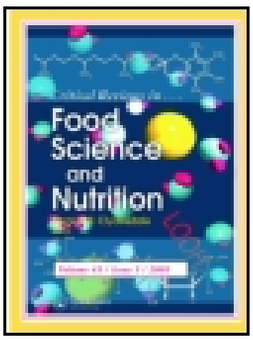

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Does cocoa/dark chocolate supplementation have favorable effect on body weight, body mass index and waist circumference? A systematic review, meta-analysis and dose-response of randomized clinical trials

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Does Cocoa/Dark Chocolate Supplementation Have *Favorable* Effect on body weight, body mass index and waist circumference? A Systematic Review, Meta-Analysis and Dose-response of Randomized Clinical Trials

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Abstract:

Background: Cocoa and dark chocolate (DC) have been reported to be effective for health promotion; however the exact effect of cocoa/DC on anthropometric measures have not been yet defined.

Methods: A comprehensive search to identify randomized clinical trials(RCT)s investigating the impact of cocoa/DC on body weight, body mass index (BMI) and waist circumference(WC) was performed up to December 2017. A meta-analysis of eligible studies was performed using random effects model to estimate pooled effect size. Fractional polynominal modeling was used to explore dose-response relationships for cocoa/DC supplementation.

Results: A total of 35 RCTs investigated the effects of cocoa/DC on weight, BMI and WC were included. Meta-analysis did not suggest any significant effect of cocoa/DC supplementation on body weight (-0.108 kg,95% CI -0.262, 0.046 P=0.168), BMI (-0.014 kg/m^{2}95% CI -0.105, 0.077, P: 0.759,) and WC (0.025 cm95% CI -0.083, 0.129, P= 0.640). Subgroup analysis revealed that that weight and BMI were reduced with cocoa/DC supplementation ≥30g chocolate per day in trials between 4-8 weeks. Chocolate consumption resulted in WC reduction in non-linear fashion (r= 0.042, P-nonlinearity=0.008).

Conclusion: Cocoa/DC supplementation reduced body weight, BMI and WC. Dose and duration were important determinates for favorable effects on anthropometric measures.

Introduction

Obesity has been cited as an important public health problem around the world which is defined as increased body fat accumulation (Abarca-Gómez et al., 2017).There is a strong relationship between obesity and several non-communicable diseases (NCDs)such as osteoarthritis, type 2 diabetes, cardiovascular disease and different types of cancers (Renehan et al., 2008, Van Gaal et al., 2006, Carman et al., 1994, Kahn et al., 2006).Furthermore, these conditions brings a high cost to societies with increasing medical costs for the treatment of associated conditions(McCormick and Stone, 2007). Lifestyle intervention including weight loss diets and exercise for reducing and managing body weight have limited success over a long time period (Soeliman and Azadbakht, 2014, Carey and Kingwell, 2009).Anti-obesity supplements can be useful in order to increase adherence of obese people to a weight loss program and escalation of weight loss with special mechanisms (Fazelian et al., 2014, Rucker et al., 2007). Numerous types of dietary supplements are marketed as weight loss aids; however, the effectiveness of many of these supplements is not clear and needs to be investigated.

Cocoa and its product, chocolate, is a largely consumed food in the world. This famous snack is rich source of various phenolic compounds (Crozier et al., 2011)which has various good health effects such as reducing blood pressure (Buijsse et al., 2010), improving endothelial function(Hooper et al., 2012), and reducing inflammation factors(Goya et al., 2016). Recently studies showed that cocoa can influence adipocyte tissue(Min et al., 2013). Animals' studies showed that supplementing cocoa alongside with a high-fat diet-induced obesity led to lower white adipose tissue compared with control groups (Matsui et al., 2005, Yang et al., 2013). Weight loss effects of cocoa was modulated by reduced fatty acid synthesis and transport

systems, inhibition of insulin receptor kinase activity, enhancement of thermogenesis mechanism in liver and white adipose tissue (Min et al., 2013, Matsui et al., 2005).

Epidemiologic studies suggest that chocolate consumption is inversely related to body mass index (BMI) and lower body weight and waist circumference (WC) even after adjusting for physical activity, dietary components and energy intake (Golomb et al., 2012, O'Neil et al., 2011). In contrast, the other study found more common intake of chocolate has been associated with greater weight gain over the long term (Greenberg and Buijsse, 2013). Inconsistent results also have been reported in randomized clinical trials (RCTs). Piehowski et al. compared the effects of dark chocolate (DC) against non-chocolate snack on body weight during energy restriction in overweight subjects. Intervention resulted in reducing weight and body fat percentage with no significant differences between the two snack groups (Piehowski et al., 2011). However the sample size of this pilot study was small. Conversely Desch et al. observed a slight weight gain after three months of consuming 25 g DC per day (Desch et al., 2010b); and Taubert et al. did not found any change in body weight after daily intake of 6.3 g of DC for 18 weeks (Taubert et al., 2007a).

Hence, trying to resolve the inconsistencies, and in order to decisively conclude, a comprehensive systematic review and meta-analyses of all available RCTs) was performed to determine the effect of cocoa intervention on body weight, waist circumference, and BMI in adults.

Methods

The PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analysis) statement guideline was used to carry out and report this systematic review meta-analysis***(Liberati et al., 2009).

Search Strategy

We systematically searched online medical databases including PubMed, SCOPUS, Cochrane and Google Scholar with no time limitation up to 26 November 2017. In search strategy, Medical subject headings (MESH) and non-MESH terms by these following keywords were used: "Cacao" OR "Cocoa" OR "Chocolate" OR "cocoa extracts" AND "Obesity" OR "Weight Loss" OR "weight reduce" OR "weight decrease" OR "weight change" OR "Body Weight"OR "Obesity, Abdominal" OR "Body Mass Index" OR "Waist Circumference" OR "Weight Loss" OR obes* OR "central obesity " OR "overweight" OR "adipose tissue" OR "fat mass" OR "adiposity" OR "Waist Circumference" AND "Intervention Studies" OR "intervention" OR "controlled trial" OR "randomized" OR "randomised" OR "random" OR "randomly" OR "placebo" OR "assignment". All reference lists of eligible articles were hand-searched to avoid omitting any pertinent articles. In addition, unpublished articles and grey literature such asconference papers, thesis, and patents were not included in this study.

Eligibility criteria

All clinical trials that evaluated the effect of Chocolate intake on weight, BMI, and WC were included in this systematic review and meta-analysis. Studies were included if they had the following criteria: 1) the study design was RCT (either parallel or crossover design), 2) prescribed Chocolate consumption (we considered studies that the supplement adjunct to another supplement/drug in both treatment and placebo groups), 3) reported sufficient information about

weight, BMI, and WC at baseline and the final of the intervention in Chocolate and the placebo group, 4) done on adult subjects (>18 years), 5) were published in English. Studies were excluded if they had the following exclusion criteria: 1) non-RCTs studies, 2) done on children, or animals, 3) investigated the effect of other interventions along with Chocolate in cases but not in placebo group, 4) studies without placebo group, 5) did not report weight, BMI, and WC at baseline and end of the intervention.

Data extraction

Two independent investigators (E.GH and A.N) scanned and extracted relevant data. Any controversy among study selection was discussed and eventually resolved and confirmed by a third reviewer (H.K-V). The relevant data were extracted including: general characteristics of the study and population (authorship, year of publication, type of study population, number of cases and controls, participants' gender, study location, study design, intervention duration and supplement dosage) and results (means and standard deviations of weight, BMI, and WC).

Quality assessment

A systematic assessment of bias in the included studies was performed based on the Cochrane criteria(Higgins and Green, 2011). Two authors (H.M. and E.G.) independently evaluated the quality of the studies by following criteria: sequence generation sufficiency, allocation concealment, blinding, elucidating of dropouts (imperfect outcome data), selective outcome reporting, and other possible sources of bias. According to Cochrane Handbook recommendation, studies were stratified as low risk of bias, high risk of bias or unclear regarding each domain **(Table1**).

