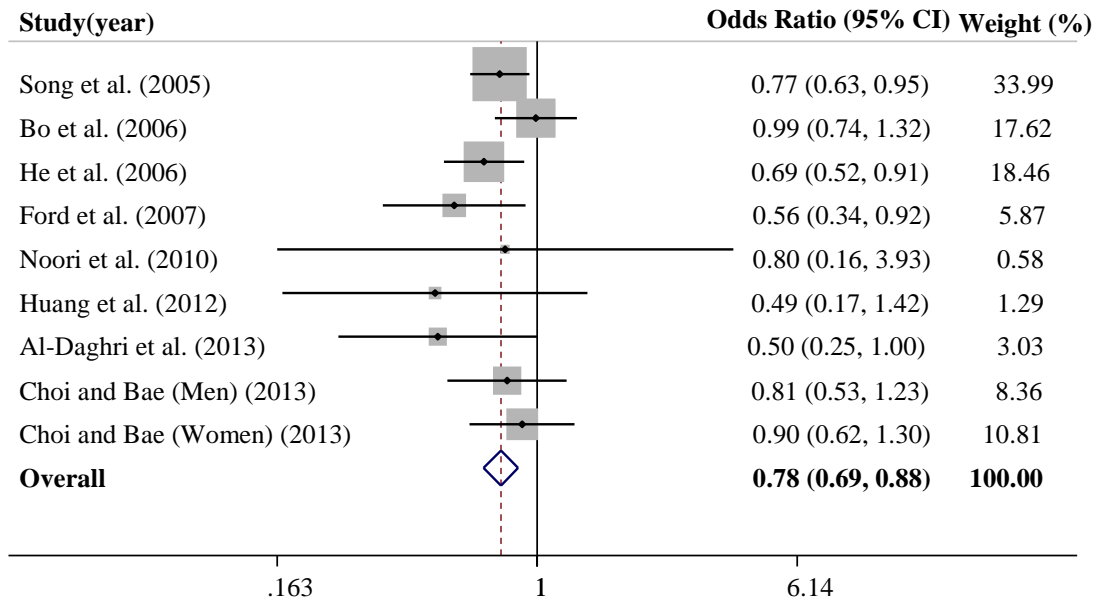


Figure.4.

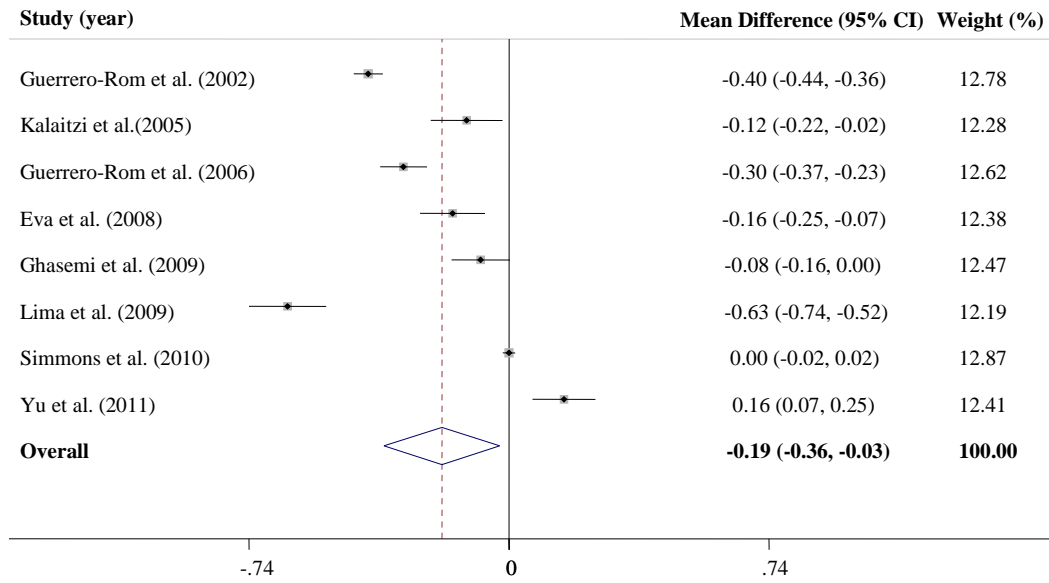


figure 5.