Data synthesis and statistical analysis

Mean change and standard deviation (SD) for weight, BMI, and WC were used to estimate the overall effect size of the intervention. The SD of the mean difference for studies that not reported was calculated by the following formula: $SD^2 = [(SD_{baseline}^2 + SD_{final}^2) - (2 \times 0.8 \times SD_{baseline} \times SD_{final})]$ (Borenstein et al., 2009). Estimates of effect sizes were expressed based on weighted mean difference (MD) and 95% CI from the random-effects model (erSimonian and Laird method). Heterogeneity across studies was assessed by using Q test and I^2 index (Higgins et al., 2003). We carried out the subgroup analysis to identify the probable source of heterogeneity among trials. To investigate the effect of each study on overall analysis, sensitivity analysiswas performed. Publication bias was evaluated using visual assessment of funnel plots and Egger's weighted regression tests. The non-linear potential effects of chocolate dosage (g/day) and treatment duration (weeks) were examined using fractional polynominal modeling (polynomials.). All statistical analyses were performed using Stata software (version 14). $P < 0.05$ was considered as statistically significant.

Results

Findings from systematic review

Letters, comments, conference abstracts, short communication, reviews, meta-analyses and animal studies were excluded. Of 687 articles identified from PubMed, Scopus, Google scholar and Cochrane Library in our initial search, 131 duplicate articles were removed. Based on initial title and abstract screening, 339 studies excluded. Out of 217 remaining articles, we excluded 182 other studies because of the following reasons: 1) studies that examined effect of cocoa in combination with other foods and supplements (n = 10) (Sanchez-Aguadero et al., 2017, Allen et al., 2008, Jenkins et al., 2000, de Jesús Romero-Prado et al., 2015, Ribeiro Vieira et al., 2017,

Tey et al., 2012, Noad et al., 2016, Codella et al., 2017, Sanguigni et al., 2017, Sarria et al., 2012); 2) trials without control group (n=7) (Sudarma et al., 2011, Sarria et al., 2012, Tholstrup et al., 2011, Fraga et al., 2005, Nogueira Lde et al., 2012, Di Renzo et al., 2013, Medeiros, 2013); 3) publications without complete data (102); Of the 35 remaining studies, two had done on the same population (n=2) (Ibero-Baraibar et al., 2014, Ibero-Baraibar et al., 2016): 4) trials without placebo or placebo which has considerable polyphenolics (n=3) (Desch et al., 2010a, Grassi et al., 2016, Almoosawi et al., 2010). We excluded studies which had duration less than two weeks (n=4) (Upshaw et al., 2016, Karp et al., 2006, Beck et al., 2008, Thomas et al., 2009). One study was excluded because data was reported as percentiles for weight and BMI (Ayoobi et al., 2017). Finally, 35 articles were considered for systematic review and meta-analysis (Alavinejad et al., 2015, Al-Faris, 2008, Almoosawi et al., 2012b, Baba et al., 2007, Balzer et al., 2008, Crews et al., 2008, Davison et al., 2008, Desideri et al., 2012, Engler et al., 2004, Farhat, 2012, Flammer et al., 2011, Grassi et al., 2005a, Grassi et al., 2005b, Ibero-Baraibar et al., 2014, Khan et al., 2012, Martínez-Lopez et al., 2014, Mastroiacovo et al., 2015, Mogollon et al., 2013, Monagas et al., 2009, Mungua et al., 2015, Muniyappa et al., 2008, Murphy et al., 2003, Neufingerl et al., 2013, Nickols-Richardson et al., 2014, Njike et al., 2011, Pereira et al., 2014, Ried et al., 2009, Sathyapalan et al., 2010, Taubert et al., 2007b, Tzounis et al., 2011, West et al., 2014, Yoon et al., 2016, Njike et al., 2016). The study identification and selection process are shown in **SupplementalFigure1**. Characteristics of eligible studies are presented in **Tables 2.** Sample size of the included studies ranged from 20 to 90 individuals (n= 1775) with mean age of 18 years or older. Studies have been published between 2003 and 2017. Of the 35 included studies, eight were conducted in the US (Engler et al., 2004, Muniyappa et al., 2008, Crews et

al., 2008, Njike et al., 2011, Nickols-Richardson et al., 2014, West et al., 2014, Njike et al., 2016), one in Canada (Mogollon et al., 2013), one in Mexico (Munguía et al., 2015), three in Australia (Ried et al., 2009, Murphy et al., 2003, Davison et al., 2008), four in Asia (Alavinejad et al., 2015, Al-Faris, 2008, Baba et al., 2007, Yoon et al., 2016) and 19 in Europe (Almoosawi et al., 2012b, Balzer et al., 2008, Desideri et al., 2012, Farhat, 2012, Flammer et al., 2011, Grassi et al., 2005a, Grassi et al., 2005b, Ibero-Baraibar et al., 2014, Khan et al., 2012, Martínez-López et al., 2014, Mastroiacovo et al., 2015, Monagas et al., 2009, Neufingerl et al., 2013, Pereira et al., 2014, Sathyapalan et al., 2010, Taubert et al., 2007b, Tzounis et al., 2011). Six studies were performed on women (Al-Faris, 2008, Almoosawi et al., 2012b, Mogollon et al., 2013, Nickols-Richardson et al., 2014, Yoon et al., 2016) and the rest of included studies were done on both gender (Alavinejad et al., 2015, Baba et al., 2007, Balzer et al., 2008, Crews et al., 2008, Davison et al., 2008, Desideri et al., 2012, Engler et al., 2004, Farhat, 2012, Flammer et al., 2011, Grassi et al., 2005a, Grassi et al., 2005b, Ibero-Baraibar et al., 2014, Khan et al., 2012, Martínez-López et al., 2014, Mastroiacovo et al., 2015, Monagas et al., 2009, Munguía et al., 2015, Muniyappa et al., 2008, Murphy et al., 2003, Neufingerl et al., 2013, Njike et al., 2011, Pereira et al., 2014, Ried et al., 2009, Sathyapalan et al., 2010, Taubert et al., 2007b, Tzounis et al., 2011, West et al., 2014, Njike et al., 2016). The duration of trials ranged between two and 24 weeks. Seven studies with two weeks duration (Al-Faris, 2008, Almoosawi et al., 2012b, Engler et al., 2004, Grassi et al., 2005a, Grassi et al., 2005b, Muniyappa et al., 2008), 12 studies with four weeks duration (Balzer et al., 2008, Flammer et al., 2011, Ibero-Baraibar et al., 2016, Khan et al., 2012, Martínez-López et al., 2014, Monagas et al., 2009, Munguía et al., 2015, Murphy et al., 2003, Neufingerl et al., 2013, Pereira et al., 2014, Tzounis et al., 2011, West et al., 2014),

two studies with six weeks (Crews et al., 2008, Njike et al., 2011), six studies with eight weeks(Desideri et al., 2012, Mastroiacovo et al., 2015, Ried et al., 2009, Sathyapalan et al., 2010, Njike et al., 2016), four studies with 12 weeks (Alavinejad et al., 2015, Baba et al., 2007, Davison et al., 2008, Mogollon et al., 2013), two studies with 18 weeks (Nickols-Richardson et al., 2014, Taubert et al., 2007b) and one study with 24 weeks duration (Yoon et al., 2016). Different forms of cocoa/Dc supplementation including cocoa and cocoa powder (from 1.4 to 40 g/day) (Murphy et al., 2003, Baba et al., 2007, Balzer et al., 2008, Davison et al., 2008, Muniyappa et al., 2008, Monagas et al., 2009, Sathyapalan et al., 2010, Njike et al., 2011, Tzounis et al., 2011, Desideri et al., 2012, Neufingerl et al., 2013, Ibero-Baraibar et al., 2014, West et al., 2014, Munguía et al., 2015, Njike et al., 2016), dark chocolate (from 6.3 to 100 g/day) (Engler et al., 2004, Grassi et al., 2005a, Grassi et al., 2005b, Taubert et al., 2007b, Al-Faris, 2008, Crews et al., 2008, Ried et al., 2009, Flammer et al., 2011, Almoosawi et al., 2012b, Mogollon et al., 2013, Pereira et al., 2014, Alavinejad et al., 2015), chocolate milk (15 to 40 g/day) and beverage (Khan et al., 2012, Martínez-López et al., 2014, Nickols-Richardson et al., 2014, Mastroiacovo et al., 2015, Yoon et al., 2016) have been used in included trials. Most studies were single-arm parallel-group (Alavinejad et al., 2015, Al-Faris, 2008, Baba et al., 2007, Crews et al., 2008, Desideri et al., 2012, Engler et al., 2004, Flammer et al., 2011, Ibero-Baraibar et al., 2014, Mastroiacovo et al., 2015, Mogollon et al., 2013, Munguía et al., 2015, Murphy et al., 2003, Neufingerl et al., 2013, Nickols-Richardson et al., 2014, Pereira et al., 2014, Taubert et al., 2007b, Yoon et al., 2016) and 17 with cross-over designed study (Almoosawi et al., 2012b, Balzer et al., 2008, Davison et al., 2008, Farhat, 2012, Grassi et al., 2005a, Grassi et al., 2005b, Khan et al., 2012, Martínez-López et al., 2014, Monagas et al., 2009, Muniyappa et al., 2008,

Njike et al., 2011, Ried et al., 2009, Sathyapalan et al., 2010, Tzounis et al., 2011, West et al., 2014, Njike et al., 2016). Selected studies conducted in subjects with type 2 diabetes (Balzer et al., 2008), healthy, obesity and overweight (Al-Faris, 2008, Almoosawi et al., 2012b, Baba et al., 2007, Balzer et al., 2008, Crews et al., 2008, Davison et al., 2008, Engler et al., 2004, Farhat, 2012, Grassi et al., 2005a, Ibero-Baraibar et al., 2014, Martínez-López et al., 2014, Monagas et al., 2009, Munguía et al., 2015, Murphy et al., 2003, Neufingerl et al., 2013, Njike et al., 2011, Pereira et al., 2014, Tzounis et al., 2011, West et al., 2014), hyperlipidemia (Martínez-López et al., 2014), premenopausal women (Nickols-Richardson et al., 2014), pregnancy (Mogollon et al., 2013), facial wrinkles (Yoon et al., 2016), nonalcoholic fatty liver disease (Alavinejad et al., 2015), elderly subjects with mild cognitive impairment (Desideri et al., 2012, Mastroiacovo et al., 2015), subjects at high-risk of cardiovascular risk factors (Khan et al., 2012), congestive heart failure (Flammer et al., 2011), chronic fatigue syndrome (Sathyapalan et al., 2010), essential hypertension and prehypertension subjects (Muniyappa et al., 2008, Ried et al., 2009, Taubert et al., 2007b, Grassi et al., 2005b, Njike et al., 2016). Characteristics of included trials are summarized in **Tables 2.**

Meta-analysis results

Thirty studies including a total of 1423 participants (case=713, and control=710) reported body weight as an outcome measure. Combined results from the random-effects model showed a non-significant reduction in body weight following chocolate consumption (MD: -0.108 kg, 95% CI: -0.262, 0.046, p = 0.168) without significant heterogeneity among the studies (I^2 = 9.8%, p = 0.314) (**Figure1**).

Thirty-one studies including a total of 1467 participants (case=728, and control=739) reported BMI as an outcome measure. Overall results from the random-effects model indicated that chocolate consumption resulted in non-significant reduction in BMI (MD: -0.014kg/m2, 95% CI: -0.105, 0.077, p = 0.759). There was significant heterogeneity among studies (I^2 = 71.2%, p = 0.000) (**Figure2**).

Among eligible studies, eighteen studies including a total of 795 participants (case=397, and control=398) reported the association of chocolate consumption with WC. Chocolate consumption did not change in WC (MD: 0.025cm, 95% CI: -0.381, 0.431, p = 0.904) with significant heterogeneity among studies (I^2 = 81.9%, p = 0.000) (**Figure3**).

Subgroup analysis

Results of the subgroup analyses are detailed in **Supplemental Table 1**. We stratified studies based on study design (parallel, cross-over), BMI (<25, ≥25), chocolate dosage (gr/day), trial duration (week), and type of study population (healthy or non-healthy). Subgroup analysis showed that BMI (<25: I^2 = 14.6%, p = 0.305), chocolate dosage (≥30 gr/day: I^2 = 4.5%, p = 0.399, <30gr/day: I^2 = 36.3%, p = 0.128), trial duration (week) (≤4: I^2 = 0.8%, p = 0.441, 4-8: I^2 = 0.0%, p = 0.797), and type of study population (non-healthy: I^2 = 0.0%, p=0.521) were potential sources of heterogeneity. Type of study population (non-healthy: I^2 = 26.2%, p=0.238) was sources of heterogeneity for WC. In addition, trial duration below or equal four weeks significantly increased BMI (MD: 0.112 kg/m^2, 95% CI: 0.029, 0.196, p = 0.009), while trial duration between 4-8 weeks significantly decreased BMI (MD: -0.131 kg/m2, 95% CI: -0.171, -0.091, p = <0.001)and weight(MD: -0.189kg, 95% CI: -0.339, -0.039, p = 0.013), and trial duration above 8 weeks significantly reduced weight (MD: -0.382 kg, 95% CI: -0.726, -0.038, p

= 0.030).Also in the group with chocolate consumption of ≥30g, BMI and weight were significantly decreased. Sensitivity analysis indicated that no study had significant impact on the overall effect sizes of body weight (**Supplemental Figure 2**), BMI (**Supplemental Figure 3**) and WC (**Supplemental Figure4**).

Non-linear dose-responses between dose and duration of chocolate intake and outcomes

Following dose-response evaluation, chocolate consumption resulted in WC reduction in non-linear fashion (r= 0.041, P-nonlinearity=0.008) with stronger effects in doses about 40-60 g the chocolate per day. However, body weight (P-nonlinearity= 0.42) and BMI (P-nonlinearity= 0.58) did not change in non-linear fashion (**Figure 4**). Moreover, duration of chocolate consumption did not show a significant non-linear relationship with body weight (P-nonlinearity=0.07), BMI (P-nonlinearity=0.63) and WC (P-nonlinearity=0.214) (**Figure 4**).

Publication bias

Assessment of publication bias by visual inspection of funnel plot indicated no evidence of publication bias in the meta-analysis of chocolate consumption on weight, BMI, and WC (**Supplementary Figure5**). Egger's linear regression test also showed the same result (weight: p=0.758, BMI: p= 0.303), and WC: p= 0.789).

Discussion

The present systematic review and meta-analyses of RCTs summarized the effects of cocoa/DC supplementation on anthropometric measures in over 18 years old subjects. Our main results showed that cocoa/DC supplementation cannot affect body weight, BMI and WC in comparison with control group. However, subgroup analyses indicated that weight and BMI were reduced with cocoa/DC supplementation ≥30g chocolate per day, and in trials between 4-8 weeks.

Moreover, trials duration with ≤4 weeks significantly increased BMI and trials duration with >8 weeks significantly reduced weight. The effect of chocolate consumption on WC was non-linear. Recent meta-analyses suggest that consumption of dietary flavanol-containing substances could reduce body mass index (BMI) and waist circumference (WC) (González-Sarrías et al., 2017).Cocoa specifically contains a large amount of epicatechin, catechin and procyanidins (Miller et al., 2009, Habauzit and Morand, 2012, Manach et al., 2004, Neveu et al., 2010). Although the exact mechanisms were not clarified yet, following probable pathways have been suggested: 1) Improving insulin sensitivity and weight loss because of cocoa-derived active components (Bowser et al., 2017, Dorenkott et al., 2014, Eteng et al., 2006, Lazaro et al., 2014). 2) Decrease the expression of genes involved in the biosynthesis of fatty acids, cholesterol and lipogenesis (Latif, 2013, Matsui et al., 2005). 3) Increase thermogenesis and energy expenditure (Viollet et al., 2006, Bowser et al., 2017). 4) Positive inhibitory effect of cocoa on pancreatic lipase and amylase (Gu et al., 2011). 5) Suppress appetite thorough different hormones, like increasing GLP-1 and decreasing ghreilin concentration (Massolt et al., 2010, Strat et al., 2016).