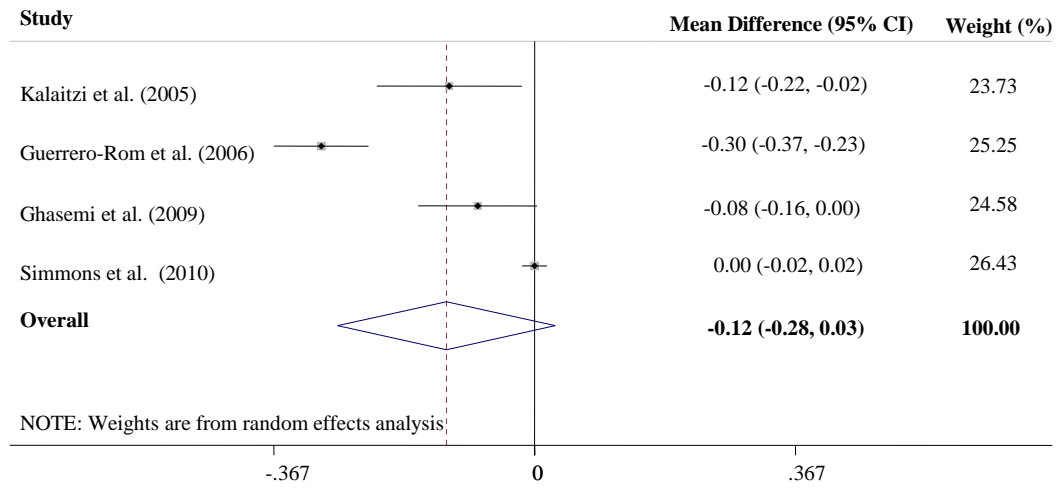


Figure. 6.A)

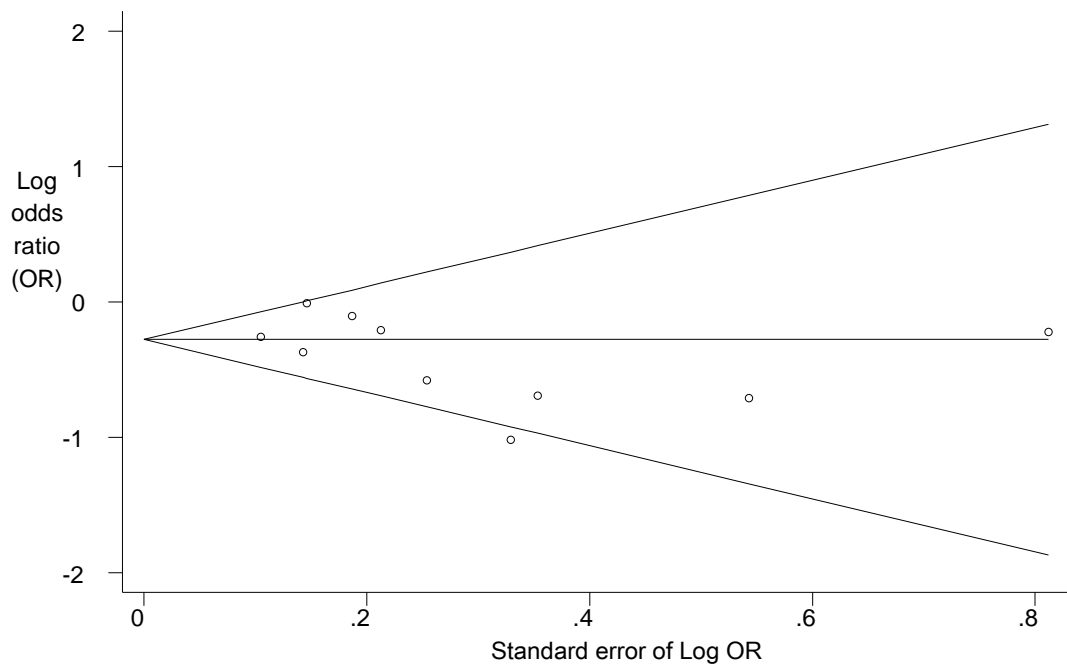


Figure.6.B)