We showed that Cocoa/DC supplementation could not affect body weight, BMI and WC in comparison with control group. However, in doses ≥30g per day, chocolate consumption could reduce body weight and BMI and effect of chocolate consumption on WC showed non-linear relation with greater reduction following consumption of 450-60 gr/day.Previous studies reported strong positive correlations between WC and visceral fat and WC have been reported as the best overall predictor of visceral fat area (KURIOKA et al., 2002, Rankinen et al., 1999). Visceral fat reduction because of catechin-induced promotion of β-oxidation in the liver has been suggested (Murase et al., 2002). These results suggest that visceral fat may have been reduced,

thus cocoa/DC supplementation may effectively reduce body fat, particularly visceral fat. Suggested dose for favorable effects on reducing obesity based on animal studies, is equivalent to a daily amount of 54g of cocoa powder in humans (Gu et al., 2014). Although previous meta-analysis reported that a daily doses higher than 260 mg polyphenols of cocoa did not cause favorable effect on serum lipids (Jia et al., 2010), but our data analysis revealed that at least 30 gram of daily chocolate must be added to diet for significant effect on weight and BMI. On the other hand previous meta-analysis noted a saturation effect with a dose of 500 mg daily on lipid profile (Approximately 100 g DC) (Tokede et al., 2011). Furthermore it must be noted that high dose of DC like 100g/day contained 561 Kcal which provides not less than 20 % and 30% of the daily usual energy intake of men and women, respectively so it must be considered, particularly over the long term. So, it seems the favorable dose for reducing weight is about 30 gram daily but for higher amounts, alongside with other dietary factors, total energy must be calculated. At last it must be noted that besides promising effect of cocoa/DC supplementation, several meta-analyses report an extensive range of benefits concerning insulin resistance, blood pressure, lipid profile and cardio-vascular diseases (Ried et al., 2012, Larsson et al., 2018, Gong et al., 2017, Lin et al., 2016, Tokede et al.. 2011, Lazaro et al., 2014).

Although lower body weight observed in regular chocolate eaters (Golomb et al., 2012) over the long term in observational studies but it could be attributed to sweet snack which reduces cravings and improves diet satisfaction (Piehowski et al., 2011). Previous meta-analyses reported that the efficacy of cocoa on blood pressure, blood sugar and lipid profile disappeared in studies lasting longer than 2, 3 and 4 weeks, respectively (Hooper et al., 2012, Jia et al., 2010, Tokede et al., 2011, Ried et al., 2012) which might be attributed to the adaptation to the quantity of

polyphenols (Almoosawi et al., 2012a). However, in this meta-analysis, the significant reduction of weight and BMI occurred in studies which lasting between 4 to 8 weeks. In studies with more than 8 weeks duration weight reduced significantly but BMI increased in studies <4 weeks. As some complaints regarding chocolate consumption and decreased palatability in long term intervention have been reported, subjects may benefit of chocolate consumption just through 4 to 8 weeks.

Overweight subjects did not respond differently to cocoa/DC supplementation, as previously have been suggested (Ried et al., 2012). Reid et al, have reported that BMI did not show possible impact neither on systolic nor diastolic blood pressure following cocoa/DC supplementation (Ried et al., 2012) .In contrast to previous meta-analysis on SBP and DBP (Ried et al., 2010), type of studies including cross- over or parallel studies did not show any effect on weight, BMI and WC.

This is the first systematic review and meta-analysis of RCTs investigating the effect of cocoa/DC supplementation on weight, BMI and WC, but there are some limitations that must be acknowledged. Heterogeneity in enrolled participants in studies is the most important limitation of the present meta-analysis. Included trials performed in subjects with different health condition (i.e., subjects with obesity, type 2 diabetes, hyperlipidemic and hypertension, chronic fatigue syndrome, congestive heart failure subjects, healthy and pregnant subjects). Another limitation is difference in duration and type of supplementation, and preparation method. Different forms and amount of cocoa/DC including flavonol rich, drink, cocoa powder, chocolate and chocolate milk and beverage have been used. The commercial or natural cocoa powder and chocolate used in the RCTs were not similar regarding composition and contents such as sugar. However, these

potential sources of inter-study heterogeneity have been addressed by performing subgroup analysis regarding BMI, study duration, baseline participants' medical condition and study design (parallel and cross-over). Usual dietary intakes were not monitored in terms of fruits and vegetables in included RCTs which might have an important effect on results. Lastly, the results of most studies were not adjusted for confounding factors which can affect the weight reduction. Accordingly, larger trials aiming to assess the optimal dose and duration along with identifying the types of flavonoids responsible for causing a favorable effect are needed. Research that considers many aspects of weight control such as satiety hormones, fatty acid metabolism, LBM, mithochondrial biogenesis, thermogenesis and molecular pathways like AMPK pathway are needed.

Conclusion:

Here we showed that cocoa/DC supplementation at least for 4 weeks and 30 g/day has favorable effect on BMI and weight, however because of high energy content of cocoa/DC supplementation, higher doses for longer times should be consider with caution. Although future larger mechanistic trials may elucidate exact mechanisms, appropriate dose and duration.

Tables and Figure Legends:

Figure1: Forest plot of randomized controlled trials investigating the effects of Chocolate on body weight.

Figure2: Forest plot of randomized controlled trials investigating the effects of Chocolate on body mass index.

Figure 3: Forest plot of randomized controlled trials investigating the effects of Chocolate on waist circumference.

Figure 4: Non-linear dose-responses between chocolate intake and unstandardized mean difference in body weight (kg), body mass index (BMI), and waist circumference (WC). The 95% CI is depicted in the shaded regions.

Supplemental Figure 1: Flow diagram for study identified and included into the meta-analysis.

Supplemental Figure 2: Results of an influence analysis in which the meta-analysis of body weight is re-estimated omitting each study in turn.

Supplemental Figure 3: .Results of an influence analysis in which the meta-analysis of Body Mass Index (BMI) is re-estimated omitting each study in turn.

Supplemental Figure 4: Results of an influence analysis in which the meta-analysis of waist circumference (WC) is re-estimated omitting each study in turn.

Supplementary Figure 5: Begg's funnel plot (with pseudo 95% CIs) of the weighted mean difference (WMD) versus the S.E. of the weighted mean difference (WMD) for studies that investigated the body weight (A), body mass index(BMI) (B) and waist circumference (WC) of participates with following chocolate consumption.

Table 1: Cochrane Risk of Bias Assessment.

Table 2: Characteristics of the included studies.

Supplemental Table 1: Pooled estimates of subgroup analysis of the included studiesin meta-analysisof chocolate intake and body composition indices.

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Study	Random Sequence Generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias

Murphy et al. (2003)	U	L	L	L	U	L
Engler et al. (2004)	U	U	L	U	U	U
Grassiet al. (2005)	U	U	U	U	U	U
Grassiet al. (2005)	U	U	U	U	U	U
Baba et al. (2007)	U	U	H	H	U	H
Taubertet al. (2007)	L	L	H	L	L	L
Al-Fariset al. (2008)	U	U	H	U	L	U
Balzaret al (2008)	L	L	L	L	U	L
Muniyappaet al. (2008)	L	L	L	U	U	U
Crews Jret al. (2008)	L	L	L	L	U	L
Davison et al. (2008)	L	L	L	L	U	U
Riedet al (2009)	L	L	H	L	L	U
Monagas et al. (2009)	U	L	H	H	H	H
Njikeet al. (2009)	L	L	L	L	U	L
Sathyapalanet al. (2010)	L	U	L	H	U	U
Flammeret al. (2011)	L	L	L	H	H	U
Tzouniset al. (2011)	L	L	L	U	H	U
Khan et al. (2012)	U	U	H	U	H	U
Desideriet al. (2012)	U	L	L	L	U	U
Almoosawiet al. (2012)	U	H	H	U	U	H
Mogollon et al. (2013)	U	L	L	L	L	L
Neufingerlet al (2013)	L	L	L	L	L	L
Ibero-Baraibaret al. (2013)	L	L	L	L	H	L
Martinez-L´opezet al. (2014)	U	U	H	H	U	U
NickolsRichardsonet al. (2014)	U	L	H	L	U	L
West et al (2014)	U	U	L	L	U	U
Pereira et al. (2014)	L	L	L	H	U	U
Farhatet al. (2014)	L	L	H	L	L	L
Munguíaet al. (2015)	U	L	L	H	L	U
Yoon et al. (2015)	L	L	L	U	L	L
Mastrojacovoet al. (2015)	U	L	L	L	L	L
Alavinejadet al. (2015)	U	L	L	L	H	L
Nijke et al (2016)	U	L	L	L	L	L

Table1. Cochrane Risk of Bias Assessment

L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

Tables 2. Characteristics of eligible studies.

Author, Country, year	Clinical trial design	Population	Sex	Sample size Chocolate/Placebo	Duration	Outcome	Intervention	
							Intervention group	Placebo group
Murphy et al, Australia, 2003	randomized, double-blind, placebo-controlled trial	Healthy	Both	16/16	4 week	Weight, BMI	234 mg cocoa flavanols and procyanidins/d	placebo (≤6 mg cocoa flavanols and procyanidins/d)
Engler et al,USA,2004	randomized, double-blind, placebo-controlled trial	Healthy Adults	Both	11/10	2week	Weight, BMI	high-flavonoiddark chocolate (213 mg procyanidins, 46 mg epicatechin)	low-flavonoid dark chocolate bars
Grassi et al, Italy, 2005	randomized, placebo-controlled, cross-over study	Essential hypertension	Both	20/20	2 week	Weight, BMI	100gr dark chocolate	90gr white chocolate
Grassi et al, Italy, 2005	randomized, placebo-controlled, cross-over study	Healthy subjects	Both	15/15	2 week	Weight, BMI	100gr dark chocolate	90gr white chocolate
Baba et al, Japan, 2007	randomized, double-blind, placebo-controlled trial	Healthy	Both	12/13	12 week	BMI	26 gr cocoa powder and 12 g sugar/d	12 gr sugar/d
Taubert et al,Germany, 2007	randomized, double-blind, placebo-controlled trial	untreated upper-range prehypertension or stage 1 hypertension	Both	22/22	18 weeks	Weight, BMI	6.3 gr dark chocolate containing 30 mg of polyphenols	polyphenol-free white chocolate
Al-Faris, Saudi Arabia,2008	randomized, double-blind, placebo-controlled trial	Healthy	Women	30/30	2 week	Weight, BMI, WC	100 gr dark chocolate	90gr white chocolate
Balzar et al, Germany, 2008	randomized, placebo-controlled, cross-over study	Medicated Diabetic Patients	Both	21/20	4 week	Weight, BMI, WC	900 mg flavanols/d	28 mg flavanols/d
Muniyappa et al, Bethesda, 2008	randomized, placebo-controlled, cross-over	Essential hypertension	Both	20/20	2 week	BMI	21gr/d cocoa	placebo beverage powder

	study							
Crews Jr et al, USA, 2008	randomized, double-blind, placebo-controlled trial	healthy, cognitively intact older adults	Both	45/45	6 week	BMI	37 gr/d dark chocolate	8 ounces/d (237 mL)of an artificially sweetened cocoa beverage
Davison et al, Australia, 2008	randomized, double-blind, placebo-controlled trial	Overweight and obese subjects	Both	12/12	12 week	BMI, WC	high-flavanol cocoa(902 mg/dflavanols)	low-flavanol cocoa(36 mg/dflavanols)
Karin Ried et al, Australia, 2009	randomized, placebo-controlled, cross-over study	Prehyperten sion	Both	11/10	8 weeks	Weight, BMI, WC	50 g/d doseof dark chocolate with 70% cocoa	Placebo capsule
Monagas et al, Spain, 2009	randomized, placebo-controlled, cross-over study	Overweight	Both	42/42	4 weeks	Weight, BMI	40 gr/d cocoa	500 mL/d skim milk
Njike et al, USA, 2009	randomized, placebo-controlled, cross-over study	overweight adults	Both	38/39	6 week	Weight, BMI, WC	22gr/d cocoa	placebo
Sathyapalan et al,UK,2010	double blinded, randomised, clinical pilot crossover	chronic fatigue syndrome	Both	10/10	8 weeks	Weight	15gr/d high cocoa liquor/polyphenol rich chocolate	cocoa liquor free/low polyphenols
Flammer et al, Switzerland, 2011	randomized, double-blind, placebo-controlled trial	Congestive heart failure	Both	10/10	4 weeks	Weight	40gr/d flavanol-rich chocolate	28.4 gr/dcocoa-liquor-free control chocolate
Tzounis et al, UK, 2011	randomized, placebo-controlled, cross-over study	Healthy humans	both	20/20	4 week	BMI	494 mg cocoa flavanols/d	23 mg cocoa flavanols/d
Khan et al, Spain, 2012	randomized, crossover and controlled clinical trial	subjects at high-risk of cardiovascular	Both	42/42	4 week	Weight, BMI	40gr of cocoa powder with 500 mL of skimmed milk/day	500 mL/day of skimmed milk
Desideri et al,Italy, 2012	randomized, double-blind, placebo-controlled trial	ElderlySubjectsWithMildCognitive Impairment	Both	30/30	8 week	Weight, BMI	990 mg/d of cocoa flavanols	45mg/ d of cocoa flavanols
Almoosawi et al, UK,	single-blind randomised	healthy, overweight	Female	21/21	2 week	Weight, WC	20 gr dark chocolatecontai	placebo dark chocolate with

2012	placebo-controlled cross-over study	and obese subjects:					ning 500 mg polyphenols	negligible polyphenol-content
Mogollon et al, Canada, 2013	randomized, double-blind, placebo-controlled trial	pregnant women	Women	22/20	12 weeks	Weight, BMI	40gr/d chocolate	placebo
Neufingerl et al, Netherlands, 2013	double-blind, randomized, placebo-controlled	healthy men and women	Both	38/38	4 week	Weight	6 gr cocoa powder	placebo
Ibero-Baraibar et al, Spain, 2013	randomized, double-blind, placebo-controlled trial	Healthy obesity	Both	23/24	4 week	Weight, BMI, WC	1.4 g of cocoa	placebo
Martinez-L´opez et al,Spain, 2014	non-randomized, controlled, crossover	healthy and moderately hypercholesterolemic subjects	Both	24/24	4 week	Weight, BMI, WC	15 gr soluble cocoa with 400ml milk/d	400ml milk/d
NickolsRichardson, USA, 2014	randomized comparative trial	overweight/ obese premenopausal women	Women	30/30	18 week	Weight, BMI, WC	236 mL/d sugar-free natural cocoa beverage	236 mL/d sugar-free cocoa-free vanilla beverage
Sheila G West et al, USA, 2014	randomized, placebo-controlled, cross-over study	Overweight adults	Both	30/30	4 weeks	Weight, BMI, WC	22 gr/d cocoa	low-flavanol chocolate bar and a cocoa-free beverage
Pereira et al,Portugal, 2014	randomized and controlled trial	healthy and young individuals	Both	30/30	4 week	BMI	10 gr/day dosage of dark chocolate with over 75% cocoa	no concomitant intervention
Farhat et al UK	randomized, double-blind, placebo-controlled trial	Health normal and overweight adults	Both	31/30	12 week	Weight, BMI, WC	20 gram dark chocolate	Low polyphenols content chocolate
Munguía et al, México, 2015	randomized, double-blind, placebo-controlled trial	overweight subjects with borderline criteria of metabolic syndrome	Both	10/5	4 weeks	Weight, BMI, WC	80mg/d supplement of cacao flavonoids	placebo
Yoon et al, Korea, 2015	randomized, double-blind, placebo-	Patients with facial wrinkles	Woman	31/31	24 weeks	Weight	beverage contained 4 gr cocoa powder/d	beverage without cocoa flavanols

Supplemental Table 1. Pooled estimates of the subgroup analyses

	controlled trial							
Mastroiacovo et al, Italy, 2015	double-blind, controlled, parallel-arm study	elderly subjects	Both	30/30	8 weeks	Weight, BMI	cocoa drinkcontaining high flavanol(993 mg flavanols/serving)	cocoa drinkcontaining low flavonol(48 mg flavanols/serving)
Alavinejad et al, Iran, 2015	randomized, double-blind, placebo-controlled trial	Nonalcoholic fatty liver disease	Both	21/21	12 week	Weight, BMI, WC	30 gr/d dark chocolate containing 83% cocoa	30gr zero calori white chocolate
Nijke et al, USA, 2016	Randomized, controlled, modified Latin square parallel design (crossover)	stage 1 hypertension	Both	51/51	8 weeks	Weight, BMI, WC	10 gr/d cocoa powder	placebo
Nijke et al, USA, 2016	Randomized, controlled, modified Latin square parallel design (crossover)	stage 1 hypertension	Both	50/50	8 weeks	Weight, BMI, WC	5 gr/d cocoa powder	placebo

Group	No of comparisons	WMD (95% CI)	P value	P-heterogeneity	I^2(%)
Total	31	-0.014(-0.105, 0.077)	0.759	0.000	71.2
Study design					
parallel	14	0.008(-0.113, 0.130)	0.894	0.002	60.1
Cross-over	17	-0.037(-0.192, 0.119)	0.642	0.000	77.6
Baseline BMI					
<25	11	-0.004(-0.089, 0.080)	0.918	0.305	14.6
≥25	19	-0.027(-0.160,0.106)	0.688	0.000	78.8
Dosage (g)					
<30	9	-0.021(-0.130, 0.089)	0.712	0.128	36.3
≥30	11	0.123(0.020, 0.225)	0.019	0.399	4.5
Intervention duration (week)					
≤4	15	0.112 (0.029, 0.196)	0.009	0.441	0.8
4-8	7	-0.131(-0.171, -0.091)	<0.001	0.797	0.0
>8	9	-0.100 (-0.361, 0.160)	0.450	0.000	85.7
Type of Study population					
Healthy	18	-0.028(-0.144, 0.089)	0.642	0.000	81.2
Non-healthy	12	0.025(-0.083, 0.129)	0.640	0.521	0.0
Total	18	0.025(-0.381, 0.431)	0.904	0.000	81.9
Study design					
parallel	5	-0.818(-2.177, 0.540)	0.238	0.033	61.9
Cross-over	13	0.205(-0.257, 0.666)	0.386	0.000	85.6
Baseline BMI					
<25	7	0.335(-0.776, 1.446)	0.021	0.005	67.7
≥25	11	-0.362(-0.814, 0.089)	0.116	0.000	83.1
Dosage (g)					
<30	8	0.660(-0.124, 1.443)	0.099	0.019	58.1
≥30	3	-3.282(-9.029, 2.465)	0.263	0.064	63.6
Intervention duration (week)					

≤4	9	0.369(-0.869, 1.606)	0.559	0.000	73.8
4-8	4	-0.826(-2.320, 0.668)	0.279	0.067	58.1
>8	5	-0.067(-0.593, 0.458)	0.802	0.000	92.0
Study population					
Healthy	12	0.114(-0.316, 0.545)	0.603	0.000	88.4
Non-healthy	6	-0.750(-2.151, 0.651)	0.294	0.238	26.2
Total	30	-0.108(-0.262, 0.046)	0.168	0.314	9.8
Study design					
parallel	14	-0.195(-0.552, 0.162)	0.285	0.171	26.4
Cross-over	16	-0.128(-0.265, 0.009)	0.067	0.491	0.0
Baseline BMI					
<25	9	0.034(-0.260, 0.328)	0.821	0.369	8.0
≥25	17	-0.146(-0.283, 0.009)	0.037	0.457	0.0
Dosage (g)					
<30	12	-0.127(-0.426, 0.171)	0.403	0.131	32.4
≥30	10	0.454(0.061, 0.843)	0.024	1.000	0.0
Intervention duration (week)					
≤4	17	0.084(-0.210, 0.378)	0.573	0.215	20.5
4-8	7	-0.189(-0.339, -0.039)	0.013	1.000	0.0
>8	6	-0.382(-0.726,-0.038)	0.030	0.467	0.0
Study population					
Healthy	17	-0.207(-0.417, 0.003)	0.053	0.155	26.1
Non-healthy	12	0.221(-0.083, 0.525)	0.154	0.974	0.0

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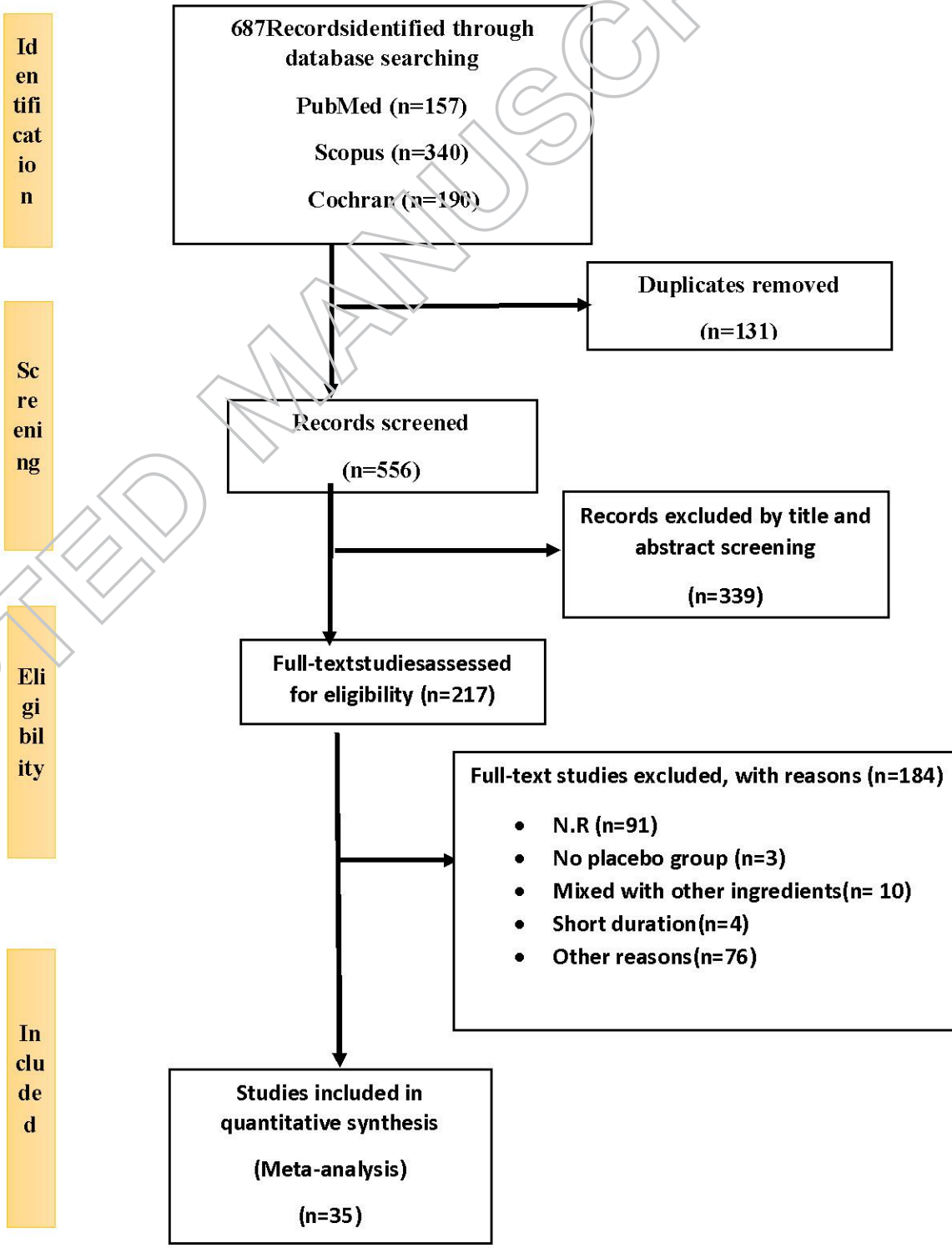

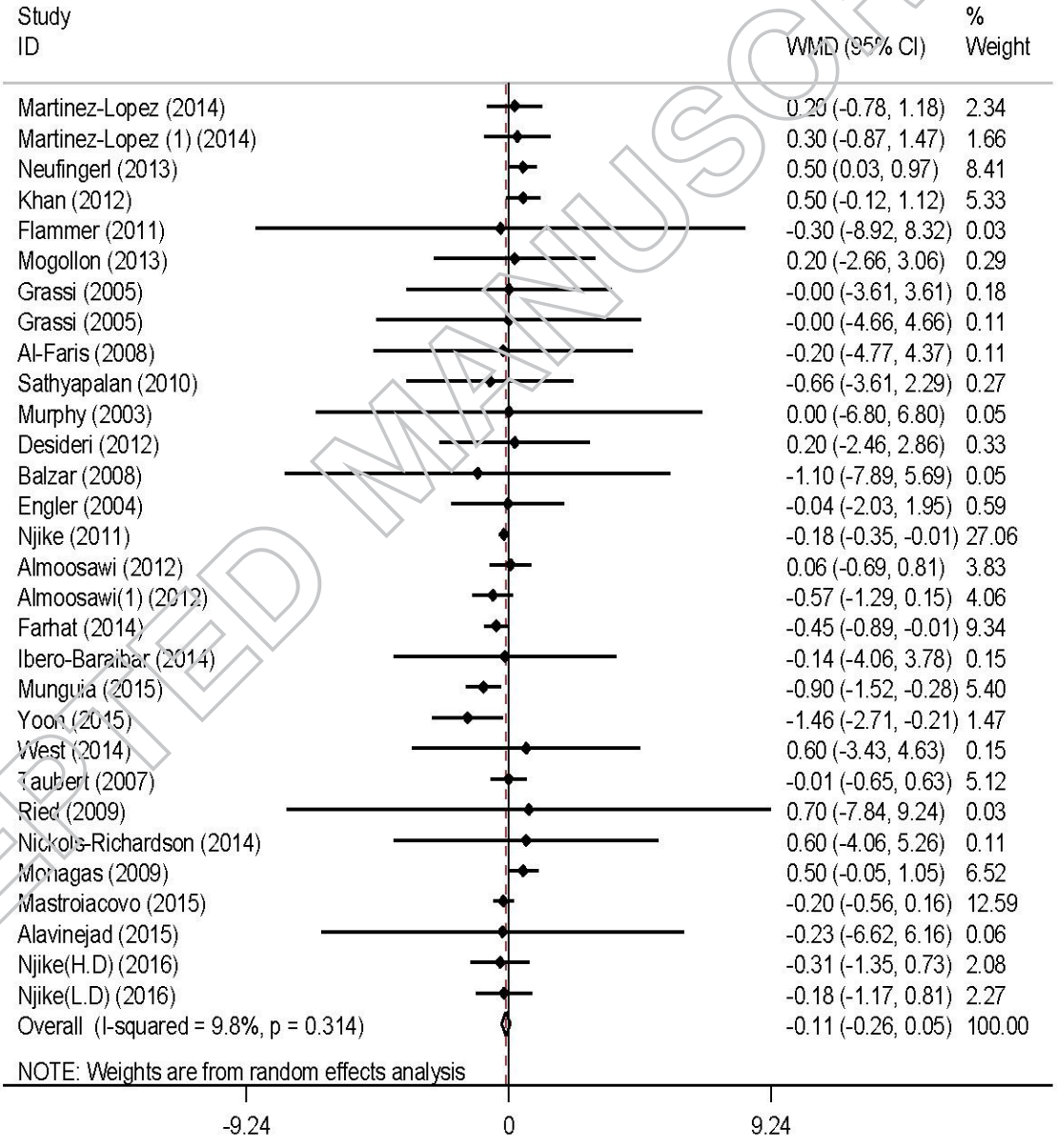

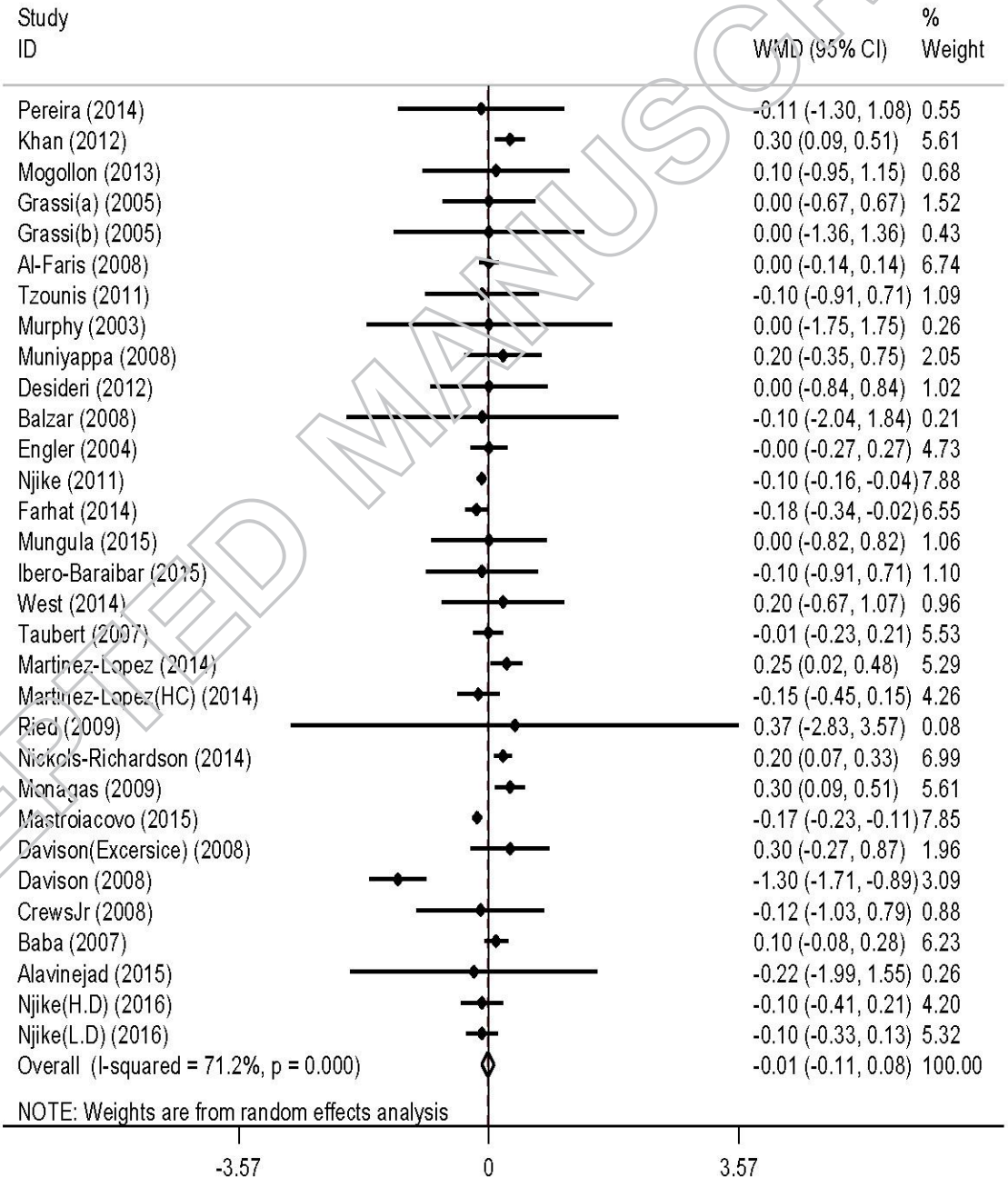

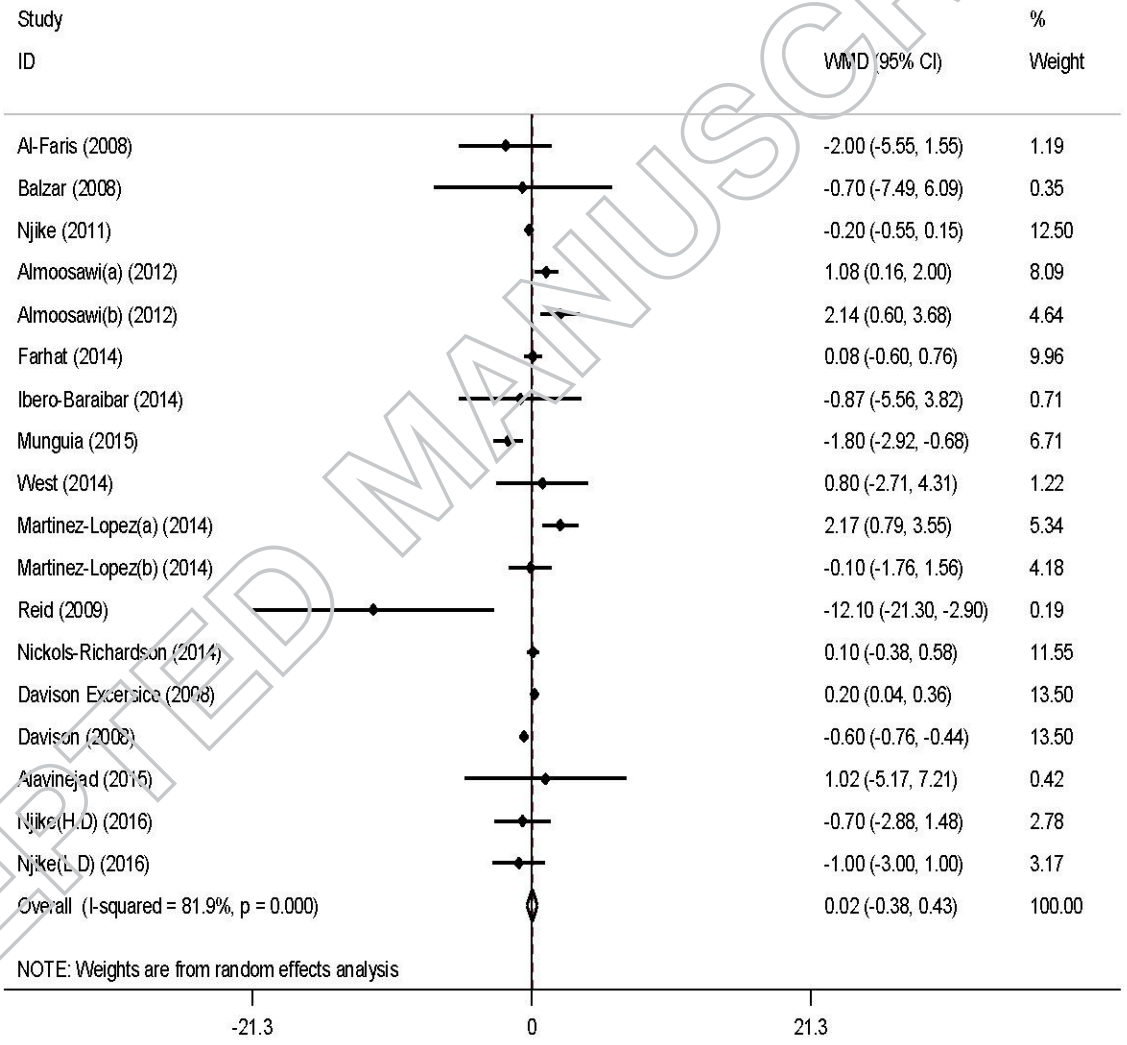

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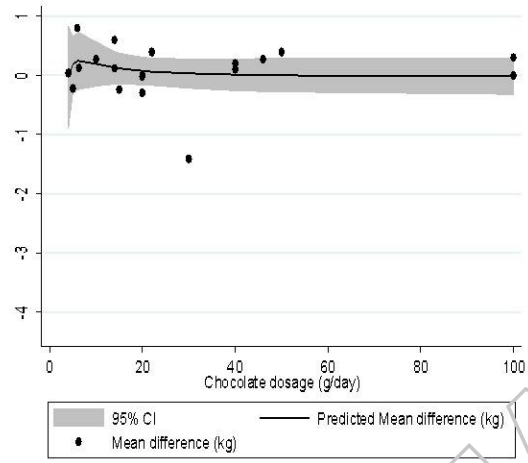

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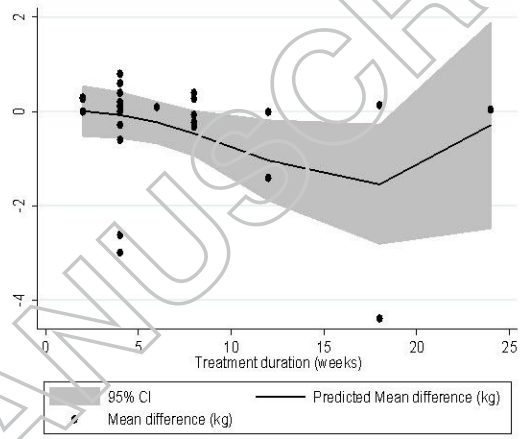

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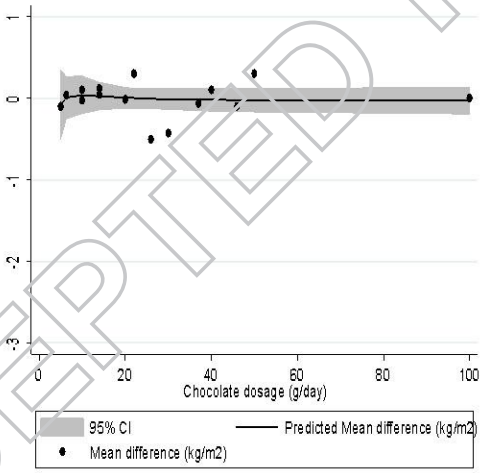

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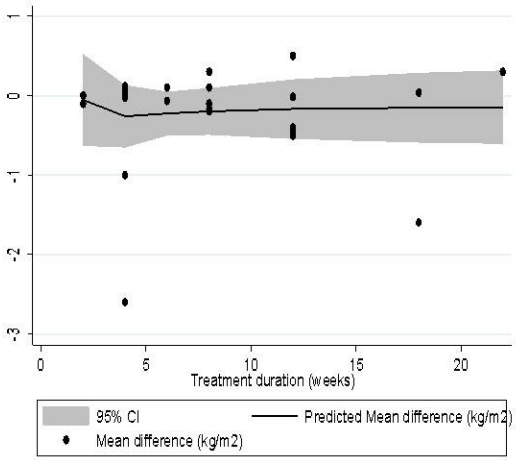

WC

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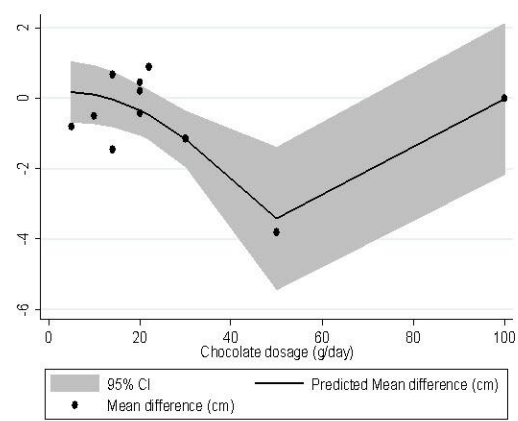

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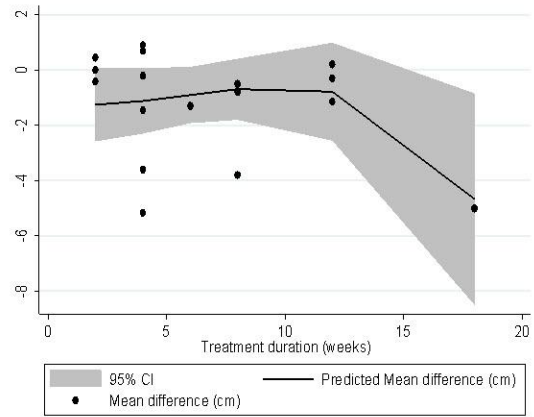
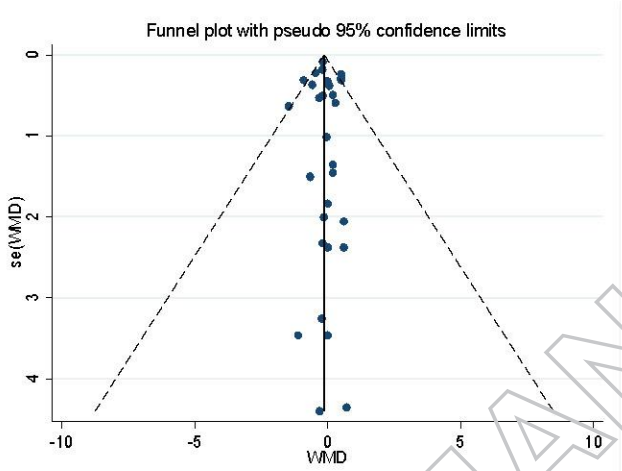


A)



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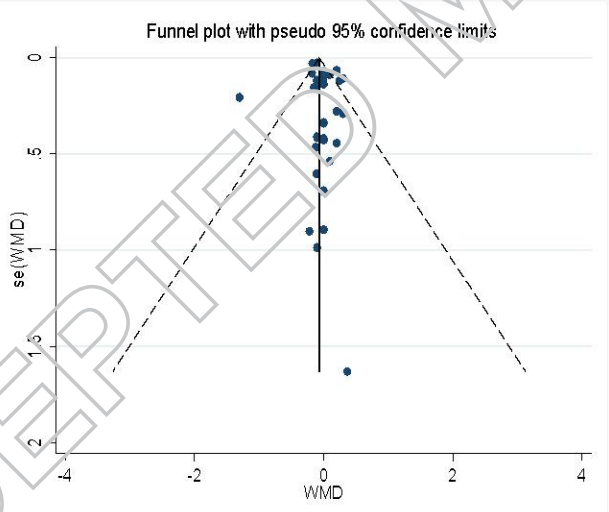

C)